表 2.7.4.2-23　Listing of Treatment Emergent Serious Adverse Events in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
019	Imeglimin	019-[redacted]-004	7[redacted]/ M/ Stage 3a/ No	Appendicitis (虫垂炎)	OL/ 209/ 219/ 11	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved
	Imeglimin	019-[redacted]-003	6[redacted]/ M/ Stage 2/ No	Subarachnoid haemorrhage (くも膜下出血)	OL/ 195/ 197/ 3	NOT RELATED/ Not Applicable	Severe/ Yes	Fatal
	Imeglimin	019-[redacted]-010	6[redacted]/ M/ Stage 2/ No	Post procedural haemorrhage (処置後出血)	OL/ 138/ 142/ 5	NOT RELATED/ Drug Interrupted	Moderate/ Yes	Recovered/Resolved
	Imeglimin	019-[redacted]-001	5[redacted]/ M/ Stage 1/ No	Atrial fibrillation (心房細動)	OL/ 179/ 394/ 216	NOT RELATED/ Dose Not Changed	Mild/ Yes	Recovered/Resolved
	Imeglimin + SU	019-[redacted]-026	4[redacted]/ M/ Stage 1/ No	Clavicle fracture (鎖骨骨折)	OL/ 73/ ./ .	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovering/Resolving
	Imeglimin + SU	019-[redacted]-013	7[redacted]/ M/ Stage 2/ No	Colon cancer stage I (結腸癌第１期)	OL/ 162/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ Yes	Not Recovered/Not Resolved
	Imeglimin + SU	019-[redacted]-004	6[redacted]/ F/ Stage 1/ No	Rectal cancer (直腸癌)	OL/ 236/ ./ .	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Not Recovered/Not Resolved
	Imeglimin + SU	019-[redacted]-006	6[redacted]/ M/ Stage 2/ Yes	Angina unstable (不安定狭心症)	OL/ 269/ 309/ 41	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin + SU	019-[redacted]-015	6[redacted]/ M/ Stage 3a/ No	Acute myocardial infarction (急性心筋梗塞)	OL/ 282/ 290/ 9	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved With Sequelae
	Imeglimin + SU	019-[redacted]-006	7[redacted]/ F/ Stage 2/ No	Contusion (挫傷)	OL/ 229/ 266/ 38	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin + SU	019-[redacted]-017	7[redacted]/ M/ Stage 2/ No	Subdural haematoma (硬膜下血腫)	OL/ 55/ 61/ 7	NOT RELATED/ Dose Not Changed	Severe/ Yes	Recovered/Resolved
	Imeglimin + SU	019-[redacted]-020	7[redacted]/ M/ Stage 2/ No	Pneumothorax traumatic (外傷性気胸)	OL/ 213/ 276/ 64	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
	Imeglimin + SU	019-[redacted]-012	6[redacted]/ F/ Stage 1/ No	Uterine leiomyoma (子宮平滑筋腫)	OL/ 306/ 317/ 12	NOT RELATED/ Drug Interrupted	Mild/ Yes	Recovered/Resolved
	Imeglimin + SU	019-[redacted]-011	7[redacted]/ F/ Stage 1/ No	Lower gastrointestinal haemorrhage (下部消化管出血)	OL/ 133/ 139/ 7	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin + SU	019-[redacted]-009	6[redacted]/ M/ Stage 2/ No	Synovitis (滑膜炎)	OL/ 271/ ./ .	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovering/Resolving
	Imeglimin + GLIN	019-[redacted]-005	5[redacted]/ M/ Stage 2/ No	Testis cancer (精巣癌)	OL/ 4/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving
	Imeglimin + BIG	019-[redacted]-014	5[redacted]/ M/ Stage 2/ No	Myocardial infarction (心筋梗塞)	OL/ 205/ 212/ 8	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved
	Imeglimin + BIG	019-[redacted]-010	7[redacted]/ M/ Stage 2/ No	Cholangiocarcinoma (胆管細胞癌)	OL/ 266/ ./ .	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Not Recovered/Not Resolved
	Imeglimin + BIG	019-[redacted]-004	5[redacted]/ M/ Stage 2/ Yes	Appendicitis (虫垂炎)	OL/ 204/ 211/ 8	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved
	Imeglimin + BIG	019-[redacted]-012	5[redacted]/ M/ Stage 2/ No	Large intestine polyp (大腸ポリープ)	OL/ 190/ 191/ 2	NOT RELATED/ Dose Not Changed	Mild/ Yes	Recovered/Resolved
	Imeglimin + AGI	019-[redacted]-042	6[redacted]/ M/ Stage 2/ No	Cholecystitis (胆嚢炎)	OL/ 167/ 177/ 11	NOT RELATED/ Dose Not Changed	Severe/ Yes	Recovered/Resolved
	Imeglimin + AGI	019-[redacted]-042	6[redacted]/ M/ Stage 2/ No	Drug-induced liver injury (薬物性肝障害)	OL/ 170/ 186/ 17	NOT RELATED/ Not Applicable	Moderate/ Yes	Recovered/Resolved
	Imeglimin + AGI	019-[redacted]-001	3[redacted]/ F/ Stage 1/ No	Ovarian cyst (卵巣嚢胞)	OL/ 368/ 375/ 8	NOT RELATED/ Not Applicable	Mild/ Yes	Recovered/Resolved
	Imeglimin + AGI	019-[redacted]-031	5[redacted]/ M/ Stage 2/ Yes	Angina unstable (不安定狭心症)	OL/ 116/ 130/ 15	NOT RELATED/ Dose Not Changed	Mild/ Yes	Recovered/Resolved
	Imeglimin + AGI	019-[redacted]-004	4[redacted]/ M/ Stage 2/ No	Heat illness (熱中症)	OL/ 41/ 42/ 2	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin + TZD	019-[redacted]-014	6[redacted]/ M/ Stage 2/ No	Enterovesical fistula (腸膀胱瘻)	OL/ 101/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Not Recovered/Not Resolved

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
	Imeglimin + TZD	019-[redacted]-015	7[redacted]/ M/ Stage 2/ No	Craniocerebral injury (頭蓋脳損傷)	OL/ 30/ 135/ 106	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved
	Imeglimin + TZD	019-[redacted]-010	5[redacted]/ M/ Stage 3a/ No	Inflammation (炎症)	OL/ 62/ 64/ 3	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin + TZD	019-[redacted]-020	7[redacted]/ M/ Stage 2/ Yes	Pneumonia bacterial (細菌性肺炎)	OL/ 222/ 232/ 11	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin + DPP4-I	019-[redacted]-008	4[redacted]/ M/ Stage 2/ No	Multiple fractures (多発骨折)	OL/ 189/ 307/ 119	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Recovered/Resolved
	Imeglimin + DPP4-I	019-[redacted]-001	6[redacted]/ F/ Stage 2/ No	Large intestine polyp (大腸ポリープ)	OL/ 237/ ./ .	NOT RELATED/ Dose Not Changed	Mild/ Yes	Recovering/Resolving
	Imeglimin + DPP4-I	019-[redacted]-001	6[redacted]/ F/ Stage 2/ No	Endometrial cancer stage III (子宮内膜癌第３期)	OL/ 233/ ./ .	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Not Recovered/Not Resolved
	Imeglimin + GLP1-RA	019-[redacted]-005	6[redacted]/ M/ Stage 1/ Yes	Lumbar spinal stenosis (腰部脊柱管狭窄症)	OL/ 286/ 300/ 15	NOT RELATED/ Drug Interrupted	Moderate/ Yes	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-010	6[redacted]/ F/ Stage 2/ No	Invasive ductal breast carcinoma (浸潤性乳管癌)	OL/ 156/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving
	Imeglimin + GLP1-RA	019-[redacted]-010	6[redacted]/ M/ Stage 2/ No	Dermoid cyst (皮様嚢腫)	OL/ 142/ 145/ 4	NOT RELATED/ Dose Not Changed	Mild/ Yes	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-011	6[redacted]/ M/ Stage 2/ No	Coronary artery stenosis (冠動脈狭窄)	OL/ 238/ 242/ 5	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-001	7[redacted]/ M/ Stage 2/ No	Cerebral infarction (脳梗塞)	OL/ 333/ 348/ 16	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-001	7[redacted]/ M/ Stage 2/ No	Coronary artery stenosis (冠動脈狭窄)	OL/ 334/ 348/ 15	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved
	Imeglimin + SGLT2-I	019-[redacted]-011	4[redacted]/ M/ Stage 2/ Yes	Cardiac failure (心不全)	OL/ 297/ ./ .	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovering/Resolving
	Imeglimin + SGLT2-I	019-[redacted]-011	4[redacted]/ M/ Stage 2/ Yes	Pneumonia (肺炎)	OL/ 297/ 309/ 13	NOT RELATED/ Drug Interrupted	Severe/ Yes	Recovered/Resolved

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
	Imeglimin + SGLT2-I	019-[redacted]-009	7[redacted]/ F/ Stage 2/ No	Lacunar infarction (ラクナ梗塞)	OL/ 187/ 221/ 35	NOT RELATED/ Drug Interrupted	Moderate/ Yes	Recovered/Resolved With Sequelae
	Imeglimin + SGLT2-I	019-[redacted]-002	5[redacted]/ M/ Stage 2/ No	Large intestine polyp (大腸ポリープ)	OL/ 17/ 18/ 2	NOT RELATED/ Dose Not Changed	Mild/ Yes	Recovered/Resolved
	Imeglimin + SGLT2-I	019-[redacted]-006	5[redacted]/ M/ Stage 2/ No	Spinal fracture (脊椎骨折)	OL/ 4/ 21/ 18	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved

- Abbreviations: M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; OL, Open-label; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- All adverse events were coded using MedDRA dictionary version 20.1.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

2.7.4.2.1.4.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

重篤な有害事象の発現割合を表 2.7.4.2-24 に、重篤な有害事象の一覧を表 2.7.4.2-25 に示す。重篤な有害事象の詳細な叙述は 2.7.6.20 項に示す。

死亡を含む重篤な有害事象の発現被験者数（発現割合）は、プラセボ群、イメグリミン群の順に 3 名（2.8%）、1 名（0.9%）であった。イメグリミン群で発現した重篤な有害事象は、肺塞栓症及び四肢静脈血栓症が 1 名であった。いずれの事象も治験薬との因果関係は否定され、転帰は回復又は軽快であった。重篤な有害事象のうち治験薬の投与中止に至った事象は、プラセボ群のギラン・バレー症候群の 1 名で、治験薬との因果関係は否定されなかった。

表 2.7.4.2-24　Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

System Organ Class Preferred Term	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Any Serious TEAE	3 (2.8%)	1 (0.9%)
Nervous system disorders (神経系障害)	2 (1.9%)	0
Dizziness (浮動性めまい)	1 (0.9%)	0
Guillain-Barre syndrome (ギラン・バレー症候群)	1 (0.9%)	0
Infections and infestations (感染症および寄生虫症)	1 (0.9%)	0
Pneumonia (肺炎)	1 (0.9%)	0
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	0	1 (0.9%)
Pulmonary embolism (肺塞栓症)	0	1 (0.9%)
Vascular disorders (血管障害)	0	1 (0.9%)
Venous thrombosis limb (四肢静脈血栓症)	0	1 (0.9%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-25　Listing of Treatment Emergent Serious Adverse Events in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
020	Placebo + Insulin	020-[redacted]-002	7[redacted]/ F/ Stage 2/ No	Pneumonia (肺炎)	DB/ 17/ 29/ 13	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Placebo + Insulin	020-[redacted]-004	6[redacted]/ F/ Stage 2/ No	Dizziness (浮動性めまい)	DB/ 16/ 27/ 12	RELATED/ Dose Not Changed	Severe/ Yes	Recovered/Resolved
	Placebo + Insulin	020-[redacted]-016	5[redacted]/ M/ Stage 2/ Yes	Guillain-Barre syndrome (ギラン・バレー症候群)	DB/ 11/ ./ .	RELATED/ Drug Withdrawn	Severe/ Yes	Recovering/Resolving
	Imeglimin 1000 mg bid + Insulin	020-[redacted]-014	4[redacted]/ M/ Stage 2/ No	Venous thrombosis limb (四肢静脈血栓症)	DB/ 114/ ./ .	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovering/Resolving
	Imeglimin 1000 mg bid + Insulin	020-[redacted]-014	4[redacted]/ M/ Stage 2/ No	Pulmonary embolism (肺塞栓症)	DB/ 114/ 189/ 76	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved

- Abbreviations: bid, Twice a day; M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; DB, Double-blind
- All adverse events were coded using MedDRA dictionary version 20.1.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

(2) 長期投与（52 週）

重篤な有害事象の発現割合を表 2.7.4.2-26 に、重篤な有害事象の一覧を表 2.7.4.2-27 に示す。重篤な有害事象の詳細な叙述は 2.7.6.20 項に示す。

死亡を含む重篤な有害事象の発現被験者数（発現割合）は 12 名（5.7%）で、乳頭様甲状腺癌が 2 名に、突然死、肝機能異常、鎖骨骨折、膵癌、網膜剥離、てんかん、丹毒、坐骨神経痛、冠動脈狭窄が各 1 名に、四肢静脈血栓症及び肺塞栓症が 1 名に発現した。いずれの事象も治験薬との因果関係は否定された。1 名が死亡（突然死）し、膵癌は未回復であったが、そのほかの事象は回復又は軽快であった。重篤な有害事象のうち治験薬の投与中止に至った事象は、乳頭様甲状腺癌が 2 名、膵癌が 1 名であった。

表 2.7.4.2-26　Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any Serious TEAE	6 (5.9%)	6 (5.6%)	12 (5.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	3 (3.0%)	0	3 (1.4%)
Papillary thyroid cancer (乳頭様甲状腺癌)	2 (2.0%)	0	2 (1.0%)
Pancreatic carcinoma (膵癌)	1 (1.0%)	0	1 (0.5%)
Nervous system disorders (神経系障害)	0	2 (1.9%)	2 (1.0%)
Epilepsy (てんかん)	0	1 (0.9%)	1 (0.5%)
Sciatica (坐骨神経痛)	0	1 (0.9%)	1 (0.5%)
Cardiac disorders (心臓障害)	0	1 (0.9%)	1 (0.5%)
Coronary artery stenosis (冠動脈狭窄)	0	1 (0.9%)	1 (0.5%)
Eye disorders (眼障害)	0	1 (0.9%)	1 (0.5%)
Retinal detachment (網膜剥離)	0	1 (0.9%)	1 (0.5%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	1 (1.0%)	0	1 (0.5%)
Sudden death (突然死)	1 (1.0%)	0	1 (0.5%)
Hepatobiliary disorders (肝胆道系障害)	1 (1.0%)	0	1 (0.5%)
Hepatic function abnormal (肝機能異常)	1 (1.0%)	0	1 (0.5%)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Infections and infestations (感染症および寄生虫症)	0	1 (0.9%)	1 (0.5%)
Erysipelas (丹毒)	0	1 (0.9%)	1 (0.5%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	1 (1.0%)	0	1 (0.5%)
Clavicle fracture (鎖骨骨折)	1 (1.0%)	0	1 (0.5%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	0	1 (0.9%)	1 (0.5%)
Pulmonary embolism (肺塞栓症)	0	1 (0.9%)	1 (0.5%)
Vascular disorders (血管障害)	0	1 (0.9%)	1 (0.5%)
Venous thrombosis limb (四肢静脈血栓症)	0	1 (0.9%)	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-27　Listing of Treatment Emergent Serious Adverse Events in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
020	Placebo/Imeglimin + Insulin	020-[redacted]-002	6[redacted]/ M/ Stage 2/ No	Sudden death (突然死)	OL/ 328/ 328/ 1	NOT RELATED/ Not Applicable	Severe/ Yes	Fatal
	Placebo/Imeglimin + Insulin	020-[redacted]-002	7[redacted]/ F/ Stage 2/ No	Hepatic function abnormal (肝機能異常)	OL/ 364/ 371/ 8	NOT RELATED/ Dose Not Changed	Severe/ Yes	Recovered/Resolved
	Placebo/Imeglimin + Insulin	020-[redacted]-003	6[redacted]/ F/ Stage 2/ No	Papillary thyroid cancer (乳頭様甲状腺癌)	OL/ 185/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving
	Placebo/Imeglimin + Insulin	020-[redacted]-005	6[redacted]/ F/ Stage 2/ No	Papillary thyroid cancer (乳頭様甲状腺癌)	OL/ 246/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving
	Placebo/Imeglimin + Insulin	020-[redacted]-001	7[redacted]/ M/ Stage 2/ No	Clavicle fracture (鎖骨骨折)	OL/ 276/ 335/ 60	NOT RELATED/ Dose Not Changed	Mild/ Yes	Recovered/Resolved
	Placebo/Imeglimin + Insulin	020-[redacted]-002	6[redacted]/ M/ Stage 2/ Yes	Pancreatic carcinoma (膵癌)	OL/ 223/ ./ .	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Not Recovered/Not Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-014	4[redacted]/ M/ Stage 2/ No	Venous thrombosis limb (四肢静脈血栓症)	DB/ 114/ ./ .	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovering/Resolving
	Imeglimin/Imeglimin + Insulin	020-[redacted]-014	4[redacted]/ M/ Stage 2/ No	Pulmonary embolism (肺塞栓症)	DB/ 114/ 189/ 76	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-001	6[redacted]/ M/ Stage 2/ No	Retinal detachment (網膜剥離)	OL/ 335/ 348/ 14	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-008	6[redacted]/ M/ Stage 2/ Yes	Epilepsy (てんかん)	OL/ 134/ 199/ 66	NOT RELATED/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-008	5[redacted]/ M/ Stage 1/ No	Erysipelas (丹毒)	OL/ 246/ 256/ 11	NOT RELATED/ Drug Interrupted	Moderate/ Yes	Recovered/Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-011	5[redacted]/ M/ Stage 1/ No	Sciatica (坐骨神経痛)	OL/ 220/ 281/ 62	NOT RELATED/ Dose Not Changed	Severe/ Yes	Recovered/Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-001	5[redacted]/ M/ Stage 2/ No	Coronary artery stenosis (冠動脈狭窄)	OL/ 125/ 127/ 3	NOT RELATED/ Drug Interrupted	Moderate/ Yes	Recovered/Resolved

- Abbreviations: M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; DB, Double-blind; OL, Open-label
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- Start/End Days were relative to the day of first dose of study treatment in the double-blind period.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

2.7.4.2.1.5　投与中止に至った有害事象

2.7.4.2.1.5.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

治験薬の投与中止に至った有害事象の発現割合を表 2.7.4.2-28 に、治験薬の投与中止に至った有害事象の一覧を表 2.7.4.2-29 に示す。治験薬の投与中止に至った有害事象の発現被験者数（発現割合）はプラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に 14 名（7.7%）、2 名（2.7%）、6 名（3.3%）、5 名（6.7%）であった。本剤群で 2 名以上に発現した治験薬の投与中止に至った有害事象は、高血糖［500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）2 名（2.7%）、1 名（0.6%）、0 名］及び嘔吐［0 名、1 名（0.6%）、2 名（2.7%）］であった。

表 2.7.4.2-28　Summary of Treatment Emergent Adverse Events Leading to Discontinuation from Treatment by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any TEAE leading to discontinuation from treatment	14 (7.7%)	2 (2.7%)	6 (3.3%)	5 (6.7%)	13 (3.9%)
Metabolism and nutrition disorders (代謝および栄養障害)	13 (7.1%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Hyperglycaemia (高血糖)	13 (7.1%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Gastrointestinal disorders (胃腸障害)	0	0	1 (0.6%)	3 (4.0%)	4 (1.2%)
Vomiting (嘔吐)	0	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Diarrhoea (下痢)	0	0	1 (0.6%)	0	1 (0.3%)
Stomatitis (口内炎)	0	0	0	1 (1.3%)	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	0	0	2 (1.1%)	1 (1.3%)	3 (0.9%)
Bladder cancer (膀胱癌)	0	0	1 (0.6%)	0	1 (0.3%)
Pancreatic carcinoma metastatic (遠隔転移を伴う膵癌)	0	0	0	1 (1.3%)	1 (0.3%)
Prostate cancer (前立腺癌)	0	0	1 (0.6%)	0	1 (0.3%)
Ear and labyrinth disorders (耳および迷路障害)	0	0	1 (0.6%)	0	1 (0.3%)
Vertigo positional (頭位性回転性めまい)	0	0	1 (0.6%)	0	1 (0.3%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	0	0	0	1 (1.3%)	1 (0.3%)
Feeling abnormal (異常感)	0	0	0	1 (1.3%)	1 (0.3%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Nervous system disorders (神経系障害)	0	0	1 (0.6%)	0	1 (0.3%)
Spondylitic myelopathy (脊椎炎性脊髄症)	0	0	1 (0.6%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	1 (0.5%)	0	0	0	0
Rash (発疹)	1 (0.5%)	0	0	0	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-29　Listing of Treatment Emergent Adverse Events Leading to Discontinuation from Treatment in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
014	Placebo	[redacted]-001	4[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 57/ 183/ 127	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Placebo	[redacted]-005	6[redacted]/ F/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 85/ ./ .	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Placebo	[redacted]-014	7[redacted]/ M/ Stage 3a/ No	Rash (発疹)	DB/ 21/ ./ .	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Placebo	[redacted]-013	5[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 5/ ./ .	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Moderate/ No	Not Recovered/Not Resolved
	Placebo	[redacted]-003	5[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 141/ 190/ 50	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Placebo	[redacted]-005	7[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 31/ 135/ 105	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Placebo	[redacted]-014	6[redacted]/ F/ Stage 3a/ No	Hyperglycaemia (高血糖)	DB/ 87/ 142/ 56	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Placebo	[redacted]-002	5[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 18/ ./ .	RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Recovering/Resolving
	Imeglimin 500 mg bid	[redacted]-004	6[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 32/ 152/ 121	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin 500 mg bid	[redacted]-010	6[redacted]/ F/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 30/ 128/ 99	RELATED TO STUDY DRUG/ Drug Withdrawn	Moderate/ No	Recovered/Resolved
	Imeglimin 1000 mg bid	[redacted]-001	6[redacted]/ M/ Stage 2/ No	Prostate cancer (前立腺癌)	DB/ 61/ ./ .	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Severe/ Yes	Not Recovered/Not Resolved
	Imeglimin 1000 mg bid	[redacted]-004	6[redacted]/ F/ Stage 2/ No	Vertigo positional (頭位性回転性めまい)	DB/ 47/ 60/ 14	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin 1000 mg bid	[redacted]-001	5[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 111/ 204/ 94	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Moderate/ No	Recovered/Resolved

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
	Imeglimin 1500 mg bid	[redacted]-001	5[redacted]/ M/ Stage 2/ No	Vomiting (嘔吐)	DB/ 8/ 8/ 1	RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin 1500 mg bid	[redacted]-001	6[redacted]/ F/ Stage 2/ No	Stomatitis (口内炎)	DB/ 32/ 97/ 66	RELATED TO STUDY DRUG/ Drug Withdrawn	Moderate/ No	Recovered/Resolved
	Imeglimin 1500 mg bid	[redacted]-009	4[redacted]/ F/ Stage 1/ No	Feeling abnormal (異常感)	DB/ 4/ 22/ 19	RELATED TO STUDY DRUG/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin 1500 mg bid	[redacted]-002	7[redacted]/ M/ Stage 2/ No	Pancreatic carcinoma metastatic (遠隔転移を伴う膵癌)	DB/ 121/ 184/ 64	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Severe/ Yes	Fatal
	Imeglimin 1500 mg bid	[redacted]-027	6[redacted]/ F/ Stage 2/ Yes	Vomiting (嘔吐)	DB/ 1/ 12/ 12	RELATED TO STUDY DRUG/ Drug Withdrawn	Moderate/ No	Recovered/Resolved
018	Placebo	018-[redacted]-008	4[redacted]/ F/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 85/ 211/ 127	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Placebo	018-[redacted]-009	6[redacted]/ M/ Stage 3a/ Yes	Hyperglycaemia (高血糖)	DB/ 113/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovering/Resolving
	Placebo	018-[redacted]-006	7[redacted]/ F/ Stage 2/ Yes	Hyperglycaemia (高血糖)	DB/ 29/ 113/ 85	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Placebo	018-[redacted]-003	5[redacted]/ F/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 84/ 143/ 60	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Placebo	018-[redacted]-005	7[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 57/ 85/ 29	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Placebo	018-[redacted]-011	4[redacted]/ M/ Stage 1/ No	Hyperglycaemia (高血糖)	DB/ 140/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin 1000 mg bid	018-[redacted]-002	5[redacted]/ M/ Stage 2/ No	Spondylitic myelopathy (脊椎炎性脊髄症)	DB/ 123/ ./ .	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Recovering/Resolving
	Imeglimin 1000 mg bid	018-[redacted]-006	5[redacted]/ F/ Stage 2/ No	Diarrhoea (下痢)	DB/ 2/ 7/ 6	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin 1000 mg bid	018-[redacted]-006	5[redacted]/ F/ Stage 2/ No	Vomiting (嘔吐)	DB/ 2/ 11/ 10	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin 1000 mg bid	018-[redacted]-003	7[redacted]/ M/ Stage 2/ No	Bladder cancer (膀胱癌)	DB/ 29/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving

- Abbreviations: bid, Twice a day; M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; DB, Double-blind
- All adverse events were coded using MedDRA dictionary version 20.1.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

2.7.4.2.1.5.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

治験薬の投与中止に至った有害事象の発現割合を表 2.7.4.2-30 に、治験薬の投与中止に至った有害事象の一覧を表 2.7.4.2-31 に示す。

- 単独療法群では、治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 3 名（2.2%）で、いずれの被験者も高血糖を発現した。
- SU 併用療法群では、治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 9 名（7.1%）で、高血糖が 7 名（5.5%）、結腸癌第 1 期及び直腸癌が各 1 名（0.8%）に発現した。
- GLIN 併用療法群では、治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 1 名（1.6%）で、精巣癌が発現した。
- BIG 併用療法群では、治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 7 名（10.9%）で、食欲減退、悪心、上腹部痛、嘔吐、下痢、胆管細胞癌、血小板数減少が各 1 名（1.6%）に発現した。
- AGI 併用療法群では、治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 2 名（3.1%）で、高血糖及び胃炎が各 1 名（1.6%）に発現した。
- TZD 併用療法群では、治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 4 名（6.2%）で、高血糖、悪心、嘔吐、腸膀胱瘻が各 1 名（1.5%）に発現した。
- DPP4-I 併用療法群では、治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 5 名（7.9%）で、高血糖、食欲減退、悪心、多発骨折、勃起不全が各 1 名（1.6%）に発現した。
- GLP1-RA 併用療法群では、治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 15 名（21.4%）で、高血糖が 8 名（11.4%）、食欲減退、悪心、上腹部痛、消化不良、浸潤性乳管癌、胆石症、糖尿病性ニューロパチーが各 1 名（1.4%）に発現した。
- SGLT2-I 併用療法群では、治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 1 名（1.6%）で、高血糖が発現した。

表 2.7.4.2-30　Summary of Treatment Emergent Adverse Events Leading to Discontinuation from Treatment by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any TEAE leading to discontinuation from treatment	3 (2.2%)	9 (7.1%)	1 (1.6%)	7 (10.9%)	2 (3.1%)	4 (6.2%)	5 (7.9%)	15 (21.4%)	1 (1.6%)	44 (7.6%)	47 (6.6%)
Metabolism and nutrition disorders (代謝および栄養障害)	3 (2.2%)	7 (5.5%)	0	1 (1.6%)	1 (1.6%)	1 (1.5%)	2 (3.2%)	9 (12.9%)	1 (1.6%)	22 (3.8%)	25 (3.5%)
Hyperglycaemia (高血糖)	3 (2.2%)	7 (5.5%)	0	0	1 (1.6%)	1 (1.5%)	1 (1.6%)	8 (11.4%)	1 (1.6%)	19 (3.3%)	22 (3.1%)
Decreased appetite (食欲減退)	0	0	0	1 (1.6%)	0	0	1 (1.6%)	1 (1.4%)	0	3 (0.5%)	3 (0.4%)
Gastrointestinal disorders (胃腸障害)	0	0	0	4 (6.3%)	1 (1.6%)	3 (4.6%)	1 (1.6%)	3 (4.3%)	0	12 (2.1%)	12 (1.7%)
Nausea (悪心)	0	0	0	1 (1.6%)	0	1 (1.5%)	1 (1.6%)	1 (1.4%)	0	4 (0.7%)	4 (0.6%)
Abdominal pain upper (上腹部痛)	0	0	0	1 (1.6%)	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Vomiting (嘔吐)	0	0	0	1 (1.6%)	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Diarrhoea (下痢)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Dyspepsia (消化不良)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Enterovesical fistula (腸膀胱瘻)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Gastritis (胃炎)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	0	2 (1.6%)	1 (1.6%)	1 (1.6%)	0	0	0	1 (1.4%)	0	5 (0.9%)	5 (0.7%)
Cholangiocarcinoma (胆管細胞癌)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Colon cancer stage I (結腸癌第１期)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Invasive ductal breast carcinoma (浸潤性乳管癌)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Rectal cancer (直腸癌)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Testis cancer (精巣癌)	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Hepatobiliary disorders (肝胆道系障害)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Cholelithiasis (胆石症)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Multiple fractures (多発骨折)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Investigations (臨床検査)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Platelet count decreased (血小板数減少)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Nervous system disorders (神経系障害)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Diabetic neuropathy (糖尿病性ニューロパチー)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Reproductive system and breast disorders (生殖系および乳房障害)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Erectile dysfunction (勃起不全)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-31　Listing of Treatment Emergent Adverse Events Leading to Discontinuation from Treatment in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
019	Imeglimin	019-[redacted]-012	6[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 282/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin	019-[redacted]-014	4[redacted]/ F/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 143/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin	019-[redacted]-016	5[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 281/ 295/ 15	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + SU	019-[redacted]-036	5[redacted]/ F/ Stage 1/ No	Hyperglycaemia (高血糖)	OL/ 57/ 144/ 88	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + SU	019-[redacted]-040	5[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 225/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + SU	019-[redacted]-013	7[redacted]/ M/ Stage 2/ No	Colon cancer stage I (結腸癌第 1 期)	OL/ 162/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ Yes	Not Recovered/Not Resolved
	Imeglimin + SU	019-[redacted]-004	4[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 283/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + SU	019-[redacted]-004	6[redacted]/ F/ Stage 1/ No	Rectal cancer (直腸癌)	OL/ 236/ ./ .	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Not Recovered/Not Resolved
	Imeglimin + SU	019-[redacted]-011	3[redacted]/ M/ Stage 1/ No	Hyperglycaemia (高血糖)	OL/ 29/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + SU	019-[redacted]-017	5[redacted]/ M/ Stage 1/ Yes	Hyperglycaemia (高血糖)	OL/ 307/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + SU	019-[redacted]-031	4[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 183/ 371/ 189	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + SU	019-[redacted]-003	4[redacted]/ F/ Stage 1/ No	Hyperglycaemia (高血糖)	OL/ 113/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + GLIN	019-[redacted]-005	5[redacted]/ M/ Stage 2/ No	Testis cancer (精巣癌)	OL/ 4/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
	Imeglimin + BIG	019-[redacted]-002	7[redacted]/ M/ Stage 2/ No	Decreased appetite (食欲減退)	OL/ 40/ 162/ 123	RELATED/ Drug Withdrawn	Moderate/ No	Recovered/Resolved
	Imeglimin + BIG	019-[redacted]-005	3[redacted]/ F/ Stage 2/ No	Abdominal pain upper (上腹部痛)	OL/ 14/ ./ .	RELATED/ Drug Withdrawn	Mild/ No	Recovering/Resolving
	Imeglimin + BIG	019-[redacted]-003	7[redacted]/ F/ Stage 3a/ No	Diarrhoea (下痢)	OL/ 58/ 64/ 7	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + BIG	019-[redacted]-011	6[redacted]/ M/ Stage 2/ No	Nausea (悪心)	OL/ 5/ 172/ 168	RELATED/ Drug Withdrawn	Severe/ No	Recovered/Resolved
	Imeglimin + BIG	019-[redacted]-010	7[redacted]/ M/ Stage 2/ No	Cholangiocarcinoma (胆管細胞癌)	OL/ 266/ ./ .	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Not Recovered/Not Resolved
	Imeglimin + BIG	019-[redacted]-011	4[redacted]/ F/ Stage 1/ No	Platelet count decreased (血小板数減少)	OL/ 225/ ./ .	RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + BIG	019-[redacted]-007	4[redacted]/ F/ Stage 1/ No	Vomiting (嘔吐)	OL/ 2/ 3/ 2	RELATED/ Drug Withdrawn	Moderate/ No	Recovered/Resolved
	Imeglimin + AGI	019-[redacted]-007	7[redacted]/ F/ Stage 2/ No	Gastritis (胃炎)	OL/ 8/ 86/ 79	RELATED/ Drug Withdrawn	Moderate/ No	Recovered/Resolved
	Imeglimin + AGI	019-[redacted]-003	6[redacted]/ M/ Stage 1/ No	Hyperglycaemia (高血糖)	OL/ 282/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + TZD	019-[redacted]-014	6[redacted]/ M/ Stage 2/ No	Enterovesical fistula (腸膀胱瘻)	OL/ 101/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Not Recovered/Not Resolved
	Imeglimin + TZD	019-[redacted]-007	5[redacted]/ M/ Stage 1/ Yes	Hyperglycaemia (高血糖)	OL/ 283/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + TZD	019-[redacted]-023	7[redacted]/ F/ Stage 2/ No	Vomiting (嘔吐)	OL/ 1/ 5/ 5	RELATED/ Drug Withdrawn	Moderate/ No	Recovered/Resolved
	Imeglimin + TZD	019-[redacted]-041	6[redacted]/ F/ Stage 3a/ No	Nausea (悪心)	OL/ 37/ 42/ 6	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + DPP4-I	019-[redacted]-004	5[redacted]/ M/ Stage 2/ No	Erectile dysfunction (勃起不全)	OL/ 1/ 36/ 36	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
	Imeglimin + DPP4-I	019-[redacted]-003	7 / M/ Stage 2/ No	Decreased appetite (食欲減退)	OL/ 1/ 73/ 73	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + DPP4-I	019-[redacted]-007	7 / F/ Stage 2/ No	Nausea (悪心)	OL/ 5/ 19/ 15	RELATED/ Drug Withdrawn	Moderate/ No	Recovered/Resolved
	Imeglimin + DPP4-I	019-[redacted]-008	4 / M/ Stage 2/ No	Multiple fractures (多発骨折)	OL/ 189/ 307/ 119	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Recovered/Resolved
	Imeglimin + DPP4-I	019-[redacted]-002	5 / M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 350/ ./ .	RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + GLP1-RA	019-[redacted]-056	5 / M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 29/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + GLP1-RA	019-[redacted]-033	5 / M/ Stage 1/ Yes	Hyperglycaemia (高血糖)	OL/ 29/ 87/ 59	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-006	4 / M/ Stage 2/ Yes	Hyperglycaemia (高血糖)	OL/ 85/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + GLP1-RA	019-[redacted]-006	5 / M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 313/ 341/ 29	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-010	4 / F/ Stage 2/ Yes	Hyperglycaemia (高血糖)	OL/ 87/ 171/ 85	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-019	7 / F/ Stage 2/ Yes	Abdominal pain upper (上腹部痛)	OL/ 4/ 80/ 77	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-012	6 / M/ Stage 2/ No	Cholelithiasis (胆石症)	OL/ 221/ 302/ 82	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-029	5 / M/ Stage 1/ No	Hyperglycaemia (高血糖)	OL/ 120/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + GLP1-RA	019-[redacted]-002	6 / M/ Stage 2/ Yes	Nausea (悪心)	OL/ 1/ 5/ 5	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + GLP1-RA	019-[redacted]-007	7 / F/ Stage 2/ No	Dyspepsia (消化不良)	OL/ 11/ 43/ 33	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
	Imeglimin + GLP1-RA	019-[redacted]-008	6[redacted]/ F/ Stage 1/ No	Hyperglycaemia (高血糖)	OL/ 197/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + GLP1-RA	019-[redacted]-012	5[redacted]/ F/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 169/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovering/Resolving
	Imeglimin + GLP1-RA	019-[redacted]-009	6[redacted]/ F/ Stage 2/ No	Diabetic neuropathy (糖尿病性ニューロパチー)	OL/ 155/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin + GLP1-RA	019-[redacted]-010	6[redacted]/ F/ Stage 2/ No	Invasive ductal breast carcinoma (浸潤性乳管癌)	OL/ 156/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving
	Imeglimin + GLP1-RA	019-[redacted]-010	6[redacted]/ M/ Stage 2/ No	Decreased appetite (食欲減退)	OL/ 37/ 334/ 298	RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Imeglimin + SGLT2-I	019-[redacted]-001	5[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 113/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved

- Abbreviations: M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; OL, Open-label; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- All adverse events were coded using MedDRA dictionary version 20.1.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

2.7.4.2.1.5.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

治験薬の投与中止に至った有害事象の発現割合を表 2.7.4.2-32 に、治験薬の投与中止に至った有害事象の一覧を表 2.7.4.2-33 に示す。治験薬の投与中止に至った有害事象の発現被験者数（発現割合）はプラセボ群で 4 名（3.7%）、イメグリミン群 1 名（0.9%）で、イメグリミン群では、悪心が発現した。

表 2.7.4.2-32　Summary of Treatment Emergent Adverse Events Leading to Discontinuation from Treatment by System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

System Organ Class Preferred Term	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Any TEAE leading to discontinuation from treatment	4 (3.7%)	1 (0.9%)
Metabolism and nutrition disorders (代謝および栄養障害)	3 (2.8%)	0
Hyperglycaemia (高血糖)	3 (2.8%)	0
Gastrointestinal disorders (胃腸障害)	0	1 (0.9%)
Nausea (悪心)	0	1 (0.9%)
Nervous system disorders (神経系障害)	1 (0.9%)	0
Guillain-Barre syndrome (ギラン・バレー症候群)	1 (0.9%)	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-33　Listing of Treatment Emergent Adverse Events Leading to Discontinuation from Treatment in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
020	Placebo + Insulin	020-[redacted]-009	5[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 84/ ./ .	RELATED/ Drug Withdrawn	Moderate/ No	Not Recovered/Not Resolved
	Placebo + Insulin	020-[redacted]-004	6[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 113/ 141/ 29	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovered/Resolved
	Placebo + Insulin	020-[redacted]-008	3[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	DB/ 40/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Placebo + Insulin	020-[redacted]-016	5[redacted]/ M/ Stage 2/ Yes	Guillain-Barre syndrome (ギラン・バレー症候群)	DB/ 11/ ./ .	RELATED/ Drug Withdrawn	Severe/ Yes	Recovering/Resolving
	Imeglimin 1000 mg bid + Insulin	020-[redacted]-012	7[redacted]/ F/ Stage 1/ No	Nausea (悪心)	DB/ 1/ 34/ 34	RELATED/ Drug Withdrawn	Moderate/ No	Recovered/Resolved

- Abbreviations: bid, Twice a day; M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; DB, Double-blind
- All adverse events were coded using MedDRA dictionary version 20.1.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

(2) 長期投与（52 週）

治験薬の投与中止に至った有害事象の発現割合を表 2.7.4.2-34 に、治験薬の投与中止に至った有害事象の一覧を表 2.7.4.2-35 に示す。治験薬の投与中止に至った有害事象の発現被験者数（発現割合）は 8 名（3.8%）で、乳頭様甲状腺腫及び高血糖が各 2 名（1.0%）に、膵癌、子宮平滑筋腫、悪心、血中ブドウ糖異常が各 1 名（0.5%）に発現した。

表 2.7.4.2-34　Summary of Treatment Emergent Adverse Events Leading to Discontinuation from Treatment by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any TEAE leading to discontinuation from treatment	3 (3.0%)	5 (4.6%)	8 (3.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	3 (3.0%)	1 (0.9%)	4 (1.9%)
Papillary thyroid cancer (乳頭様甲状腺癌)	2 (2.0%)	0	2 (1.0%)
Pancreatic carcinoma (膵癌)	1 (1.0%)	0	1 (0.5%)
Uterine leiomyoma (子宮平滑筋腫)	0	1 (0.9%)	1 (0.5%)
Metabolism and nutrition disorders (代謝および栄養障害)	0	2 (1.9%)	2 (1.0%)
Hyperglycaemia (高血糖)	0	2 (1.9%)	2 (1.0%)
Gastrointestinal disorders (胃腸障害)	0	1 (0.9%)	1 (0.5%)
Nausea (悪心)	0	1 (0.9%)	1 (0.5%)
Investigations (臨床検査)	0	1 (0.9%)	1 (0.5%)
Blood glucose abnormal (血中ブドウ糖異常)	0	1 (0.9%)	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-35　Listing of Treatment Emergent Adverse Events Leading to Discontinuation from Treatment in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
020	Placebo/Imeglimin + Insulin	020-[redacted]-003	6[redacted]/ F/ Stage 2/ No	Papillary thyroid cancer (乳頭様甲状腺癌)	OL/ 185/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving
	Placebo/Imeglimin + Insulin	020-[redacted]-005	6[redacted]/ F/ Stage 2/ No	Papillary thyroid cancer (乳頭様甲状腺癌)	OL/ 246/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving
	Placebo/Imeglimin + Insulin	020-[redacted]-002	6[redacted]/ M/ Stage 2/ Yes	Pancreatic carcinoma (膵癌)	OL/ 223/ ./ .	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Not Recovered/Not Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-012	7[redacted]/ F/ Stage 1/ No	Nausea (悪心)	DB/ 1/ 34/ 34	RELATED/ Drug Withdrawn	Moderate/ No	Recovered/Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-008	3[redacted]/ F/ Stage 2/ Yes	Hyperglycaemia (高血糖)	OL/ 281/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Recovering/Resolving
	Imeglimin/Imeglimin + Insulin	020-[redacted]-004	4[redacted]/ F/ Stage 1/ No	Uterine leiomyoma (子宮平滑筋腫)	OL/ 206/ 276/ 71	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-007	7[redacted]/ M/ Stage 2/ No	Hyperglycaemia (高血糖)	OL/ 227/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved
	Imeglimin/Imeglimin + Insulin	020-[redacted]-003	4[redacted]/ F/ Stage 2/ No	Blood glucose abnormal (血中ブドウ糖異常)	OL/ 281/ ./ .	NOT RELATED/ Drug Withdrawn	Mild/ No	Not Recovered/Not Resolved

- Abbreviations: M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; DB, Double-blind; OL, Open-label
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- Start/End Days were relative to the day of first dose of study treatment in the double-blind period.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

2.7.4.2.1.6　器官別又は症候群別有害事象の解析

本項では、器官別及び注目すべき有害事象を評価した。

2.7.4.2.1.6.1　器官別

2.7.4.2.1.6.1.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

SOC ごとの有害事象の発現割合を表 2.7.4.2-36 に示す。発現割合が本剤群合計で 10%以上の SOC 別有害事象は、感染症および寄生虫症（31.2%）、胃腸障害（18.5%）であった。

表 2.7.4.2-36　Summary of Treatment Emergent Adverse Events by System Organ Class in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any TEAE	99 (54.4%)	51 (68.0%)	93 (51.7%)	55 (73.3%)	199 (60.3%)
Infections and infestations (感染症および寄生虫症)	32 (17.6%)	27 (36.0%)	50 (27.8%)	26 (34.7%)	103 (31.2%)
Gastrointestinal disorders (胃腸障害)	20 (11.0%)	11 (14.7%)	26 (14.4%)	24 (32.0%)	61 (18.5%)
Metabolism and nutrition disorders (代謝および栄養障害)	21 (11.5%)	8 (10.7%)	9 (5.0%)	5 (6.7%)	22 (6.7%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	17 (9.3%)	9 (12.0%)	11 (6.1%)	5 (6.7%)	25 (7.6%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	6 (3.3%)	5 (6.7%)	8 (4.4%)	6 (8.0%)	19 (5.8%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	12 (6.6%)	3 (4.0%)	5 (2.8%)	5 (6.7%)	13 (3.9%)
Nervous system disorders (神経系障害)	10 (5.5%)	6 (8.0%)	7 (3.9%)	1 (1.3%)	14 (4.2%)
Investigations (臨床検査)	7 (3.8%)	5 (6.7%)	4 (2.2%)	6 (8.0%)	15 (4.5%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	5 (2.7%)	1 (1.3%)	4 (2.2%)	5 (6.7%)	10 (3.0%)
Eye disorders (眼障害)	4 (2.2%)	2 (2.7%)	4 (2.2%)	3 (4.0%)	9 (2.7%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	4 (2.2%)	3 (4.0%)	0	2 (2.7%)	5 (1.5%)
Cardiac disorders (心臓障害)	2 (1.1%)	0	2 (1.1%)	3 (4.0%)	5 (1.5%)
Vascular disorders (血管障害)	3 (1.6%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Ear and labyrinth disorders (耳および迷路障害)	1 (0.5%)	0	2 (1.1%)	3 (4.0%)	5 (1.5%)
Hepatobiliary disorders (肝胆道系障害)	3 (1.6%)	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	0	0	4 (2.2%)	1 (1.3%)	5 (1.5%)
Psychiatric disorders (精神障害)	1 (0.5%)	1 (1.3%)	0	1 (1.3%)	2 (0.6%)

System Organ Class	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Renal and urinary disorders (腎および尿路障害)	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Reproductive system and breast disorders (生殖系および乳房障害)	2 (1.1%)	1 (1.3%)	0	0	1 (0.3%)
Blood and lymphatic system disorders (血液およびリンパ系障害)	0	0	1 (0.6%)	0	1 (0.3%)
Endocrine disorders (内分泌障害)	0	0	0	1 (1.3%)	1 (0.3%)
Social circumstances (社会環境)	1 (0.5%)	0	0	0	0
Surgical and medical procedures (外科および内科処置)	0	0	1 (0.6%)	0	1 (0.3%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Percentages are based on Population N.

2.7.4.2.1.6.1.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

SOC ごとの有害事象の発現割合を表 2.7.4.2-37 に示す。

- 単独療法群では、発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（42.5%）、胃腸障害（21.6%）、筋骨格系および結合組織障害（11.2%）であった。
- SU 併用療法群では、発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（44.9%）、胃腸障害（22.0%）、筋骨格系および結合組織障害（17.3%）、代謝および栄養障害（22.0%）、傷害、中毒および処置合併症（10.2%）、呼吸器、胸郭および縦隔障害（10.2%）であった。
- GLIN 併用療法群では、発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（57.8%）、胃腸障害（18.8%）、筋骨格系および結合組織障害（15.6%）、代謝および栄養障害（15.6%）、傷害、中毒および処置合併症（12.5%）、眼障害（12.5%）であった。
- BIG 併用療法群では、発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（43.8%）、胃腸障害（39.1%）、筋骨格系および結合組織障害（10.9%）、代謝および栄養障害（12.5%）であった。
- AGI 併用療法群では、発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（20.3%）であった。
- TZD 併用療法群では、発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（49.2%）、胃腸障害（13.8%）であった。
- DPP4-I 併用療法群では、発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（44.4%）、胃腸障害（33.3%）、筋骨格系および結合組織障害（25.4%）、代謝および栄養障害（12.7%）、傷害、中毒および処置合併症（22.2%）、皮膚および皮下組織障害（19.0%）であった。

- GLP1-RA 併用療法群では、発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（42.9%）、胃腸障害（20.0%）、筋骨格系および結合組織障害（15.7%）、代謝および栄養障害（18.6%）、傷害、中毒および処置合併症（10.0%）、皮膚および皮下組織障害（10.0%）であった。
- SGLT2-I 併用療法群では、発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（46.0%）、胃腸障害（23.8%）であった。

表 2.7.4.2-37　Summary of Treatment Emergent Adverse Events by System Organ Class in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any TEAE	98 (73.1%)	102 (80.3%)	54 (84.4%)	48 (75.0%)	33 (51.6%)	50 (76.9%)	50 (79.4%)	56 (80.0%)	48 (76.2%)	441 (76.0%)	539 (75.5%)
Infections and infestations (感染症および寄生虫症)	57 (42.5%)	57 (44.9%)	37 (57.8%)	28 (43.8%)	13 (20.3%)	32 (49.2%)	28 (44.4%)	30 (42.9%)	29 (46.0%)	254 (43.8%)	311 (43.6%)
Gastrointestinal disorders (胃腸障害)	29 (21.6%)	28 (22.0%)	12 (18.8%)	25 (39.1%)	5 (7.8%)	9 (13.8%)	21 (33.3%)	14 (20.0%)	15 (23.8%)	129 (22.2%)	158 (22.1%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	15 (11.2%)	22 (17.3%)	10 (15.6%)	7 (10.9%)	6 (9.4%)	6 (9.2%)	16 (25.4%)	11 (15.7%)	4 (6.3%)	82 (14.1%)	97 (13.6%)
Metabolism and nutrition disorders (代謝および栄養障害)	13 (9.7%)	28 (22.0%)	10 (15.6%)	8 (12.5%)	4 (6.3%)	5 (7.7%)	8 (12.7%)	13 (18.6%)	6 (9.5%)	82 (14.1%)	95 (13.3%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	11 (8.2%)	13 (10.2%)	8 (12.5%)	5 (7.8%)	4 (6.3%)	6 (9.2%)	14 (22.2%)	7 (10.0%)	4 (6.3%)	61 (10.5%)	72 (10.1%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	4 (3.0%)	10 (7.9%)	6 (9.4%)	3 (4.7%)	0	4 (6.2%)	12 (19.0%)	7 (10.0%)	5 (7.9%)	47 (8.1%)	51 (7.1%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	7 (5.2%)	13 (10.2%)	4 (6.3%)	1 (1.6%)	5 (7.8%)	5 (7.7%)	2 (3.2%)	2 (2.9%)	5 (7.9%)	37 (6.4%)	44 (6.2%)
Eye disorders (眼障害)	5 (3.7%)	7 (5.5%)	8 (12.5%)	2 (3.1%)	0	6 (9.2%)	5 (7.9%)	5 (7.1%)	4 (6.3%)	37 (6.4%)	42 (5.9%)
Nervous system disorders (神経系障害)	8 (6.0%)	3 (2.4%)	5 (7.8%)	2 (3.1%)	4 (6.3%)	6 (9.2%)	4 (6.3%)	4 (5.7%)	4 (6.3%)	32 (5.5%)	40 (5.6%)
Investigations (臨床検査)	6 (4.5%)	8 (6.3%)	2 (3.1%)	2 (3.1%)	3 (4.7%)	2 (3.1%)	6 (9.5%)	1 (1.4%)	2 (3.2%)	26 (4.5%)	32 (4.5%)
Vascular disorders (血管障害)	2 (1.5%)	7 (5.5%)	2 (3.1%)	1 (1.6%)	4 (6.3%)	3 (4.6%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	21 (3.6%)	23 (3.2%)

System Organ Class	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Renal and urinary disorders (腎および尿路障害)	1 (0.7%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	3 (4.7%)	3 (4.6%)	3 (4.8%)	4 (5.7%)	3 (4.8%)	20 (3.4%)	21 (2.9%)
Cardiac disorders (心臓障害)	2 (1.5%)	3 (2.4%)	0	4 (6.3%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	4 (5.7%)	1 (1.6%)	16 (2.8%)	18 (2.5%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	4 (3.0%)	1 (0.8%)	1 (1.6%)	2 (3.1%)	0	2 (3.1%)	4 (6.3%)	1 (1.4%)	2 (3.2%)	13 (2.2%)	17 (2.4%)
Psychiatric disorders (精神障害)	3 (2.2%)	2 (1.6%)	1 (1.6%)	2 (3.1%)	0	1 (1.5%)	3 (4.8%)	2 (2.9%)	1 (1.6%)	12 (2.1%)	15 (2.1%)
Hepatobiliary disorders (肝胆道系障害)	0	2 (1.6%)	1 (1.6%)	0	2 (3.1%)	3 (4.6%)	0	5 (7.1%)	1 (1.6%)	14 (2.4%)	14 (2.0%)
Surgical and medical procedures (外科および内科処置)	3 (2.2%)	3 (2.4%)	1 (1.6%)	3 (4.7%)	1 (1.6%)	0	0	1 (1.4%)	0	9 (1.6%)	12 (1.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	0	4 (3.1%)	1 (1.6%)	1 (1.6%)	0	1 (1.5%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	11 (1.9%)	11 (1.5%)
Reproductive system and breast disorders (生殖系および乳房障害)	3 (2.2%)	1 (0.8%)	2 (3.1%)	0	1 (1.6%)	0	3 (4.8%)	1 (1.4%)	0	8 (1.4%)	11 (1.5%)
Ear and labyrinth disorders (耳および迷路障害)	2 (1.5%)	1 (0.8%)	1 (1.6%)	3 (4.7%)	0	1 (1.5%)	0	2 (2.9%)	0	8 (1.4%)	10 (1.4%)
Immune system disorders (免疫系障害)	2 (1.5%)	0	1 (1.6%)	1 (1.6%)	0	1 (1.5%)	0	3 (4.3%)	1 (1.6%)	7 (1.2%)	9 (1.3%)
Blood and lymphatic system disorders (血液およびリンパ系障害)	2 (1.5%)	1 (0.8%)	0	1 (1.6%)	0	1 (1.5%)	0	1 (1.4%)	2 (3.2%)	6 (1.0%)	8 (1.1%)
Endocrine disorders (内分泌障害)	0	1 (0.8%)	0	0	0	2 (3.1%)	0	0	0	3 (0.5%)	3 (0.4%)

System Organ Class	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Congenital, familial and genetic disorders (先天性、家族性および遺伝性障害)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Product issues (製品の問題)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Percentages are based on Population N.

2.7.4.2.1.6.1.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

SOC ごとの有害事象の発現割合を表 2.7.4.2-38 に示す。発現割合がイメグリミン群で 10%以上の SOC 別有害事象は、代謝および栄養障害（21.3%）、感染症および寄生虫症（22.2%）であった。

表 2.7.4.2-38　Summary of Treatment Emergent Adverse Events by System Organ Class in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

System Organ Class	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Any TEAE	51 (47.7%)	57 (52.8%)
Metabolism and nutrition disorders (代謝および栄養障害)	20 (18.7%)	23 (21.3%)
Infections and infestations (感染症および寄生虫症)	15 (14.0%)	24 (22.2%)
Gastrointestinal disorders (胃腸障害)	7 (6.5%)	10 (9.3%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	4 (3.7%)	9 (8.3%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	8 (7.5%)	2 (1.9%)
Nervous system disorders (神経系障害)	6 (5.6%)	1 (0.9%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	2 (1.9%)	3 (2.8%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	3 (2.8%)	1 (0.9%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	2 (1.9%)	2 (1.9%)
Vascular disorders (血管障害)	0	3 (2.8%)
Eye disorders (眼障害)	0	2 (1.9%)
Cardiac disorders (心臓障害)	1 (0.9%)	0
Ear and labyrinth disorders (耳および迷路障害)	1 (0.9%)	0
Hepatobiliary disorders (肝胆道系障害)	0	1 (0.9%)
Investigations (臨床検査)	0	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	0	1 (0.9%)
Renal and urinary disorders (腎および尿路障害)	0	1 (0.9%)
Reproductive system and breast disorders (生殖系および乳房障害)	1 (0.9%)	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Percentages are based on Population N.

(2) 長期投与（52 週）

SOC ごとの有害事象の発現割合を表 2.7.4.2-39 に示す。発現割合が 10%以上の SOC 別有害事象は、感染症および寄生虫症（39.2%）、代謝および栄養障害（37.8%）、筋骨格系および結合組織障害（15.8%）、胃腸障害（14.4%）であった。

表 2.7.4.2-39　Summary of Treatment Emergent Adverse Events by System Organ Class in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any TEAE	77 (76.2%)	92 (85.2%)	169 (80.9%)
Infections and infestations (感染症および寄生虫症)	30 (29.7%)	52 (48.1%)	82 (39.2%)
Metabolism and nutrition disorders (代謝および栄養障害)	37 (36.6%)	42 (38.9%)	79 (37.8%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	9 (8.9%)	24 (22.2%)	33 (15.8%)
Gastrointestinal disorders (胃腸障害)	10 (9.9%)	20 (18.5%)	30 (14.4%)
Eye disorders (眼障害)	6 (5.9%)	10 (9.3%)	16 (7.7%)
Nervous system disorders (神経系障害)	6 (5.9%)	8 (7.4%)	14 (6.7%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	2 (2.0%)	11 (10.2%)	13 (6.2%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	7 (6.9%)	4 (3.7%)	11 (5.3%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	2 (2.0%)	8 (7.4%)	10 (4.8%)
Vascular disorders (血管障害)	2 (2.0%)	7 (6.5%)	9 (4.3%)
Investigations (臨床検査)	1 (1.0%)	6 (5.6%)	7 (3.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	4 (4.0%)	3 (2.8%)	7 (3.3%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	3 (3.0%)	3 (2.8%)	6 (2.9%)
Hepatobiliary disorders (肝胆道系障害)	3 (3.0%)	2 (1.9%)	5 (2.4%)
Immune system disorders (免疫系障害)	1 (1.0%)	4 (3.7%)	5 (2.4%)
Ear and labyrinth disorders (耳および迷路障害)	1 (1.0%)	3 (2.8%)	4 (1.9%)
Cardiac disorders (心臓障害)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Reproductive system and breast disorders (生殖系および乳房障害)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Psychiatric disorders (精神障害)	1 (1.0%)	1 (0.9%)	2 (1.0%)

System Organ Class	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Renal and urinary disorders (腎および尿路障害)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Blood and lymphatic system disorders (血液およびリンパ系障害)	1 (1.0%)	0	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Percentages are based on Population N.

2.7.4.2.1.6.2　注目すべき有害事象

本剤の注目すべき有害事象を定義し（表 2.7.4.1-9）、その発現状況を評価した。

2.7.4.2.1.6.2.1　低血糖

PT が「低血糖」に該当する有害事象（表 2.7.4.1-8）の発現状況を評価した。

2.7.4.2.1.6.2.1.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

低血糖の発現状況を表 2.7.4.2-40 に示す。低血糖の発現割合（発現被験者数、発現件数）は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に 1.1%（2/182 名、7 件）、6.7%（5/75 名、5 件）、2.8%（5/180 名、9 件）、5.3%（4/75 名、7 件）であった。「重度の低血糖」は発現せず、「裏付けされた症候性低血糖」は 1000 mg bid 群で 1 名に 2 件発現した。低血糖の多くが「SMBG に基づき報告された無症候性低血糖」であった。

表 2.7.4.2-40　Summary of Treatment Emergent Adverse Events of Hypoglycemia Classification in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

	Placebo N = 182		Imeglimin 500 mg bid N = 75		Imeglimin 1000 mg bid N = 180		Imeglimin 1500 mg bid N = 75		Imeglimin Total N = 330	
Classification	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Any hypoglycemia	2 (1.1%)	7	5 (6.7%)	5	5 (2.8%)	9	4 (5.3%)	7	14 (4.2%)	21
Severe hypoglycemia	0	0	0	0	0	0	0	0	0	0
Documented symptomatic hypoglycemia	0	0	0	0	1 (0.6%)	2	0	0	1 (0.3%)	2
Asymptomatic hypoglycemia	0	0	0	0	0	0	0	0	0	0
Asymptomatic hypoglycemia reported from SMBG	2 (1.1%)	7	5 (6.7%)	5	3 (1.7%)	6	3 (4.0%)	6	11 (3.3%)	17
Probable symptomatic hypoglycemia	0	0	0	0	1 (0.6%)	1	1 (1.3%)	1	2 (0.6%)	2

- Abbreviations: bid, Twice a day; SMBG, Self-monitoring blood glucose
- All adverse events were coded using MedDRA dictionary version 20.1.
- Percentages are based on Population N.
- n and % are respectively the number and proportion of subjects who experienced the event. e is the number of events.

2.7.4.2.1.6.2.1.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

低血糖の発現状況を表 2.7.4.2-41 に示す。

- 単独療法群では、低血糖の発現割合（発現被験者数、発現件数）は 3.7%（5/134 名、8 件）であった。「重度の低血糖」及び「裏付けされた症候性低血糖」は発現せず、いずれも「SMBG に基づき報告された無症候性低血糖」であった。
- SU 併用療法群では、低血糖の発現割合（発現被験者数、発現件数）は 16.5%（21/127 名、64 件）であった。「重度の低血糖」は発現せず、「裏付けされた症候性低血糖」が 5 名に 8 件発現した。低血糖の多くが「SMBG に基づき報告された無症候性低血糖」で 17 名に 45 件発現した。
- GLIN 併用療法群では、低血糖の発現割合（発現被験者数、発現件数）は 14.1%（9/64 名、42 件）であった。「重度の低血糖」は発現せず、「裏付けされた症候性低血糖」が 2 名に 7 件発現した。そのほかの低血糖はすべて「SMBG に基づき報告された無症候性低血糖」で 8 名に 35 件発現した。
- BIG 併用療法群では、低血糖の発現割合（発現被験者数、発現件数）は 9.4%（6/64 名、8 件）であった。「重度の低血糖」は発現せず、「裏付けされた症候性低血糖」が 2 名に 3 件発現した。そのほかの低血糖はすべて「SMBG に基づき報告された無症候性低血糖」で 4 名に 5 件発現した。
- AGI 併用療法群では、低血糖の発現割合（発現被験者数、発現件数）は 3.1%（2/64 名、3 件）であった。「重度の低血糖」及び「裏付けされた症候性低血糖」は発現せず、いずれも「SMBG に基づき報告された無症候性低血糖」であった。
- TZD 併用療法群では、低血糖の発現割合（発現被験者数、発現件数）は 3.1%（2/65 名、3 件）であった。「重度の低血糖」及び「裏付けされた症候性低血糖」は発現せず、いずれも「SMBG に基づき報告された無症候性低血糖」であった。
- DPP4-I 併用療法群では、低血糖の発現割合（発現被験者数、発現件数）は 7.9%（5/63 名、8 件）であった。「重度の低血糖」は発現せず、「裏付けされた症候性低血糖」が 1 名に 1 件発現した。そのほかの低血糖はすべて「SMBG に基づき報告された無症候性低血糖」で 5 名に 7 件発現した。
- GLP1-RA 併用療法群では、低血糖の発現割合（発現被験者数、発現件数）は 2.9%（2/70 名、2 件）であった。「重度の低血糖」及び「裏付けされた症候性低血糖」は発現せず、いずれも「SMBG に基づき報告された無症候性低血糖」であった。
- SGLT2-I 併用療法群では、低血糖の発現割合（発現被験者数、発現件数）は 6.3%（4/63 名、4 件）であった。「重度の低血糖」及び「裏付けされた症候性低血糖」は発現しなかった。「可能性のある症候性低血糖」が 1 名に 1 件、「SMBG に基づき報告された無症候性低血糖」が 3 名に 3 件発現した。

表 2.7.4.2-41　Summary of Treatment Emergent Adverse Events of Hypoglycemia Classification in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63		Combination Total N = 580		Imeglimin Total N = 714	
Classification	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Any hypoglycemia	5 (3.7%)	8	21 (16.5%)	64	9 (14.1%)	42	6 (9.4%)	8	2 (3.1%)	3	2 (3.1%)	2	5 (7.9%)	8	2 (2.9%)	2	4 (6.3%)	4	51 (8.8%)	133	56 (7.8%)	141
Severe hypoglycemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Documented symptomatic hypoglycemia	0	0	5 (3.9%)	8	2 (3.1%)	7	2 (3.1%)	3	0	0	0	0	1 (1.6%)	1	0	0	0	0	10 (1.7%)	19	10 (1.4%)	19
Asymptomatic hypoglycemia	0	0	1 (0.8%)	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.2%)	4	1 (0.1%)	4
Asymptomatic hypoglycemia reported from SMBG	5 (3.7%)	8	17 (13.4%)	45	8 (12.5%)	35	4 (6.3%)	5	2 (3.1%)	3	2 (3.1%)	2	5 (7.9%)	7	2 (2.9%)	2	3 (4.8%)	3	43 (7.4%)	102	48 (6.7%)	110
Probable symptomatic hypoglycemia	0	0	4 (3.1%)	7	0	0	0	0	0	0	0	0	0	0	0	0	1 (1.6%)	1	5 (0.9%)	8	5 (0.7%)	8

- Abbreviations: SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor; SMBG, Self-monitoring blood glucose
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Percentages are based on Population N.
- n and % are respectively the number and proportion of subjects who experienced the event. e is the number of events.

2.7.4.2.1.6.2.1.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

低血糖の発現状況を表 2.7.4.2-42 に示す。低血糖の発現割合（発現被験者数、発現件数）は、プラセボ群、イメグリミン群の順に（以下同順）15.9%（17/107 名、25 件）、21.3%（23/108 名、95 件）であった。「重度の低血糖」は発現せず、「裏付けされた症候性低血糖」がプラセボ群で 5 名に 7 件、イメグリミン群で 8 名に 21 件発現した。低血糖の多くが「SMBG に基づき報告された無症候性低血糖」で、プラセボ群で 6 名に 11 件、イメグリミン群で 17 名に 69 件発現した。

表 2.7.4.2-42　Summary of Treatment Emergent Adverse Events of Hypoglycemia Classification in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

	Placebo + Insulin N = 107		Imeglimin 1000 mg bid + Insulin N = 108	
Classification	n (%)	e	n (%)	e
Any hypoglycemia	17 (15.9%)	25	23 (21.3%)	95
Severe hypoglycemia	0	0	0	0
Documented symptomatic hypoglycemia	5 (4.7%)	7	8 (7.4%)	21
Asymptomatic hypoglycemia	3 (2.8%)	4	2 (1.9%)	2
Asymptomatic hypoglycemia reported from SMBG	6 (5.6%)	11	17 (15.7%)	69
Probable symptomatic hypoglycemia	2 (1.9%)	2	1 (0.9%)	1
Symptomatic hypoglycemia	1 (0.9%)	1	2 (1.9%)	2

- Abbreviations: bid, Twice a day; SMBG, Self-monitoring blood glucose
- All adverse events were coded using MedDRA dictionary version 20.1.
- Percentages are based on Population N.
- n and % are respectively the number and proportion of subjects who experienced the event. e is the number of events.

(2) 長期投与（52 週）

低血糖の発現状況を表 2.7.4.2-43 に示す。低血糖の発現割合（発現被験者数、発現件数）は 35.9%（75/209 名、540 件）であった。「重度の低血糖」は発現せず、「裏付けされた症候性低血糖」が 42 名に 173 件発現した。低血糖の多くが「SMBG に基づき報告された無症候性低血糖」で 50 名に 344 件発現した。

表 2.7.4.2-43　Summary of Treatment Emergent Adverse Events of Hypoglycemia Classification in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

	Placebo/Imeglimin + Insulin N = 101		Imeglimin/Imeglimin + Insulin N = 108		Imeglimin + Insulin Total N = 209	
Classification	n (%)	e	n (%)	e	n (%)	e
Any hypoglycemia	36 (35.6%)	161	39 (36.1%)	379	75 (35.9%)	540
Severe hypoglycemia	0	0	0	0	0	0
Documented symptomatic hypoglycemia	20 (19.8%)	37	22 (20.4%)	136	42 (20.1%)	173
Asymptomatic hypoglycemia	3 (3.0%)	5	4 (3.7%)	7	7 (3.3%)	12
Asymptomatic hypoglycemia reported from SMBG	20 (19.8%)	118	30 (27.8%)	226	50 (23.9%)	344
Probable symptomatic hypoglycemia	0	0	4 (3.7%)	6	4 (1.9%)	6
Symptomatic hypoglycemia	1 (1.0%)	1	3 (2.8%)	4	4 (1.9%)	5

- Abbreviations: SMBG, Self-monitoring blood glucose
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Percentages are based on Population N.
- n and % are respectively the number and proportion of subjects who experienced the event. e is the number of events.

2.7.4.2.1.6.2.2　乳酸アシドーシス関連事象

乳酸アシドーシス関連事象の発現状況を以下に、各被験者の乳酸値の推移を 2.7.4.3.1.2.1 項に示す。

- 単独療法［二重盲検試験併合（24 週）: 014 試験・018 試験］では、乳酸アシドーシス関連事象は発現しなかった。
- 単独及び血糖降下薬との併用療法［長期投与（52 週）: 019 試験］では、SU 併用療法群で軽度の血中乳酸増加が 2 名に発現した。SU 以外の併用療法群及び単独療法群では、乳酸アシドーシス関連事象は発現しなかった（2.7.4.7 項付録 Table S-031 及び Table S-063）。
- インスリン製剤併用療法［二重盲検治療（16 週）、長期投与（52 週）: 020 試験］では、長期投与で軽度の血中乳酸増加が 1 名に発現した（2.7.4.7 項付録 Table S-053 及び Table S-067）。二重盲検治療では、乳酸アシドーシス関連事象は発現しなかった。

2.7.4.2.1.6.2.3　心血管イベント

心血管イベントの発現状況を以下に示す。

- 単独療法［二重盲検試験併合（24 週）: 014 試験・018 試験］では、心血管イベントと

して報告された有害事象はなかった。

- 単独及び血糖降下薬との併用療法［長期投与（52 週）：019 試験］では、SU 併用療法群で急性心筋梗塞（1 名）、BIG 併用療法群で心筋梗塞（1 名）、GLP1-RA 併用療法群で脳梗塞（1 名）、SGLT2-I 併用療法群でラクナ梗塞（1 名）が発現し、いずれも重篤な有害事象として報告されたが、治験薬との因果関係は否定された（2.7.4.2.1.4.2 項）。GLIN、AGI、TZD、DPP4-I の各併用療法群及び単独療法群では、心血管イベントとして報告された有害事象はなかった（2.7.4.7 項付録 Table S-032）。
- インスリン製剤併用療法［二重盲検治療（16 週）、長期投与（52 週）：020 試験］では、心血管イベントとして報告された有害事象はなかった。

2.7.4.2.1.6.2.4　心血管関連事象

2.7.4.2.1.6.2.4.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

心血管関連事象の発現状況を表 2.7.4.2-44 に示す。心血管関連事象の発現割合は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に 3.8%、2.7%、1.7%、8.0%であった。1000 mg bid 群の 1 名に発現した徐脈は、重篤な有害事象として報告された（2.7.4.2.1.4.1 項）。本剤群合計で 2 名以上に発現した事象は、高血圧及び動悸であった。

表 2.7.4.2-44　Summary of Cardiovascular-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any Cardiovascular-Related TEAE	7 (3.8%)	2 (2.7%)	3 (1.7%)	6 (8.0%)	11 (3.3%)
Cardiac disorders (心臓障害)	2 (1.1%)	0	2 (1.1%)	3 (4.0%)	5 (1.5%)
Palpitations (動悸)	2 (1.1%)	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Atrial fibrillation (心房細動)	0	0	0	1 (1.3%)	1 (0.3%)
Bradycardia (徐脈)	0	0	1 (0.6%)	0	1 (0.3%)
Ventricular extrasystoles (心室性期外収縮)	0	0	0	1 (1.3%)	1 (0.3%)
Vascular disorders (血管障害)	3 (1.6%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Hypertension (高血圧)	2 (1.1%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Arteriosclerosis (動脈硬化症)	1 (0.5%)	0	0	0	0
Investigations (臨床検査)	2 (1.1%)	0	0	1 (1.3%)	1 (0.3%)
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)	2 (1.1%)	0	0	0	0
Electrocardiogram T wave inversion (心電図T波逆転)	0	0	0	1 (1.3%)	1 (0.3%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	0	0	0	1 (1.3%)	1 (0.3%)
Oedema peripheral (末梢性浮腫)	0	0	0	1 (1.3%)	1 (0.3%)
Nervous system disorders (神経系障害)	0	0	1 (0.6%)	0	1 (0.3%)
Loss of consciousness (意識消失)	0	0	1 (0.6%)	0	1 (0.3%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.4.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

心血管関連事象の発現状況を表 2.7.4.2-45 に示す。

- 単独療法群では心血管関連事象の発現割合は 3.0%で、くも膜下出血及び心房細動（各 1 名）は重篤な有害事象として報告され、くも膜下出血を発現した被験者は死亡した（2.7.4.2.1.3.2 項）。2 名以上に発現した事象はなかった。
- SU 併用療法群では心血管関連事象の発現割合は 8.7%で、不安定狭心症、急性心筋梗塞及び硬膜下血腫（各 1 名）は重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。2 名以上に発現した事象は高血圧であった。
- GLIN 併用療法群では心血管関連事象の発現割合は 4.7%で、重度の事象は発現しなかった。2 名以上に発現した事象は高血圧であった。
- BIG 併用療法群では心血管関連事象の発現割合は 9.4%で、心筋梗塞（1 名）が重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。2 名以上に発現した事象は動悸であった。
- AGI 併用療法群では心血管関連事象の発現割合は 9.4%で、重度の事象は発現しなかった。2 名以上に発現した事象は高血圧であった。
- TZD 併用療法群では心血管関連事象の発現割合は 12.3%で、重度の事象は発現しなかった。2 名以上に発現した事象は高血圧、洞性徐脈、頸動脈硬化症であった。
- DPP4-I 併用療法群では心血管関連事象の発現割合は 4.8%で、重度の事象は発現しなかった。2 名以上に発現した事象はなかった。
- GLP1-RA 併用療法群では心血管関連事象の発現割合は 7.1%で、冠動脈狭窄及び脳梗塞（1 名）、冠動脈狭窄（1 名）が重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。2 名以上に発現した事象は冠動脈狭窄及び高血圧であった。
- SGLT2-I 併用療法群では心血管関連事象の発現割合は 6.3%で、心不全及びラクナ梗塞（各 1 名）が重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。2 名以上に発現

した事象はなかった。

表 2.7.4.2-45　Summary of Cardiovascular-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any Cardiovascular-Related TEAE	4 (3.0%)	11 (8.7%)	3 (4.7%)	6 (9.4%)	6 (9.4%)	8 (12.3%)	3 (4.8%)	5 (7.1%)	4 (6.3%)	46 (7.9%)	50 (7.0%)
Vascular disorders (血管障害)	0	7 (5.5%)	2 (3.1%)	1 (1.6%)	4 (6.3%)	3 (4.6%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	21 (3.6%)	21 (2.9%)
Hypertension (高血圧)	0	7 (5.5%)	2 (3.1%)	1 (1.6%)	3 (4.7%)	3 (4.6%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	20 (3.4%)	20 (2.8%)
Arteriosclerosis (動脈硬化症)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Cardiac disorders (心臓障害)	2 (1.5%)	2 (1.6%)	0	4 (6.3%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	4 (5.7%)	1 (1.6%)	15 (2.6%)	17 (2.4%)
Atrial fibrillation (心房細動)	1 (0.7%)	0	0	0	0	1 (1.5%)	1 (1.6%)	1 (1.4%)	0	3 (0.5%)	4 (0.6%)
Angina unstable (不安定狭心症)	0	1 (0.8%)	0	0	1 (1.6%)	0	0	0	0	2 (0.3%)	2 (0.3%)
Coronary artery stenosis (冠動脈狭窄)	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)
Palpitations (動悸)	0	0	0	2 (3.1%)	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Sinus bradycardia (洞性徐脈)	0	0	0	0	0	2 (3.1%)	0	0	0	2 (0.3%)	2 (0.3%)
Ventricular extrasystoles (心室性期外収縮)	1 (0.7%)	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	2 (0.3%)
Acute myocardial infarction (急性心筋梗塞)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Cardiac aneurysm (心臓瘤)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Cardiac failure (心不全)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Extrasystoles (期外収縮)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Myocardial infarction (心筋梗塞)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Myocardial ischaemia (心筋虚血)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Sinus tachycardia (洞性頻脈)	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Supraventricular extrasystoles (上室性期外収縮)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Nervous system disorders (神経系障害)	0	0	1 (1.6%)	1 (1.6%)	1 (1.6%)	3 (4.6%)	0	2 (2.9%)	2 (3.2%)	10 (1.7%)	10 (1.4%)
Carotid arteriosclerosis (頚動脈硬化症)	0	0	1 (1.6%)	1 (1.6%)	0	2 (3.1%)	0	0	0	4 (0.7%)	4 (0.6%)
Loss of consciousness (意識消失)	0	0	0	0	1 (1.6%)	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Carotid artery stenosis (頚動脈狭窄)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Cerebral infarction (脳梗塞)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Lacunar infarction (ラクナ梗塞)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Syncope (失神)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Investigations (臨床検査)	1 (0.7%)	1 (0.8%)	0	0	0	1 (1.5%)	1 (1.6%)	0	0	3 (0.5%)	4 (0.6%)
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)	1 (0.7%)	0	0	0	0	1 (1.5%)	1 (1.6%)	0	0	2 (0.3%)	3 (0.4%)
Electrocardiogram repolarisation abnormality (心電図再分極異常)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	1 (0.7%)	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	2 (0.3%)
Subarachnoid haemorrhage (くも膜下出血)	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Subdural haematoma (硬膜下血腫)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Oedema peripheral (末梢性浮腫)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.4.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

心血管関連事象の発現状況を表 2.7.4.2-46 に示す。心血管関連事象の発現割合は、プラセボ群、イメグリミン群の順に 0.9%、3.7%であった。重度の事象は発現せず、2 名以上に発現した事象はなかった。

表 2.7.4.2-46　Summary of Cardiovascular-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

System Organ Class Preferred Term	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Any Cardiovascular-Related TEAE	1 (0.9%)	4 (3.7%)
Vascular disorders (血管障害)	0	3 (2.8%)
Hypertension (高血圧)	0	1 (0.9%)
Peripheral arterial occlusive disease (末梢動脈閉塞性疾患)	0	1 (0.9%)
Venous thrombosis limb (四肢静脈血栓症)	0	1 (0.9%)
Cardiac disorders (心臓障害)	1 (0.9%)	0
Bundle branch block right (右脚ブロック)	1 (0.9%)	0
Investigations (臨床検査)	0	1 (0.9%)
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)	0	1 (0.9%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

(2) 長期投与（52 週）

心血管関連事象の発現状況を表 2.7.4.2-47 に示す。心血管関連事象の発現割合は、7.2%で、突然死（1 名）が重篤な有害事象として報告された（2.7.4.2.1.3.3 項 (2) ）。2 名以上に発現した事象は高血圧、血中クレアチンホスホキナーゼ増加であった。

表 2.7.4.2-47　Summary of Cardiovascular-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any Cardiovascular-Related TEAE	7 (6.9%)	8 (7.4%)	15 (7.2%)
Vascular disorders (血管障害)	2 (2.0%)	7 (6.5%)	9 (4.3%)
Hypertension (高血圧)	2 (2.0%)	5 (4.6%)	7 (3.3%)
Peripheral arterial occlusive disease (末梢動脈閉塞性疾患)	0	1 (0.9%)	1 (0.5%)
Venous thrombosis limb (四肢静脈血栓症)	0	1 (0.9%)	1 (0.5%)
Cardiac disorders (心臓障害)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Atrial fibrillation (心房細動)	1 (1.0%)	0	1 (0.5%)
Cardiac failure congestive (うっ血性心不全)	1 (1.0%)	0	1 (0.5%)
Coronary artery stenosis (冠動脈狭窄)	0	1 (0.9%)	1 (0.5%)
Extrasystoles (期外収縮)	1 (1.0%)	0	1 (0.5%)
Investigations (臨床検査)	1 (1.0%)	2 (1.9%)	3 (1.4%)
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)	1 (1.0%)	2 (1.9%)	3 (1.4%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Oedema peripheral (末梢性浮腫)	0	1 (0.9%)	1 (0.5%)
Sudden death (突然死)	1 (1.0%)	0	1 (0.5%)
Nervous system disorders (神経系障害)	1 (1.0%)	0	1 (0.5%)
Syncope (失神)	1 (1.0%)	0	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.5　消化器症状

2.7.4.2.1.6.2.5.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

消化器症状の発現状況を表 2.7.4.2-48 に示す。消化器症状の発現割合は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に 11.0%（20/182 名）、14.7%（11/75 名）、14.4%（26/180 名）、32.0%（24/75 名）で、1500 mg bid 群での発現割合がほかの群と比較して高かった。本剤群で発現割合が高かった下痢、腹部不快感、嘔吐、悪心の発現割合も、1500 mg bid 群でほかの群より高かったが、いずれの事象も軽度又は中等度であった。

1000 mg bid 群でイレウスが 1 名に発現し、重篤な有害事象として報告された（表 2.7.4.2-20）。治験薬投与中止に至った消化器症状は、1000 mg bid 群で下痢及び嘔吐が 1 名、1500 mg bid 群で嘔吐が 2 名、口内炎が 1 名であった（2.7.4.2.1.5.1 項）。

表 2.7.4.2-48　Summary of Digestive Symptoms by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any Digestive Symptoms	20 (11.0%)	11 (14.7%)	26 (14.4%)	24 (32.0%)	61 (18.5%)
Gastrointestinal disorders (胃腸障害)	20 (11.0%)	11 (14.7%)	26 (14.4%)	24 (32.0%)	61 (18.5%)
Diarrhoea (下痢)	1 (0.5%)	3 (4.0%)	5 (2.8%)	6 (8.0%)	14 (4.2%)
Abdominal discomfort (腹部不快感)	0	1 (1.3%)	3 (1.7%)	7 (9.3%)	11 (3.3%)
Vomiting (嘔吐)	4 (2.2%)	0	1 (0.6%)	4 (5.3%)	5 (1.5%)
Nausea (悪心)	1 (0.5%)	1 (1.3%)	1 (0.6%)	5 (6.7%)	7 (2.1%)
Dental caries (齲歯)	4 (2.2%)	0	2 (1.1%)	1 (1.3%)	3 (0.9%)
Constipation (便秘)	2 (1.1%)	1 (1.3%)	2 (1.1%)	1 (1.3%)	4 (1.2%)
Abdominal pain upper (上腹部痛)	1 (0.5%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)	1 (0.5%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Dyspepsia (消化不良)	0	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Gastritis (胃炎)	0	1 (1.3%)	2 (1.1%)	0	3 (0.9%)
Periodontal disease (歯周病)	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Abdominal distension (腹部膨満)	0	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Abdominal pain (腹痛)	0	0	2 (1.1%)	0	2 (0.6%)
Chronic gastritis (慢性胃炎)	0	0	2 (1.1%)	0	2 (0.6%)
Duodenal ulcer (十二指腸潰瘍)	2 (1.1%)	0	0	0	0
Faeces soft (軟便)	2 (1.1%)	0	0	0	0
Stomatitis (口内炎)	0	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Abdominal pain lower (下腹部痛)	1 (0.5%)	0	0	0	0
Abnormal faeces (異常便)	0	0	1 (0.6%)	0	1 (0.3%)
Duodenal polyp (十二指腸ポリープ)	0	1 (1.3%)	0	0	1 (0.3%)
Duodenitis (十二指腸炎)	0	1 (1.3%)	0	0	1 (0.3%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Enteritis (小腸炎)	0	0	0	1 (1.3%)	1 (0.3%)
Enterocolitis (腸炎)	1 (0.5%)	0	0	0	0
Epigastric discomfort (心窩部不快感)	0	0	1 (0.6%)	0	1 (0.3%)
Gastric polyps (胃ポリープ)	1 (0.5%)	0	0	0	0
Ileus (イレウス)	0	0	1 (0.6%)	0	1 (0.3%)
Large intestine polyp (大腸ポリープ)	0	0	1 (0.6%)	0	1 (0.3%)
Loose tooth (弛緩歯)	0	0	1 (0.6%)	0	1 (0.3%)
Melaena (メレナ)	1 (0.5%)	0	0	0	0
Tooth loss (歯の脱落)	1 (0.5%)	0	0	0	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.5.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

消化器症状の発現状況を表 2.7.4.2-49 に示す。消化器症状の発現割合は、単独療法群で 22.4%、併用療法群で 7.8～40.6%で、BIG 併用療法群で 40.6%とほかの群より高かった。BIG 併用療法群で発現割合が高かった事象は下痢（17.2%）及び悪心（12.5%）で、いずれもほかの群より高かった。

重篤な消化器症状は、SU 併用療法群で下部消化管出血が 127 名中 1 名に、BIG 併用療法群で大腸ポリープが 64 名中 1 名に、TZD 併用療法群で腸膀胱瘻が 65 名中 1 名に、DPP4-I 併用療法群で大腸ポリープが 63 名中 1 名に、SGLT2-I 併用療法群で大腸ポリープが 63 名中 1 名に発現した（表 2.7.4.2-22）。BIG 併用療法群で重度の悪心が 64 名中 1 名に発現し、治験薬の投与を中止した。このほかに治験薬の投与中止に至った有害事象として、BIG 併用療法群で食欲減退、上腹部痛、嘔吐、下痢が 64 名中各 1 名に、AGI 併用療法群で胃炎が 64 名中 1 名に、TZD 併用療法群で嘔吐、悪心が 65 名中各 1 名に、DPP4-I 併用療法群で食欲減退、悪心が 63 名中各 1 名に、GLP1-RA 併用療法群で食欲減退、悪心、上腹部痛、消化不良が 70 名中各 1 名に発現した（表 2.7.4.2-31）。

表 2.7.4.2-49　Summary of Digestive Symptoms by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any Digestive Symptoms	30 (22.4%)	28 (22.0%)	12 (18.8%)	26 (40.6%)	5 (7.8%)	10 (15.4%)	21 (33.3%)	15 (21.4%)	15 (23.8%)	132 (22.8%)	162 (22.7%)
Gastrointestinal disorders (胃腸障害)	29 (21.6%)	28 (22.0%)	12 (18.8%)	25 (39.1%)	5 (7.8%)	9 (13.8%)	21 (33.3%)	14 (20.0%)	15 (23.8%)	129 (22.2%)	158 (22.1%)
Nausea (悪心)	9 (6.7%)	1 (0.8%)	0	8 (12.5%)	1 (1.6%)	1 (1.5%)	5 (7.9%)	3 (4.3%)	4 (6.3%)	23 (4.0%)	32 (4.5%)
Diarrhoea (下痢)	4 (3.0%)	3 (2.4%)	4 (6.3%)	11 (17.2%)	0	2 (3.1%)	2 (3.2%)	3 (4.3%)	2 (3.2%)	27 (4.7%)	31 (4.3%)
Constipation (便秘)	5 (3.7%)	8 (6.3%)	2 (3.1%)	1 (1.6%)	2 (3.1%)	1 (1.5%)	5 (7.9%)	1 (1.4%)	2 (3.2%)	22 (3.8%)	27 (3.8%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)	3 (2.2%)	9 (7.1%)	1 (1.6%)	2 (3.1%)	0	0	0	1 (1.4%)	0	13 (2.2%)	16 (2.2%)
Abdominal pain upper (上腹部痛)	4 (3.0%)	1 (0.8%)	1 (1.6%)	3 (4.7%)	0	0	2 (3.2%)	1 (1.4%)	0	8 (1.4%)	12 (1.7%)
Dental caries (齲歯)	5 (3.7%)	0	1 (1.6%)	1 (1.6%)	0	3 (4.6%)	2 (3.2%)	0	0	7 (1.2%)	12 (1.7%)
Vomiting (嘔吐)	1 (0.7%)	0	0	4 (6.3%)	0	2 (3.1%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	11 (1.9%)	12 (1.7%)
Abdominal discomfort (腹部不快感)	0	2 (1.6%)	1 (1.6%)	3 (4.7%)	1 (1.6%)	0	2 (3.2%)	0	0	9 (1.6%)	9 (1.3%)
Chronic gastritis (慢性胃炎)	0	2 (1.6%)	0	1 (1.6%)	0	0	2 (3.2%)	1 (1.4%)	1 (1.6%)	7 (1.2%)	7 (1.0%)
Dyspepsia (消化不良)	0	2 (1.6%)	1 (1.6%)	0	0	0	2 (3.2%)	2 (2.9%)	0	7 (1.2%)	7 (1.0%)
Faeces soft (軟便)	1 (0.7%)	1 (0.8%)	1 (1.6%)	2 (3.1%)	0	0	0	0	1 (1.6%)	5 (0.9%)	6 (0.8%)
Large intestine polyp (大腸ポリープ)	1 (0.7%)	0	0	2 (3.1%)	0	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	5 (0.9%)	6 (0.8%)
Abdominal pain (腹痛)	0	1 (0.8%)	1 (1.6%)	0	0	0	1 (1.6%)	0	1 (1.6%)	4 (0.7%)	4 (0.6%)
Gastritis (胃炎)	0	0	0	0	1 (1.6%)	0	0	1 (1.4%)	2 (3.2%)	4 (0.7%)	4 (0.6%)
Abdominal distension (腹部膨満)	0	0	0	0	0	0	1 (1.6%)	0	2 (3.2%)	3 (0.5%)	3 (0.4%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Aphthous ulcer (アフタ性潰瘍)	1 (0.7%)	0	0	1 (1.6%)	0	0	1 (1.6%)	0	0	2 (0.3%)	3 (0.4%)
Food poisoning (食中毒)	1 (0.7%)	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	2 (0.3%)
Abdominal pain lower (下腹部痛)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Change of bowel habit (便習慣変化)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Colitis (大腸炎)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Colitis ulcerative (潰瘍性大腸炎)	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Diverticulum intestinal (腸憩室)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Enteritis (小腸炎)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Enterocolitis (腸炎)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Enterovesical fistula (腸膀胱瘻)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Epigastric discomfort (心窩部不快感)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Flatulence (鼓腸)	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Gastric polyps (胃ポリープ)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Gastritis erosive (びらん性胃炎)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorder (胃腸障害)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Glossitis (舌炎)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Haematochezia (血便排泄)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Inguinal hernia (鼠径ヘルニア)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Irritable bowel syndrome (過敏性腸症候群)	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Lower gastrointestinal haemorrhage (下部消化管出血)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Mouth ulceration (口腔内潰瘍形成)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Pancreatic steatosis (膵脂肪変性)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Periodontal disease (歯周病)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Stomatitis (口内炎)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Tooth loss (歯の脱落)	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Toothache (歯痛)	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Metabolism and nutrition disorders (代謝および栄養障害)	3 (2.2%)	0	0	2 (3.1%)	0	2 (3.1%)	2 (3.2%)	3 (4.3%)	1 (1.6%)	10 (1.7%)	13 (1.8%)
Decreased appetite (食欲減退)	3 (2.2%)	0	0	2 (3.1%)	0	2 (3.1%)	2 (3.2%)	3 (4.3%)	1 (1.6%)	10 (1.7%)	13 (1.8%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.5.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

消化器症状の発現状況を表 2.7.4.2-50 に示す。消化器症状の発現割合は、プラセボ群、イメグリミン群の順に 6.5%（7/107 名）、9.3%（10/108 名）であった。イメグリミン群で中等度の悪心が 1 名に発現し、治験薬の投与を中止した（表 2.7.4.2-33）。重篤な消化器症状は発現しなかった（表 2.7.4.2-24）。

表 2.7.4.2-50　Summary of Digestive Symptoms by System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

System Organ Class Preferred Term	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Any Digestive Symptoms	7 (6.5%)	10 (9.3%)
Gastrointestinal disorders (胃腸障害)	7 (6.5%)	10 (9.3%)
Constipation (便秘)	1 (0.9%)	3 (2.8%)
Diarrhoea (下痢)	2 (1.9%)	2 (1.9%)
Nausea (悪心)	2 (1.9%)	2 (1.9%)
Abdominal discomfort (腹部不快感)	1 (0.9%)	1 (0.9%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)	1 (0.9%)	1 (0.9%)
Vomiting (嘔吐)	1 (0.9%)	1 (0.9%)
Abdominal distension (腹部膨満)	0	1 (0.9%)
Colitis ulcerative (潰瘍性大腸炎)	0	1 (0.9%)
Dental caries (齲歯)	0	1 (0.9%)
Periodontal disease (歯周病)	0	1 (0.9%)
Toothache (歯痛)	0	1 (0.9%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

(2) 長期投与（52 週）

消化器症状の発現状況を表 2.7.4.2-51 に示す。消化器症状の発現割合は、14.4%（30/209 名）であった。非盲検治療期に新たに消化器症状で治験薬の投与を中止した被験者はいなかった（表 2.7.4.2-35）。重篤な消化器症状は発現しなかった（表 2.7.4.2-26）。

表 2.7.4.2-51　Summary of Digestive Symptoms by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any Digestive Symptoms	10 (9.9%)	20 (18.5%)	30 (14.4%)
Gastrointestinal disorders (胃腸障害)	10 (9.9%)	20 (18.5%)	30 (14.4%)
Constipation (便秘)	0	6 (5.6%)	6 (2.9%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)	2 (2.0%)	3 (2.8%)	5 (2.4%)
Nausea (悪心)	2 (2.0%)	3 (2.8%)	5 (2.4%)
Abdominal discomfort (腹部不快感)	1 (1.0%)	3 (2.8%)	4 (1.9%)
Diarrhoea (下痢)	2 (2.0%)	2 (1.9%)	4 (1.9%)
Toothache (歯痛)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Abdominal pain upper (上腹部痛)	0	2 (1.9%)	2 (1.0%)
Chronic gastritis (慢性胃炎)	2 (2.0%)	0	2 (1.0%)
Dental caries (齲歯)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Gastritis (胃炎)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Periodontal disease (歯周病)	0	2 (1.9%)	2 (1.0%)
Vomiting (嘔吐)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Abdominal distension (腹部膨満)	0	1 (0.9%)	1 (0.5%)
Colitis ulcerative (潰瘍性大腸炎)	0	1 (0.9%)	1 (0.5%)
Large intestine polyp (大腸ポリープ)	1 (1.0%)	0	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.6　腎機能関連事象

2.7.4.2.1.6.2.6.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

腎機能関連事象の発現状況を表 2.7.4.2-52 に示す。腎機能関連事象の発現割合は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に 1.1%、1.3%、1.1%、0%で、重度の事象は発現しなかった。本剤群で 2 名以上にみられた事象はなかった。

表 2.7.4.2-52　Summary of Renal Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any Renal TEAE	2 (1.1%)	1 (1.3%)	2 (1.1%)	0	3 (0.9%)
Renal and urinary disorders (腎および尿路障害)	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Calculus urinary (尿路結石)	1 (0.5%)	0	0	0	0
Diabetic nephropathy (糖尿病性腎症)	0	1 (1.3%)	0	0	1 (0.3%)
Ureterolithiasis (尿管結石症)	0	0	1 (0.6%)	0	1 (0.3%)
Investigations (臨床検査)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Urine albumin/creatinine ratio increased (尿中アルブミン／クレアチニン比増加)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.6.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

腎機能関連事象の発現状況を表 2.7.4.2-53 に示す。腎機能関連事象の発現割合は、単独療法群で 0.7%、併用療法群で 1.6～5.7%であった。重度の有害事象は発現しなかった。同じ群で 2 名以上にみられた事象は、糖尿病性腎症（AGI 併用療法群で 2 名）、腎結石症（AGI 併用療法群、TZD 併用療法群で各 2 名）、頻尿（GLP1-RA 併用療法群で 2 名）であった。

表 2.7.4.2-53　Summary of Renal Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any Renal TEAE	1 (0.7%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	3 (4.7%)	3 (4.6%)	3 (4.8%)	4 (5.7%)	3 (4.8%)	20 (3.4%)	21 (2.9%)
Renal and urinary disorders (腎および尿路障害)	1 (0.7%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	3 (4.7%)	3 (4.6%)	3 (4.8%)	4 (5.7%)	3 (4.8%)	20 (3.4%)	21 (2.9%)
Diabetic nephropathy (糖尿病性腎症)	0	1 (0.8%)	0	1 (1.6%)	2 (3.1%)	1 (1.5%)	1 (1.6%)	0	1 (1.6%)	7 (1.2%)	7 (1.0%)
Nephrolithiasis (腎結石症)	1 (0.7%)	0	0	0	2 (3.1%)	2 (3.1%)	1 (1.6%)	1 (1.4%)	0	6 (1.0%)	7 (1.0%)
Pollakiuria (頻尿)	0	0	0	0	0	0	0	2 (2.9%)	1 (1.6%)	3 (0.5%)	3 (0.4%)
Calculus urinary (尿路結石)	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Haematuria (血尿)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Hypertonic bladder (緊張性膀胱)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Polyuria (多尿)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Renal cyst (腎嚢胞)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Urinary tract disorder (尿路障害)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Investigations (臨床検査)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Blood creatinine increased (血中クレアチニン増加)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.

- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.6.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

腎機能関連事象の発現状況を表 2.7.4.2-54 に示す。腎機能関連事象はプラセボ群ではみられなかった。イメグリミン群での発現割合は 0.9%で、重度の事象は発現しなかった。

表 2.7.4.2-54　Summary of Renal Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

System Organ Class Preferred Term	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Any Renal TEAE	0	1 (0.9%)
Renal and urinary disorders (腎および尿路障害)	0	1 (0.9%)
Haematuria (血尿)	0	1 (0.9%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

(2) 長期投与（52 週）

腎機能関連事象の発現状況を表 2.7.4.2-55 に示す。腎機能関連事象の発現割合は 1.0%で、重度の事象は発現しなかった。

表 2.7.4.2-55　Summary of Renal Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any Renal TEAE	1 (1.0%)	1 (0.9%)	2 (1.0%)
Renal and urinary disorders (腎および尿路障害)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Haematuria (血尿)	0	1 (0.9%)	1 (0.5%)
Renal cyst (腎嚢胞)	1 (1.0%)	0	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.

- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.7　肝機能関連事象

2.7.4.2.1.6.2.7.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

肝機能関連事象の発現状況を表 2.7.4.2-56 に示す。肝機能関連事象の発現割合は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に 2.2%、1.3%、1.1%、4.0%で、重度の事象は発現しなかった。本剤群で 2 名以上にみられた事象はなかった。

表 2.7.4.2-56　Summary of Hepatic Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any Hepatic TEAE	4 (2.2%)	1 (1.3%)	2 (1.1%)	3 (4.0%)	6 (1.8%)
Hepatobiliary disorders (肝胆道系障害)	2 (1.1%)	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Hepatic steatosis (脂肪肝)	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Hepatic function abnormal (肝機能異常)	0	0	1 (0.6%)	0	1 (0.3%)
Hepatomegaly (肝腫大)	0	0	0	1 (1.3%)	1 (0.3%)
Liver injury (肝損傷)	1 (0.5%)	0	0	0	0
Investigations (臨床検査)	2 (1.1%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Blood bilirubin increased (血中ビリルビン増加)	2 (1.1%)	0	0	0	0
Gamma-glutamyltransferase increased (γ－グルタミルトランスフェラーゼ増加)	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Alanine aminotransferase increased (アラニンアミノトランスフェラーゼ増加)	1 (0.5%)	0	0	0	0
Aspartate aminotransferase increased (アスパラギン酸アミノトランスフェラーゼ増加)	1 (0.5%)	0	0	0	0
International normalised ratio increased (国際標準比増加)	0	1 (1.3%)	0	0	1 (0.3%)
Liver function test increased (肝機能検査値上昇)	0	0	1 (0.6%)	0	1 (0.3%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.7.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

肝機能関連事象の発現状況を表 2.7.4.2-57 に示す。肝機能関連事象は、単独療法群及び BIG 併用療法群ではみられず、その他の併用療法群での発現割合は 1.6～4.8%であった。

AGI 併用療法群で薬物性肝障害が 1 名に発現し、重篤な有害事象として報告された（表 2.7.4.2-23）。同じ群で 2 名以上に発現した事象は SU 併用療法群の肝酵素上昇（2 名）及び GLP1-RA 併用療法群の脂肪肝（2 名）であった。

表 2.7.4.2-57　Summary of Hepatic Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any Hepatic TEAE	0	3 (2.4%)	1 (1.6%)	0	1 (1.6%)	3 (4.6%)	1 (1.6%)	2 (2.9%)	3 (4.8%)	14 (2.4%)	14 (2.0%)
Hepatobiliary disorders (肝胆道系障害)	0	1 (0.8%)	1 (1.6%)	0	1 (1.6%)	3 (4.6%)	0	2 (2.9%)	1 (1.6%)	9 (1.6%)	9 (1.3%)
Hepatic steatosis (脂肪肝)	0	1 (0.8%)	1 (1.6%)	0	0	1 (1.5%)	0	2 (2.9%)	0	5 (0.9%)	5 (0.7%)
Drug-induced liver injury (薬物性肝障害)	0	0	0	0	1 (1.6%)	1 (1.5%)	0	0	1 (1.6%)	3 (0.5%)	3 (0.4%)
Non-alcoholic steatohepatitis (非アルコール性脂肪性肝炎)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Investigations (臨床検査)	0	2 (1.6%)	0	0	0	0	1 (1.6%)	0	2 (3.2%)	5 (0.9%)	5 (0.7%)
Hepatic enzyme increased (肝酵素上昇)	0	2 (1.6%)	0	0	0	0	0	0	1 (1.6%)	3 (0.5%)	3 (0.4%)
Gamma-glutamyltransferase increased (γーグルタミルトランスフェラーゼ増加)	0	0	0	0	0	0	1 (1.6%)	0	1 (1.6%)	2 (0.3%)	2 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Haemangioma of liver (肝臓血管腫)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione;

DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.1.6.2.7.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

プラセボ群、イメグリミン群共に肝機能関連事象は発現しなかった。

(2) 長期投与（52 週）

肝機能関連事象の発現状況を表 2.7.4.2-58 に示す。肝機能関連事象の発現割合は、2.4%であった。重度の肝機能異常が 1 名に発現し、重篤な有害事象として報告された（表 2.7.4.2-27）。2 名以上に発現した事象は脂肪肝（2 名）であった。

表 2.7.4.2-58　Summary of Hepatic Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any Hepatic TEAE	2 (2.0%)	3 (2.8%)	5 (2.4%)
Hepatobiliary disorders (肝胆道系障害)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Hepatic steatosis (脂肪肝)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Hepatic function abnormal (肝機能異常)	1 (1.0%)	0	1 (0.5%)
Investigations (臨床検査)	0	2 (1.9%)	2 (1.0%)
Aspartate aminotransferase increased (アスパラギン酸アミノトランスフェラーゼ増加)	0	1 (0.9%)	1 (0.5%)
Blood alkaline phosphatase increased (血中アルカリホスファターゼ増加)	0	1 (0.9%)	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

2.7.4.2.2　個別有害事象の文章による説明

死亡及び他の重篤な有害事象の叙述は 2.7.6 項に示す。

2.7.4.3　臨床検査値の評価

2.7.4.3.1　臨床検査値

2.7.4.3.1.1　臨床検査値の推移と顕著な異常値

臨床検査値の推移をシフトテーブルで評価し、臨床検査項目ごとに設定した基準を超える値を顕著な異常値として評価した。乳酸値は 2.7.4.3.1.2.1 項で評価した。

2.7.4.3.1.1.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

臨床検査で顕著な異常値を示した被験者の割合を 2.7.4.7 項付録 Table S-092 に、臨床検査値のシフトテーブルを 2.7.4.7 項付録 Table S-178～Table S-181 及び Table S-183 に示す。治験期間を通していずれの群でも臨床検査値に臨床的に意義のある変動はなかった。

好酸球割合が顕著な高値（10%以上）を示した被験者の割合（被験者数、以下同様）はプラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）、4.4%（8/181 名）、12.0%（9/75 名）、6.1%（11/180 名）、10.7%（8/75 名）であったが、好酸球数が顕著な高値（1.6×10^9/L 超）を示した被験者は 1000 mg bid 群の 1 名のみであった。単球割合が顕著な高値（15%以上）を示した被験者の割合は 0 名、5.3%（4/75 名）、2.2%（4/180 名）、6.7%（5/75 名）で、プラセボ群と比較して本剤群で高かったが、用量依存的に高くなることはなかった。また、単球数が顕著な高値（2.5×10^9/L 超）を示した被験者はいなかった。γ-GTP が顕著な高値（基準値上限の 2.5 倍以上）を示した被験者の割合は 5.0%（9/181 名）、10.7%（8/75 名）、2.8%（5/180）、8.0%（6/75 名）で、プラセボ群と比較して本剤群で高かったが、用量依存的に高くなることはなかった。ほかの臨床検査項目は、いずれの群でも顕著な異常値を示した被験者の割合に大きな違いはなかった。

2.7.4.3.1.1.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

臨床検査で顕著な異常値を示した被験者の割合を 2.7.4.7 項付録 Table S-093 に、臨床検査値のシフトテーブルを 2.7.4.7 項付録 Table S-186～Table S-189 及び Table S-191 に示す。治験期間を通していずれの群でも臨床検査値に臨床的に意義のある変動はなかった。

- 単独療法群で 2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）は、ヘマトクリット（低値：男性 0.37 以下、女性 0.32 以下）で 8.2%（11/134 名）、γ-GTP（高値：基準値上限の 2.5 倍以上）で 6.0%（8/134 名）、クレアチンキナーゼ（高値：基準値上限の 2.5 倍超）で 5.2%（7/134 名）、好酸球割合（高値：10%以上）及びヘモグロビン（低値：男性 115 g/L 以下、女性 95 g/L 以下）で各 3.0%（4/134 名）、白血球数（低値：2.8×10^9/L 以下）で 2.2%（3/134 名）、リパーゼ（高値：基準値上限の 3 倍以上）、ビリルビン（高値：34.2 μmol/L 以上又は基準値上限の 2 倍超）、赤血球数（低値：3.5×10^{12}/L 以下）及びカリウム（高値：5.5 mmol/L 超）で各 1.5%（2/134 名）であった。
- SU 併用療法群で 2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）は、ヘマトクリット（低値）で 8.7%（11/127 名）、γ-

GTP（高値）及び赤血球数（低値）で各 4.7%（6/127 名）、クレアチンキナーゼ（高値）で 3.1%（4/127 名）、ビリルビン（高値）、白血球数（低値）及びカリウム（高値）で各 2.4%（3/127 名）、好酸球割合（高値）、ヘモグロビン（低値）、リパーゼ（高値）及び好中球割合（高値：85%超）で各 1.6%（2/127 名）であった。

- GLIN 併用療法群で 2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）はヘマトクリット（低値）で 10.9%（7/64 名）、クレアチンキナーゼ（高値）で 4.7%（3/64 名）、γ-GTP（高値）及びカリウム（高値）で各 3.1%（2/64 名）であった。
- BIG 併用療法群で 2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）は、ヘマトクリット（低値）で 18.8%（12/64 名）、γ-GTP（高値）で 6.3%（4/64 名）、赤血球数（低値）で 4.7%（3/64 名）、ヘモグロビン（低値）及び尿素窒素（高値：10.7 mmol/L 以上）で各 3.1%（2/64 名）であった。
- AGI 併用療法群で 2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）は、ヘマトクリット（低値）で 7.8%（5/64 名）、クレアチンキナーゼ（高値）、好酸球割合（高値）、γ-GTP（高値）及び白血球数（低値）で各 4.7%（3/64 名）、ALT（高値：基準値上限の 3 倍以上）、ヘモグロビン（低値）及びリパーゼ（高値）で各 3.1%（2/64 名）であった。
- TZD 併用療法群で 2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）は、ヘマトクリット（低値）で 18.5%（12/65 名）、ヘモグロビン（低値）及び白血球数（低値）で各 6.2%（4/65 名）、クレアチンキナーゼ（高値）及び赤血球数（低値）で各 4.6%（3/65 名）、カリウム（高値）で 3.1%（2/65 名）であった。
- DPP4-I 併用療法群で 2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）は、γ-GTP（高値）で 7.9%（5/63 名）、赤血球数（低値）で 6.3%（4/63 名）、ヘマトクリット（低値）で 4.8%（3/63 名）、クレアチンキナーゼ（高値）、リパーゼ（高値）、リン酸（高値：1.65 mmol/L 超）及びカリウム（高値）で各 3.2%（2/63 名）であった。
- GLP1-RA 併用療法群で 2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）は、γ-GTP（高値）で 7.1%（5/70 名）、ヘマトクリット（低値）で 4.3%（3/70 名）、クレアチンキナーゼ（高値）及び好酸球割合（高値）で各 2.9%（2/70 名）であった。
- SGLT2-I 併用療法群で 2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）は、γ-GTP（高値）で 11.1%（7/63 名）、カリウム（高値）で 4.8%（3/63 名）、ALT（高値）及びクロール（低値：90 mmol/L 以下）で各 3.2%（2/63 名）であった。

2.7.4.3.1.1.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

臨床検査で顕著な異常値を示した被験者の割合を 2.7.4.7 項付録 Table S-094 に、臨床検査値のシフトテーブルを 2.7.4.7 項付録 Table S-194～Table S-197 及び Table S-199 に示す。治験期間を通していずれの群でも臨床検査値に臨床的に意義のある変動はなかった。

いずれの群でも顕著な異常値を示した被験者の割合に大きな違いはなかった。イメグリミン群でのみ顕著な異常値がみられた検査項目は、アルカリホスファターゼ（高値：基準値上限の 1.5 倍以上）、クレアチンキナーゼ（高値：基準値上限の 2.5 倍超）、赤血球数（高値：6.4×10^{12}/L 以上）、乳酸（高値：5 mmol/L 超）、リン酸（高値：1.65 mmol/L 超）が各 1 名であった。

(2) 長期投与（52 週）

臨床検査で顕著な異常値を示した被験者の割合を 2.7.4.7 項付録 Table S-095 に、臨床検査値のシフトテーブルを 2.7.4.7 項付録 Table S-202～Table S-205 及び Table S-207 に示す。治験期間を通して臨床検査値に臨床的に意義のある変動はなかった。

2 名以上に顕著な異常値がみられた検査項目での顕著な異常値を示した被験者の割合（被験者数）は、ヘマトクリット（低値：男性 0.37 以下、女性 0.32 以下）で 4.8%（10/209 名）、クレアチニンキナーゼ（高値：基準値上限の 2.5 倍超）で 3.8%（8/209 名）、γ-GTP（高値：基準値上限の 2.5 倍以上）で 2.4%（5/209 名）、白血球数（低値：2.8×10^{9}/L 以下）及び尿素窒素（高値：10.7 mmol/L 以上）で 1.4%（3/209 名）、好酸球割合（高値：10%以上）、赤血球数（低値：3.5×10^{12}/L 以下）、リン酸（高値：1.65 mmol/L 超）及びカリウム（高値：5.5 mmol/L 超）で各 1.0%（2/209 名）であった。

2.7.4.3.1.2　注目すべき臨床検査値

2.7.4.3.1.2.1　乳酸

2.7.4.3.1.2.1.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

乳酸値の Week 12 及び Week 24 のベースラインからの変化量を表 2.7.4.3-1 に、すべての評価時点のベースラインからの変化量を 2.7.4.7 項付録 Table S-232 に、乳酸値のシフトテーブルを 2.7.4.7 項付録 Table S-184 に示す。治験期間を通していずれの群でも乳酸値に臨床的に意義のある変動はなかった。乳酸値（mmol/L）の LOCF endpoint のベースラインからの変化量（平均値±SD）はプラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に、−0.02±0.477、0.12±0.580、−0.02±0.490、0.03±0.463 であった。

乳酸の顕著な異常値（5 mmol/L 超）を示した被験者の割合を 2.7.4.7 項付録 Table S-092 に示す。乳酸が顕著な高値を示した被験者は 1000 mg bid 群及び 1500 mg bid 群に各 1 名で、いずれの被験者でも有害事象として乳酸アシドーシス関連事象は報告されなかった（2.7.4.2.1.6.2.2 項）。1000 mg bid 群の 1 名は 018 試験の被験者で、当該試験の乳酸の基準値範囲は 0.4～2.2 mmol/L であった。当該被験者の乳酸値は、ベースライン、Week 12、Week 24

の順に 5.5、5.1、4.2 mmol/L でベースラインから継続して基準値上限より高値であった（5.3.5.1.02 項 Listing 16.2.8.8）。1500 mg bid 群の 1 名は 014 試験の被験者で、当該試験の乳酸の基準値範囲は 0.5～2.2 mmol/L であった。当該被験者の乳酸値は、ベースライン、Week 2、Week 4、Week 8、Week 12、Week 16、Week 20、Week 24（二重盲検治療期終了時）、Week 25（治験終了時）の順に 2.8、1.2、1.8、2.8、2.4、5.1、1.7、3.0、3.0 mmol/L で、ベースライン時に基準値上限より高値で、二重盲検治療期中及び二重盲検治療期終了後に複数回、基準値上限より高値を示した（5.3.5.1.01 項 Listing 16.2.8.1）。

表 2.7.4.3-1　Summary of Change from Baseline in Plasma Lactate Concentration (mmol/L) to Week 24 in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Lactic Acid (mmol/L)					
Placebo (N = 182)					
Baseline	181	1.26 (0.539)	1.10 [0.4, 3.3]		
Week 12	168	1.27 (0.510)	1.20 [0.5, 3.9]	0.00 (0.483)	0.00 [-2.2, 1.2]
Week 24	167	1.26 (0.574)	1.10 [0.5, 3.7]	-0.01 (0.481)	0.00 [-1.4, 2.7]
LOCF Endpoint	176	1.25 (0.560)	1.10 [0.5, 3.7]	-0.02 (0.477)	0.00 [-1.4, 2.7]
Imeglimin 500 mg bid (N = 75)					
Baseline	75	1.21 (0.507)	1.10 [0.4, 2.6]		
Week 12	72	1.25 (0.524)	1.15 [0.5, 3.3]	0.06 (0.504)	0.00 [-1.2, 1.5]
Week 24	69	1.32 (0.616)	1.20 [0.5, 3.9]	0.13 (0.596)	0.00 [-1.0, 1.9]
LOCF Endpoint	75	1.33 (0.606)	1.20 [0.5, 3.9]	0.12 (0.580)	0.00 [-1.0, 1.9]
Imeglimin 1000 mg bid (N = 180)					
Baseline	179	1.27 (0.588)	1.10 [0.5, 5.5]		
Week 12	172	1.22 (0.523)	1.10 [0.4, 5.1]	-0.05 (0.400)	0.00 [-1.7, 0.8]
Week 24	169	1.24 (0.541)	1.10 [0.4, 4.2]	-0.03 (0.473)	0.00 [-1.5, 1.9]
LOCF Endpoint	178	1.25 (0.546)	1.10 [0.4, 4.2]	-0.02 (0.490)	0.00 [-1.5, 1.9]
Imeglimin 1500 mg bid (N = 75)					
Baseline	75	1.28 (0.453)	1.20 [0.6, 3.0]		
Week 12	67	1.31 (0.483)	1.20 [0.6, 2.7]	0.01 (0.313)	0.00 [-0.7, 0.8]
Week 24	67	1.34 (0.567)	1.20 [0.5, 3.3]	0.04 (0.469)	0.00 [-1.4, 1.8]
LOCF Endpoint	75	1.31 (0.556)	1.20 [0.5, 3.3]	0.03 (0.463)	0.00 [-1.4, 1.8]

- Abbreviations: bid, Twice a day; SD, standard deviation; LOCF, Last Observation Carried Forward

2.7.4.3.1.2.1.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

乳酸値のすべての評価時点のベースラインからの変化量を表 2.7.4.3-2 に、乳酸値のシフトテーブルを 2.7.4.7 項付録 Table S-192 に示す。治験期間を通していずれの群でも乳酸値に

臨床的に意義のある変動はなかった。

乳酸値（mmol/L）の LOCF endpoint のベースラインからの変化量（平均値±SD）は、単独療法群で−0.01±0.480 であった。併用療法群では、SU 併用療法群で 0.06±0.540、GLIN 併用療法群で−0.02±0.491、BIG 併用療法群で 0.07±0.491、AGI 併用療法群−0.05±0.423、TZD 併用療法群で−0.01±0.505、DPP4-I 併用療法群で 0.03±0.383、GLP1-RA 併用療法群で 0.03±0.510、SGLT2-I 併用療法群で−0.04±0.447 であった。

乳酸の顕著な異常値（5 mmol/L 超）を示した被験者の割合を 2.7.4.7 項付録 Table S-093 に示す。本試験の乳酸の基準値範囲は 0.4〜2.2 mmol/L で、乳酸の顕著な高値を示した被験者は、SU 併用療法群及び SGLT2-I 併用療法群の各 1 名であった。SU 併用療法群で乳酸の顕著な高値を示した被験者では有害事象として血中乳酸増加が報告され、乳酸値はベースライン（Day 1）、Week 24（Day 168）、Week 52（Day 363）、規定外（Day 396）の順に 0.9、1.3、5.5、2.5 mmol/L であった。SGLT2-I 併用療法群で乳酸の顕著な高値を示した被験者では有害事象として乳酸アシドーシス関連事象は報告されず、乳酸値はベースライン、Week 24 の順に 4.4、5.2 mmol/L とベースラインから基準値上限より高値であった。乳酸の顕著な高値を示さなかったが有害事象として血中乳酸増加が報告された SU 併用療法群の被験者（1 名）の乳酸値は、ベースライン、Week 24、Week 52 の順に 2.0、2.4、3.2 mmol/L と治験薬投与開始後に基準値上限より高値となった（2.7.4.2.1.6.2.2 項、5.3.5.2.01 項 Listing 16.2.8.8.1〜Listing 16.2.8.8.9）。SU 併用療法群、SGLT2-I 以外の併用療法群及び単独療法群では、乳酸の顕著な高値を示した被験者はいなかった。

表 2.7.4.3-2　Summary of Change from Baseline in Plasma Lactate Concentration (mmol/L) to Week 52 in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Lactic Acid (mmol/L)					
Imeglimin (N = 134)					
Baseline	134	1.22 (0.531)	1.10 [0.4, 4.0]		
Week 24	128	1.20 (0.465)	1.10 [0.5, 2.8]	-0.02 (0.453)	0.00 [-2.2, 1.6]
Week 52	126	1.22 (0.495)	1.10 [0.5, 2.7]	0.00 (0.483)	0.00 [-2.4, 1.5]
LOCF Endpoint	130	1.21 (0.491)	1.10 [0.5, 2.7]	-0.01 (0.480)	0.00 [-2.4, 1.5]
Imeglimin + SU (N = 127)					
Baseline	127	1.32 (0.599)	1.20 [0.5, 4.0]		
Week 24	122	1.30 (0.545)	1.20 [0.5, 3.4]	0.00 (0.500)	0.00 [-2.2, 1.4]
Week 52	116	1.42 (0.723)	1.30 [0.5, 5.5]	0.12 (0.650)	0.05 [-1.5, 4.6]
LOCF Endpoint	122	1.36 (0.560)	1.30 [0.5, 3.7]	0.06 (0.540)	0.00 [-1.9, 2.0]
Imeglimin + GLIN (N = 64)					
Baseline	64	1.23 (0.559)	1.05 [0.5, 3.5]		
Week 24	62	1.20 (0.482)	1.10 [0.5, 2.8]	-0.03 (0.422)	0.00 [-2.1, 0.7]
Week 52	59	1.20 (0.487)	1.10 [0.5, 3.0]	-0.04 (0.497)	0.00 [-2.0, 1.2]
LOCF Endpoint	62	1.21 (0.483)	1.10 [0.5, 3.0]	-0.02 (0.491)	0.00 [-2.0, 1.2]
Imeglimin + BIG (N = 64)					
Baseline	64	1.33 (0.473)	1.25 [0.6, 2.6]		
Week 4	63	1.39 (0.471)	1.30 [0.5, 2.6]	0.06 (0.372)	0.00 [-0.8, 0.9]
Week 8	64	1.29 (0.413)	1.20 [0.6, 2.5]	-0.04 (0.410)	0.00 [-1.3, 0.9]
Week 12	64	1.40 (0.508)	1.25 [0.6, 2.6]	0.07 (0.460)	0.00 [-1.1, 1.3]
Week 16	63	1.41 (0.490)	1.40 [0.8, 2.5]	0.08 (0.430)	0.10 [-1.2, 1.1]
Week 20	63	1.41 (0.484)	1.30 [0.7, 2.7]	0.08 (0.376)	0.10 [-0.8, 1.2]
Week 24	61	1.40 (0.493)	1.40 [0.6, 2.6]	0.09 (0.492)	0.10 [-1.3, 1.3]
Week 28	59	1.37 (0.554)	1.30 [0.6, 3.4]	0.06 (0.520)	0.00 [-1.3, 1.9]
Week 32	60	1.33 (0.431)	1.30 [0.6, 2.5]	0.02 (0.468)	0.00 [-1.4, 1.4]
Week 36	59	1.35 (0.521)	1.20 [0.7, 2.9]	0.03 (0.500)	0.00 [-1.0, 1.5]
Week 40	59	1.41 (0.535)	1.30 [0.6, 3.1]	0.09 (0.451)	0.00 [-0.8, 1.8]
Week 44	59	1.38 (0.556)	1.30 [0.7, 3.3]	0.06 (0.541)	0.10 [-1.1, 2.0]
Week 48	57	1.36 (0.589)	1.30 [0.5, 3.6]	0.05 (0.595)	0.00 [-1.7, 2.3]
Week 52	58	1.38 (0.506)	1.30 [0.5, 2.9]	0.06 (0.508)	0.00 [-1.6, 1.8]
LOCF Endpoint	64	1.40 (0.512)	1.30 [0.5, 2.9]	0.07 (0.491)	0.00 [-1.6, 1.8]
Imeglimin + AGI (N = 64)					
Baseline	64	1.15 (0.366)	1.10 [0.5, 2.2]		
Week 24	63	1.13 (0.498)	1.00 [0.4, 3.2]	-0.02 (0.432)	0.00 [-1.3, 1.1]
Week 52	62	1.10 (0.493)	1.00 [0.4, 3.2]	-0.05 (0.426)	-0.10 [-1.0, 1.0]
LOCF Endpoint	63	1.10 (0.489)	1.00 [0.4, 3.2]	-0.05 (0.423)	-0.10 [-1.0, 1.0]

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Imeglimin + TZD (N = 65)					
Baseline	65	1.27 (0.509)	1.10 [0.5, 3.1]		
Week 24	65	1.26 (0.505)	1.10 [0.5, 2.6]	0.00 (0.507)	0.00 [-1.4, 1.1]
Week 52	65	1.25 (0.501)	1.20 [0.6, 2.9]	-0.01 (0.505)	0.00 [-1.5, 1.7]
LOCF Endpoint	65	1.25 (0.501)	1.20 [0.6, 2.9]	-0.01 (0.505)	0.00 [-1.5, 1.7]
Imeglimin + DPP4-I (N = 63)					
Baseline	62	1.15 (0.468)	1.00 [0.5, 2.5]		
Week 24	59	1.12 (0.530)	0.90 [0.5, 3.2]	-0.02 (0.335)	-0.05 [-1.0, 0.7]
Week 52	60	1.17 (0.532)	1.00 [0.5, 2.6]	0.03 (0.384)	0.00 [-1.0, 1.1]
LOCF Endpoint	60	1.17 (0.532)	1.00 [0.5, 2.6]	0.03 (0.383)	0.00 [-1.0, 1.1]
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	1.31 (0.510)	1.20 [0.6, 3.1]		
Week 24	69	1.31 (0.515)	1.20 [0.5, 3.1]	0.03 (0.413)	0.00 [-1.0, 1.1]
Week 52	66	1.31 (0.668)	1.10 [0.4, 4.4]	0.01 (0.512)	0.00 [-1.0, 2.4]
LOCF Endpoint	69	1.31 (0.654)	1.10 [0.4, 4.4]	0.03 (0.510)	0.00 [-1.0, 2.4]
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	1.43 (0.693)	1.20 [0.6, 4.4]		
Week 24	62	1.44 (0.880)	1.25 [0.5, 5.2]	0.02 (0.655)	-0.10 [-1.8, 2.7]
Week 52	61	1.33 (0.568)	1.20 [0.5, 3.6]	-0.05 (0.441)	0.00 [-1.7, 1.2]
LOCF Endpoint	63	1.39 (0.743)	1.20 [0.5, 5.2]	-0.04 (0.447)	0.00 [-1.7, 1.2]

- Abbreviations: SD, standard deviation; LOCF, Last Observation Carried Forward; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".

2.7.4.3.1.2.1.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

乳酸値の Week 16 のベースラインからの変化量を表 2.7.4.3-3 に、乳酸値のシフトテーブルを 2.7.4.7 項付録 Table S-200 に示す。治験期間を通していずれの群でも乳酸値に臨床的に意義のある変動はなかった。乳酸値（mmol/L）の LOCF endpoint のベースラインからの変化量（平均値±SD）はプラセボ群、イメグリミン群の順に−0.01±0.466、0.07±0.398 で、イメグリミン群で大きかった。

乳酸の顕著な異常値（5 mmol/L 超）を示した被験者の割合を 2.7.4.7 項付録 Table S-094 に示す。イメグリミン群の 1 名では乳酸が顕著な高値を示したが、有害事象として乳酸アシドーシス関連事象は報告されなかった（2.7.4.2.1.6.2.2 項）。本試験の乳酸の基準値範囲は 0.4～2.2 mmol/L で、当該被験者の乳酸値はベースライン（Day 1）、規定外（Day 13）、Week 16（Day 114）、規定外（Day 127）の順に 8.9、6.4、8.9、8.2 mmol/L とベースラインから継続して基準値上限より高値であった（5.3.5.1.03 項 Listing 16.2.8.8）。

表 2.7.4.3-3　Summary of Change from Baseline in Plasma Lactate Concentration (mmol/L) to Week 16 in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Lactic Acid (mmol/L)					
Placebo + Insulin (N = 107)					
Baseline	107	1.18 (0.557)	1.10 [0.4, 4.2]		
Week 16	104	1.13 (0.431)	1.10 [0.3, 3.5]	-0.01 (0.466)	0.00 [-1.5, 2.4]
LOCF Endpoint	104	1.13 (0.431)	1.10 [0.3, 3.5]	-0.01 (0.466)	0.00 [-1.5, 2.4]
Imeglimin 1000 mg bid + Insulin (N = 108)					
Baseline	108	1.22 (0.877)	1.00 [0.5, 8.9]		
Week 16	108	1.29 (0.924)	1.00 [0.5, 8.9]	0.07 (0.398)	0.00 [-0.8, 2.0]
LOCF Endpoint	108	1.29 (0.924)	1.00 [0.5, 8.9]	0.07 (0.398)	0.00 [-0.8, 2.0]

- Abbreviations: bid, Twice a day; SD, standard deviation; LOCF, Last Observation Carried Forward

(2) 長期投与（52 週）

乳酸値のすべての評価時点のベースラインからの変化量を表 2.7.4.3-4 に、乳酸値のシフトテーブルを 2.7.4.7 項付録 Table S-208 に示す。治験期間を通して乳酸値に臨床的に意義のある変動はなかった。乳酸値（mmol/L）のベースラインからの変化量（平均値±SD）は、Week 36、Week 52 及び LOCF endpoint の順に 0.12±0.468、0.00±0.418、0.04±0.418 であった。

乳酸の顕著な異常値（5 mmol/L 超）を示した被験者の割合を 2.7.4.7 項付録 Table S-095 に示す。本試験の乳酸の基準値範囲は 0.4～2.2 mmol/L であった。二重盲検治療期にイメグリミン群であった 1 名では乳酸が顕著な高値を示したが、有害事象として乳酸アシドーシス関連事象は報告されなかった。当該被験者の乳酸値はベースライン（Day 1）、規定外（Day 13）、Week 16（Day 114）、規定外（Day 127）、Week 36（Day 253）、Week 52（Day 365）の順に 8.9、6.4、8.9、8.2、9.8、8.3 mmol/L とベースラインから継続して基準値上限より高値であった。乳酸の顕著な高値を示さなかったが有害事象として血中乳酸増加が報告された 1 名では、乳酸値がベースライン（Day 1）、Week 16（Day 113）、Week 36（Day 256）、規定外（Day 285）、規定外（Day 309）、Week 52（Day 361）の順に 1.5、2.3、4.2、3.6、1.5、1.8 mmol/L と治験薬投与開始後に基準値上限より高値となった（2.7.4.2.1.6.2.2 項、5.3.5.1.03 項 Listing 16.2.8.8.2）。

表 2.7.4.3-4　Summary of Change from Baseline in Plasma Lactate Concentration (mmol/L) to Week 52 in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Lactic Acid (mmol/L)					
Placebo/Imeglimin + Insulin (N = 101)					
Baseline	101	1.13 (0.437)	1.10 [0.3, 3.5]		
Week 20	99	1.12 (0.391)	1.10 [0.3, 2.2]	-0.02 (0.425)	0.00 [-1.9, 0.9]
Week 36	98	1.23 (0.437)	1.20 [0.5, 2.5]	0.10 (0.413)	0.10 [-1.1, 1.3]
LOCF Endpoint	99	1.23 (0.437)	1.20 [0.5, 2.5]	0.09 (0.413)	0.10 [-1.1, 1.3]
Imeglimin/Imeglimin + Insulin (N = 108)					
Baseline	108	1.22 (0.877)	1.00 [0.5, 8.9]		
Week 16	108	1.29 (0.924)	1.00 [0.5, 8.9]	0.07 (0.398)	0.00 [-0.8, 2.0]
Week 36	107	1.36 (1.032)	1.10 [0.5, 9.8]	0.14 (0.516)	0.10 [-1.0, 2.7]
Week 52	107	1.22 (0.847)	1.10 [0.5, 8.3]	0.00 (0.418)	0.00 [-0.9, 1.8]
LOCF Endpoint	108	1.22 (0.843)	1.10 [0.5, 8.3]	0.00 (0.419)	0.00 [-0.9, 1.8]
Imeglimin + Insulin Total (N = 209)					
Baseline	209	1.18 (0.699)	1.10 [0.3, 8.9]		
Week 16	108	1.29 (0.924)	1.00 [0.5, 8.9]	0.07 (0.398)	0.00 [-0.8, 2.0]
Week 20	99	1.12 (0.391)	1.10 [0.3, 2.2]	-0.02 (0.425)	0.00 [-1.9, 0.9]
Week 36	205	1.30 (0.805)	1.10 [0.5, 9.8]	0.12 (0.468)	0.10 [-1.1, 2.7]
Week 52	107	1.22 (0.847)	1.10 [0.5, 8.3]	0.00 (0.418)	0.00 [-0.9, 1.8]
LOCF Endpoint	207	1.22 (0.678)	1.10 [0.5, 8.3]	0.04 (0.418)	0.00 [-1.1, 1.8]

- Abbreviations: SD, standard deviation; LOCF, Last Observation Carried Forward
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.

2.7.4.3.1.2.2　eGFR

2.7.4.3.1.2.2.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

腎機能区分別の被験者数を評価時点ごと及びベースラインの腎機能区分ごとに集計したシフトテーブルを表 2.7.4.3-5 に、eGFR の Week 24 のベースラインからの変化量を 2.7.4.7 項付録 Table S-097 に示す。治験期間を通していずれの群でも eGFR に臨床的に意義のある変動はなかった。

LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合（被験者数、以下

同様）は、ベースラインの腎機能区分が CKD 1 であった被験者（LOCF endpoint では CKD 2）でプラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）3.0%（5/167 名）、5.7%（4/70 名）、5.4%（9/168 名）、6.0%（4/67 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 7.2%（12/167 名）、2.9%（2/70 名）、5.4%（9/168 名）、7.5%（5/67 名）、ベースラインの腎機能区分が CKD 3a の被験者（LOCF endpoint では CKD 3b）で 0%、0%、1.8%（3/168 名）、0%であった。

表 2.7.4.3-5　Shift of Laboratory Findings of eGFR (CKD Stage) in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

Parameter Week	Baseline	Post-baseline	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
eGFR (CKD Stage)							
Week 24	m		167	70	168	67	305
	1	1	10 (6.0%)	4 (5.7%)	11 (6.5%)	9 (13.4%)	24 (7.9%)
		2	5 (3.0%)	4 (5.7%)	9 (5.4%)	4 (6.0%)	17 (5.6%)
	2	1	8 (4.8%)	0	7 (4.2%)	1 (1.5%)	8 (2.6%)
		2	106 (63.5%)	52 (74.3%)	104 (61.9%)	40 (59.7%)	196 (64.3%)
		3a	12 (7.2%)	2 (2.9%)	9 (5.4%)	5 (7.5%)	16 (5.2%)
	3a	2	10 (6.0%)	1 (1.4%)	7 (4.2%)	1 (1.5%)	9 (3.0%)
		3a	16 (9.6%)	7 (10.0%)	18 (10.7%)	7 (10.4%)	32 (10.5%)
		3b	0	0	3 (1.8%)	0	3 (1.0%)
LOCF Endpoint	m		167	70	168	67	305
	1	1	10 (6.0%)	4 (5.7%)	11 (6.5%)	9 (13.4%)	24 (7.9%)
		2	5 (3.0%)	4 (5.7%)	9 (5.4%)	4 (6.0%)	17 (5.6%)
	2	1	8 (4.8%)	0	7 (4.2%)	1 (1.5%)	8 (2.6%)
		2	106 (63.5%)	52 (74.3%)	104 (61.9%)	40 (59.7%)	196 (64.3%)
		3a	12 (7.2%)	2 (2.9%)	9 (5.4%)	5 (7.5%)	16 (5.2%)
	3a	2	10 (6.0%)	1 (1.4%)	7 (4.2%)	1 (1.5%)	9 (3.0%)
		3a	16 (9.6%)	7 (10.0%)	18 (10.7%)	7 (10.4%)	32 (10.5%)
		3b	0	0	3 (1.8%)	0	3 (1.0%)

- Abbreviations: LOCF, Last Observation Carried Forward; bid, Twice a day; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2, CKD Stage 3b includes subjects with eGFR >= 30 to < 45 mL/min/1.73m2.
- m in row headings is the total number of subjects with both baseline and the corresponding visit values available, and is used as the denominator to calculate percentages.

2.7.4.3.1.2.2.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

腎機能区分別の被験者数を評価時点ごと及びベースラインの腎機能区分ごとに集計したシフトテーブルを表 2.7.4.3-6 に、eGFR の Week 24 及び Week 52 のベースラインからの変化量を 2.7.4.7 項付録 Table S-101 に示す。治験期間を通していずれの群でも eGFR に臨床的に意義のある変動はなかった。

- 単独療法群で LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合（被験者数、以下同様）は、ベースラインの腎機能区分が CKD 1 の被験者（LOCF endpoint では CKD 2）で 6.2%（8/130 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 8.5%（11/130 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかった。
- SU 併用療法群で LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合は、ベースラインの腎機能区分が CKD 1 の被験者（LOCF endpoint では CKD 2）で 9.0%（11/122 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 7.4%（9/122 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかった。
- GLIN 併用療法群で LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合は、ベースラインの腎機能区分が CKD 1 の被験者（LOCF endpoint では CKD 2）で 8.1%（5/62 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 8.1%（5/62 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかった。
- BIG 併用療法群で LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合は、ベースラインの腎機能区分が CKD 1 の被験者（LOCF endpoint では CKD 2）で 13.1%（8/61 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 4.9%（3/61 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかったが、1 名が Week 24 で CKD 3b となった。
- AGI 併用療法群で LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合は、ベースラインの腎機能区分が CKD 1 の被験者（LOCF endpoint では CKD 2）で 9.5%（6/63 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 7.9%（5/63 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかった。
- TZD 併用療法群で LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合は、ベースラインの腎機能区分が CKD 1 の被験者（LOCF endpoint では CKD 2）

で 7.7%（5/65 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 10.8%（7/65 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかった。

- DPP4-I 併用療法群で LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合は、ベースラインの腎機能区分が CKD 1 の被験者（LOCF endpoint では CKD 2）で 11.5%（7/61 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 8.2%（5/61 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかった。ベースラインの腎機能区分が CKD 2 の被験者 1 名が、Week 24 で CKD 3b となった。
- GLP1-RA 併用療法群で LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合は、ベースラインの腎機能区分が CKD 1 の被験者（LOCF endpoint では CKD 2）で 7.2%（5/69 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 5.8%（4/69 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかった。
- SGLT2-I 併用療法群で LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合は、ベースラインの腎機能区分が CKD 1 の被験者（LOCF endpoint では CKD 2）で 9.5%（6/63 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 4.8%（3/63 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかった。

表 2.7.4.3-6　Shift of Laboratory Findings of eGFR (CKD Stage) in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

Parameter / Week	Baseline	Post-baseline	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
eGFR (CKD Stage)													
Week 24	m		130	122	62	61	63	65	61	69	63	566	696
	1	1	11 (8.5%)	10 (8.2%)	7 (11.3%)	10 (16.4%)	9 (14.3%)	9 (13.8%)	2 (3.3%)	7 (10.1%)	14 (22.2%)	68 (12.0%)	79 (11.4%)
		2	11 (8.5%)	11 (9.0%)	4 (6.5%)	8 (13.1%)	4 (6.3%)	7 (10.8%)	7 (11.5%)	8 (11.6%)	7 (11.1%)	56 (9.9%)	67 (9.6%)
	2	1	3 (2.3%)	4 (3.3%)	1 (1.6%)	0	5 (7.9%)	2 (3.1%)	0	6 (8.7%)	4 (6.3%)	22 (3.9%)	25 (3.6%)
		2	78 (60.0%)	82 (67.2%)	40 (64.5%)	34 (55.7%)	37 (58.7%)	41 (63.1%)	42 (68.9%)	41 (59.4%)	32 (50.8%)	349 (61.7%)	427 (61.4%)
		3a	9 (6.9%)	7 (5.7%)	8 (12.9%)	5 (8.2%)	6 (9.5%)	1 (1.5%)	2 (3.3%)	4 (5.8%)	4 (6.3%)	37 (6.5%)	46 (6.6%)
		3b	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
	3a	2	2 (1.5%)	5 (4.1%)	1 (1.6%)	2 (3.3%)	0	2 (3.1%)	5 (8.2%)	3 (4.3%)	1 (1.6%)	19 (3.4%)	21 (3.0%)
		3a	16 (12.3%)	3 (2.5%)	1 (1.6%)	1 (1.6%)	2 (3.2%)	3 (4.6%)	2 (3.3%)	0	1 (1.6%)	13 (2.3%)	29 (4.2%)
		3b	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Week 52	m		126	116	59	58	62	65	60	66	61	547	673
	1	1	13 (10.3%)	9 (7.8%)	6 (10.2%)	9 (15.5%)	7 (11.3%)	11 (16.9%)	2 (3.3%)	10 (15.2%)	14 (23.0%)	68 (12.4%)	81 (12.0%)
		2	8 (6.3%)	9 (7.8%)	5 (8.5%)	7 (12.1%)	5 (8.1%)	5 (7.7%)	7 (11.7%)	5 (7.6%)	6 (9.8%)	49 (9.0%)	57 (8.5%)
	2	1	2 (1.6%)	4 (3.4%)	5 (8.5%)	1 (1.7%)	2 (3.2%)	2 (3.1%)	1 (1.7%)	3 (4.5%)	1 (1.6%)	19 (3.5%)	21 (3.1%)
		2	75 (59.5%)	79 (68.1%)	36 (61.0%)	34 (58.6%)	41 (66.1%)	35 (53.8%)	39 (65.0%)	41 (62.1%)	36 (59.0%)	341 (62.3%)	416 (61.8%)
		3a	10 (7.9%)	8 (6.9%)	5 (8.5%)	3 (5.2%)	5 (8.1%)	7 (10.8%)	4 (6.7%)	4 (6.1%)	2 (3.3%)	38 (6.9%)	48 (7.1%)

Parameter Week	Baseline	Post-baseline	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
	3a	2	7 (5.6%)	4 (3.4%)	0	3 (5.2%)	1 (1.6%)	1 (1.5%)	4 (6.7%)	1 (1.5%)	2 (3.3%)	16 (2.9%)	23 (3.4%)
		3a	11 (8.7%)	3 (2.6%)	2 (3.4%)	1 (1.7%)	1 (1.6%)	4 (6.2%)	3 (5.0%)	2 (3.0%)	0	16 (2.9%)	27 (4.0%)
LOCF Endpoint	m		130	122	62	61	63	65	61	69	63	566	696
	1	1	14 (10.8%)	10 (8.2%)	6 (9.7%)	10 (16.4%)	7 (11.1%)	11 (16.9%)	2 (3.3%)	10 (14.5%)	15 (23.8%)	71 (12.5%)	85 (12.2%)
		2	8 (6.2%)	11 (9.0%)	5 (8.1%)	8 (13.1%)	6 (9.5%)	5 (7.7%)	7 (11.5%)	5 (7.2%)	6 (9.5%)	53 (9.4%)	61 (8.8%)
	2	1	2 (1.5%)	4 (3.3%)	5 (8.1%)	1 (1.6%)	2 (3.2%)	2 (3.1%)	1 (1.6%)	4 (5.8%)	1 (1.6%)	20 (3.5%)	22 (3.2%)
		2	77 (59.2%)	80 (65.6%)	39 (62.9%)	35 (57.4%)	41 (65.1%)	35 (53.8%)	39 (63.9%)	43 (62.3%)	36 (57.1%)	348 (61.5%)	425 (61.1%)
		3a	11 (8.5%)	9 (7.4%)	5 (8.1%)	3 (4.9%)	5 (7.9%)	7 (10.8%)	5 (8.2%)	4 (5.8%)	3 (4.8%)	41 (7.2%)	52 (7.5%)
	3a	2	7 (5.4%)	4 (3.3%)	0	3 (4.9%)	1 (1.6%)	1 (1.5%)	4 (6.6%)	1 (1.4%)	2 (3.2%)	16 (2.8%)	23 (3.3%)
		3a	11 (8.5%)	4 (3.3%)	2 (3.2%)	1 (1.6%)	1 (1.6%)	4 (6.2%)	3 (4.9%)	2 (2.9%)	0	17 (3.0%)	28 (4.0%)

- Abbreviations: LOCF, Last Observation Carried Forward; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2, CKD Stage 3b includes subjects with eGFR >= 30 to < 45 mL/min/1.73m2.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- m in row headings is the total number of subjects with both baseline and the corresponding visit values available, and is used as the denominator to calculate percentages.

2.7.4.3.1.2.2.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

腎機能区分別の被験者数を評価時点ごと及びベースラインの腎機能区分ごとに集計したシフトテーブルを表 2.7.4.3-7 に、eGFR の Week 16 のベースラインからの変化量を 2.7.4.7 項付録 Table S-105 に示す。治験期間を通していずれの群でも eGFR に臨床的に意義のある変動はなかった。

LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合（被験者数、以下同様）は、ベースラインの腎機能区分が CKD 1 であった被験者（LOCF endpoint では CKD 2）でプラセボ群、イメグリミン群の順に（以下同順）2.9%（3/104 名）、3.7%（4/108 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 6.7%（7/104 名）、6.5%（7/108 名）であった。

表 2.7.4.3-7　Shift of Laboratory Findings of eGFR (CKD Stage) in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

Parameter Week	Baseline	Post-baseline	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
eGFR (CKD Stage)				
Week 16	m		104	108
	1	1	11 (10.6%)	12 (11.1%)
		2	3 (2.9%)	4 (3.7%)
	2	1	3 (2.9%)	6 (5.6%)
		2	80 (76.9%)	79 (73.1%)
		3a	7 (6.7%)	7 (6.5%)
LOCF Endpoint	m		104	108
	1	1	11 (10.6%)	12 (11.1%)
		2	3 (2.9%)	4 (3.7%)
	2	1	3 (2.9%)	6 (5.6%)
		2	80 (76.9%)	79 (73.1%)
		3a	7 (6.7%)	7 (6.5%)

- Abbreviations: LOCF, Last Observation Carried Forward; bid, Twice a day; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- m in row headings is the total number of subjects with both baseline and the corresponding visit values available, and is used as the denominator to calculate percentages.

(2) 長期投与（52 週）

腎機能区分別の被験者数を評価時点ごと及びベースラインの腎機能区分ごとに集計したシフトテーブルを表 2.7.4.3-8 に、eGFR のすべての評価時点のベースラインからの変化量

を 2.7.4.7 項付録 Table S-109 に示す。治験期間を通して eGFR に臨床的に意義のある変動はなかった。

LOCF endpoint の腎機能区分がベースラインより悪化した被験者の割合（被験者数、以下同様）は、ベースラインの腎機能区分が CKD 1 であった被験者（LOCF endpoint では CKD 2）で 6.3%（13/207 名）、ベースラインの腎機能区分が CKD 2 の被験者（LOCF endpoint では CKD 3a）で 6.3%（13/207 名）であった。ベースラインの腎機能区分が CKD 3a の被験者で、LOCF endpoint の腎機能区分がベースラインより悪化した被験者はいなかった。

表 2.7.4.3-8　Shift of Laboratory Findings of eGFR (CKD Stage) in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

Parameter Week	Baseline	Post-baseline	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
eGFR (CKD Stage)					
Week 16	m		0	108	108
	1	1	.	12 (11.1%)	12 (11.1%)
		2	.	4 (3.7%)	4 (3.7%)
	2	1	.	6 (5.6%)	6 (5.6%)
		2	.	79 (73.1%)	79 (73.1%)
		3a	.	7 (6.5%)	7 (6.5%)
Week 20	m		99	0	99
	1	1	9 (9.1%)	.	9 (9.1%)
		2	4 (4.0%)	.	4 (4.0%)
	2	1	7 (7.1%)	.	7 (7.1%)
		2	67 (67.7%)	.	67 (67.7%)
		3a	5 (5.1%)	.	5 (5.1%)
	3a	2	2 (2.0%)	.	2 (2.0%)
		3a	5 (5.1%)	.	5 (5.1%)
Week 36	m		98	107	205
	1	1	6 (6.1%)	10 (9.3%)	16 (7.8%)
		2	7 (7.1%)	6 (5.6%)	13 (6.3%)
	2	1	3 (3.1%)	8 (7.5%)	11 (5.4%)
		2	71 (72.4%)	75 (70.1%)	146 (71.2%)
		3a	4 (4.1%)	8 (7.5%)	12 (5.9%)
	3a	2	3 (3.1%)	0	3 (1.5%)
		3a	4 (4.1%)	0	4 (2.0%)
Week 52	m		0	107	107
	1	1	.	10 (9.3%)	10 (9.3%)
		2	.	6 (5.6%)	6 (5.6%)
	2	1	.	7 (6.5%)	7 (6.5%)

Parameter Week	Baseline	Post-baseline	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
		2	.	75 (70.1%)	75 (70.1%)
		3a	.	9 (8.4%)	9 (8.4%)
LOCF Endpoint	m		99	108	207
	1	1	6 (6.1%)	10 (9.3%)	16 (7.7%)
		2	7 (7.1%)	6 (5.6%)	13 (6.3%)
	2	1	4 (4.0%)	7 (6.5%)	11 (5.3%)
		2	71 (71.7%)	76 (70.4%)	147 (71.0%)
		3a	4 (4.0%)	9 (8.3%)	13 (6.3%)
	3a	2	3 (3.0%)	0	3 (1.4%)
		3a	4 (4.0%)	0	4 (1.9%)

- Abbreviations: LOCF, Last Observation Carried Forward; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- m in row headings is the total number of subjects with both baseline and the corresponding visit values available, and is used as the denominator to calculate percentages.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.

2.7.4.4　バイタルサイン、身体的所見及び安全性に関連する他の観察項目

2.7.4.4.1　バイタルサイン（血圧及び心拍数）

2.7.4.4.1.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

血圧及び心拍数の Week 24 のベースラインからの変化量を 2.7.4.7 項付録 Table S-565 に、すべての評価時点のベースラインからの変化量を 2.7.4.7 項付録 Table S-566 に示す。治験期間を通していずれの群でも血圧及び心拍数に臨床的に意義のある変動はなかった。

収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）1.712±11.4514、2.507±12.1959、2.554±12.6985、−0.947±13.2644 であった。拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は、0.958±7.3221、0.640±8.4175、1.400±8.6607、−2.533±8.9734 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は、0.5±7.68、1.6±8.18、0.3±9.39、0.2±8.52 であった。

2.7.4.4.1.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

血圧及び心拍数の Week 24 及び Week 52 のベースラインからの変化量を 2.7.4.7 項付録

Table S-567 に、すべての評価時点のベースラインからの変化量を 2.7.4.7 項付録 Table S-568 に示す。治験期間を通していずれの群でも血圧及び心拍数に臨床的に意義のある変動はなかった。

- 単独療法群では、収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は−0.018±10.9859、拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は−0.326±6.9502 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は、1.2±9.31 であった。
- SU 併用療法群では、収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.767±11.4321、拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.197±7.3650 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.4±7.74 であった。
- GLIN 併用療法群では、収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 1.417±10.3534、拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.755±5.9033 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.3±7.94 であった。
- BIG 併用療法群では、収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.433±10.3680、拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.173±6.6794 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は−1.0±7.43 であった。
- AGI 併用療法群では、収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 1.750±11.4729、拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.489±6.9993 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 1.2±10.31 であった。
- TZD 併用療法群では、収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.868±11.5022、拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は−0.323±8.2404 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 1.3±9.09 であった。
- DPP4-I 併用療法群では、収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 1.143±13.1303、拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は−0.201±8.8671 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.4±6.52 であった。
- GLP1-RA 併用療法群では、収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は−1.552±12.1218、拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は−1.776±6.7522 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.3±6.79 であった。
- SGLT2-I 併用療法群では、収縮期血圧（mmHg）の LOCF endpoint のベースラインか

らの変化量（平均値±SD）は 0.027±11.5491、拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は−0.063±6.5717 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は−1.8±7.53 であった。

2.7.4.4.1.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

血圧及び心拍数の Week 16 のベースラインからの変化量を 2.7.4.7 項付録 Table S-569 に、すべての評価時点のベースラインからの変化量を 2.7.4.7 項付録 Table S-570 に示す。治験期間を通していずれの群でも血圧及び心拍数に臨床的に意義のある変動はなかった。

収縮期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は、プラセボ群、イメグリミン群の順に（以下同順）−0.327±10.1950、2.735±11.3795 であった。拡張期血圧（mmHg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.317±6.5353、1.136±8.0318 であった。心拍数（beats/min）の LOCF endpoint のベースラインからの変化量（平均値±SD）は 0.2±8.85、−0.7±7.39 であった。

(2) 長期投与（52 週）

血圧及び心拍数の Week 36 及び Week 52 のベースラインからの変化量を 2.7.4.7 項付録 Table S-571 に、すべての評価時点のベースラインからの変化量を 2.7.4.7 項付録 Table S-572 に示す。治験期間を通して血圧及び心拍数に臨床的に意義のある変動はなかった。

収縮期血圧（mmHg）のベースラインからの変化量（平均値±SD）は、Week 36、Week 52、LOCF endpoint の順に（以下同順）0.905±10.9151、1.236±11.8689、0.994±11.0358 であった。拡張期血圧（mmHg）のベースラインからの変化量（平均値±SD）は、1.154±7.0477、0.903±7.7347、0.815±7.0975 であった。心拍数（beats/min）のベースラインからの変化量（平均値±SD）は、0.2±7.59、0.4±7.64、0.4±7.71 であった。

2.7.4.4.2　体重

2.7.4.4.2.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

体重の Week 24 のベースラインからの変化量を表 2.7.4.4-1 に、すべての評価時点のベースラインからの変化量を 2.7.4.7 項付録 Table S-099 に示す。治験期間を通していずれの群でも体重に臨床的に意義のある変動はなかった。体重（kg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）−0.47±1.678、0.11±2.054、−0.21±1.552、−0.03±1.972 であった。

表 2.7.4.4-1　Summary of Change from Baseline in Weight (kg) to Week 24 in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Weight (kg)					
Placebo (N = 182)					
Baseline	182	69.74 (13.668)	67.90 [40.2, 113.2]		
Week 24	167	69.56 (13.518)	68.20 [39.7, 112.4]	-0.41 (1.653)	-0.20 [-11.9, 3.2]
LOCF Endpoint	182	69.27 (13.483)	67.90 [39.7, 112.4]	-0.47 (1.678)	-0.25 [-11.9, 3.2]
Imeglimin 500 mg bid (N = 75)					
Baseline	75	68.51 (15.183)	67.00 [35.6, 115.8]		
Week 24	70	67.74 (14.683)	65.75 [37.0, 115.0]	0.20 (2.037)	0.25 [-6.3, 4.9]
LOCF Endpoint	75	68.62 (14.802)	66.20 [37.0, 115.0]	0.11 (2.054)	0.20 [-6.3, 4.9]
Imeglimin 1000 mg bid (N = 180)					
Baseline	180	69.65 (13.548)	68.90 [42.5, 124.0]		
Week 24	169	69.35 (13.811)	67.90 [40.9, 123.7]	-0.20 (1.572)	-0.20 [-6.9, 5.8]
LOCF Endpoint	180	69.44 (13.731)	68.40 [40.9, 123.7]	-0.21 (1.552)	-0.20 [-6.9, 5.8]
Imeglimin 1500 mg bid (N = 75)					
Baseline	75	73.13 (15.486)	73.00 [41.5, 122.3]		
Week 24	67	74.59 (15.903)	74.90 [40.4, 125.2]	0.07 (2.028)	0.00 [-3.6, 4.8]
LOCF Endpoint	75	73.10 (16.025)	72.30 [40.4, 125.2]	-0.03 (1.972)	0.00 [-3.6, 4.8]

- Abbreviations: bid, Twice a day; SD, standard deviation; LOCF, Last Observation Carried Forward

2.7.4.4.2.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

体重の Week 52 のベースラインからの変化量を表 2.7.4.4-2 に、すべての評価時点のベースラインからの変化量を 2.7.4.7 項付録 Table S-103 に示す。治験期間を通していずれの群でも体重に臨床的に意義のある変動はなかった。体重（kg）の LOCF endpoint のベースラインからの変化量は、単独療法で−0.78±2.451（平均値±SD、以下同様）、SU 併用療法群で 0.28±2.077、GLIN 併用療法群で−0.39±4.025、BIG 併用療法群で−0.07±1.956、AGI 併用療法群−0.65±3.184、TZD 併用療法群で 0.79±2.786、DPP4-I 併用療法群で−0.07±1.832、GLP1-RA 併用療法群で−0.30±2.356、SGLT2-I 併用療法群で−0.10±2.008 であった。

表 2.7.4.4-2　Summary of Change from Baseline in Weight (kg) to Week 52 in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Weight (kg)					
Imeglimin (N = 134)					
Baseline	134	71.02 (13.785)	69.10 [44.6, 129.0]		
Week 24	130	70.27 (13.689)	68.03 [43.5, 133.0]	-0.67 (2.103)	-0.70 [-7.5, 4.2]
Week 52	126	70.07 (13.846)	68.25 [43.1, 131.0]	-0.71 (2.410)	-0.60 [-9.2, 5.4]
LOCF Endpoint	134	70.24 (14.050)	68.25 [43.1, 131.0]	-0.78 (2.451)	-0.65 [-9.2, 5.4]
Imeglimin + SU (N = 127)					
Baseline	127	70.64 (13.761)	67.80 [44.3, 114.6]		
Week 24	122	71.32 (13.739)	69.05 [44.1, 116.0]	0.42 (1.613)	0.60 [-5.9, 4.2]
Week 52	116	70.89 (13.554)	68.65 [43.9, 114.6]	0.46 (1.912)	0.25 [-4.4, 6.0]
LOCF Endpoint	127	70.92 (13.796)	68.50 [43.9, 114.6]	0.28 (2.077)	0.20 [-8.2, 6.0]
Imeglimin + GLIN (N = 64)					
Baseline	64	68.28 (13.850)	68.30 [43.3, 104.7]		
Week 24	62	67.95 (13.904)	66.95 [42.2, 102.6]	0.09 (2.836)	0.60 [-15.2, 4.9]
Week 52	59	67.62 (13.718)	65.90 [42.5, 101.6]	-0.43 (4.169)	0.30 [-27.1, 3.7]
LOCF Endpoint	64	67.89 (13.593)	66.35 [42.5, 101.6]	-0.39 (4.025)	0.30 [-27.1, 3.7]
Imeglimin + BIG (N = 64)					
Baseline	64	72.25 (11.451)	72.30 [46.9, 99.1]		
Week 24	63	71.54 (12.170)	69.90 [46.1, 99.7]	-0.70 (1.996)	-0.60 [-6.0, 3.7]
Week 52	58	72.47 (11.686)	72.80 [46.1, 100.2]	-0.08 (1.911)	0.00 [-4.4, 4.6]
LOCF Endpoint	64	72.18 (11.944)	72.10 [46.1, 100.2]	-0.07 (1.956)	-0.15 [-4.4, 4.6]

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Imeglimin + AGI (N = 64)					
Baseline	64	72.62 (16.757)	68.55 [46.6, 132.8]		
Week 24	63	72.56 (17.510)	68.80 [44.4, 134.0]	-0.05 (2.020)	0.20 [-6.9, 4.0]
Week 52	62	71.78 (16.636)	69.25 [45.2, 132.2]	-0.60 (3.207)	-0.35 [-17.5, 4.9]
LOCF Endpoint	64	71.97 (16.469)	69.60 [45.2, 132.2]	-0.65 (3.184)	-0.40 [-17.5, 4.9]
Imeglimin + TZD (N = 65)					
Baseline	65	75.57 (16.133)	74.00 [44.2, 117.2]		
Week 24	65	76.17 (16.639)	74.10 [45.0, 120.6]	0.60 (2.255)	0.60 [-10.3, 3.9]
Week 52	65	76.37 (16.781)	74.85 [46.8, 123.3]	0.79 (2.786)	0.90 [-10.1, 6.3]
LOCF Endpoint	65	76.37 (16.781)	74.85 [46.8, 123.3]	0.79 (2.786)	0.90 [-10.1, 6.3]
Imeglimin + DPP4-I (N = 63)					
Baseline	63	64.88 (12.882)	63.00 [45.4, 117.4]		
Week 24	61	64.74 (13.505)	62.50 [42.7, 118.7]	-0.05 (1.829)	-0.20 [-4.3, 4.0]
Week 52	60	64.76 (13.244)	62.65 [42.4, 117.3]	-0.01 (1.809)	0.10 [-4.3, 5.4]
LOCF Endpoint	63	64.82 (13.005)	62.40 [42.4, 117.3]	-0.07 (1.832)	0.10 [-4.3, 5.4]
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	70.85 (15.130)	72.60 [39.0, 119.2]		
Week 24	69	71.05 (15.020)	73.40 [38.6, 121.0]	-0.04 (2.289)	-0.20 [-5.7, 6.1]
Week 52	67	70.85 (14.949)	72.00 [39.9, 119.0]	-0.34 (2.378)	-0.40 [-7.5, 4.6]
LOCF Endpoint	70	70.55 (14.918)	71.60 [39.9, 119.0]	-0.30 (2.356)	-0.35 [-7.5, 4.6]
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	72.76 (16.512)	70.70 [41.2, 129.8]		
Week 24	63	73.02 (16.532)	71.10 [41.5, 132.4]	0.26 (1.578)	0.30 [-5.9, 4.0]
Week 52	62	73.03 (16.148)	71.50 [41.3, 129.2]	-0.04 (1.973)	0.15 [-7.5, 3.9]
LOCF Endpoint	63	72.66 (16.278)	71.50 [41.3, 129.2]	-0.10 (2.008)	0.10 [-7.5, 3.9]

- Abbreviations: SD, standard deviation; LOCF, Last Observation Carried Forward; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".

2.7.4.4.2.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

体重の Week 16 のベースラインから変化量を表 2.7.4.4-3 に、すべての評価時点のベースラインからの変化量を 2.7.4.7 項付録 Table S-107 に示す。治験期間を通していずれの群でも体重に臨床的に意義のある変動はなかった。体重（kg）の LOCF endpoint のベースラインからの変化量（平均値±SD）は、プラセボ群、イメグリミン群の順に−0.18±1.484、0.48±1.472 であった。

表 2.7.4.4-3　Summary of Change from Baseline in Weight (kg) to Week 16 in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Weight (kg)					
Placebo + Insulin (N = 107)					
Baseline	107	67.54 (11.816)	66.90 [44.2, 106.2]		
Week 16	104	67.02 (11.406)	66.50 [43.4, 102.9]	-0.23 (1.393)	-0.10 [-5.3, 2.9]
LOCF Endpoint	106	67.05 (11.301)	66.75 [43.4, 102.9]	-0.18 (1.484)	-0.10 [-5.3, 5.4]
Imeglimin 1000 mg bid + Insulin (N = 108)					
Baseline	108	67.13 (12.266)	65.40 [41.8, 104.1]		
Week 16	108	67.61 (12.334)	66.55 [41.2, 104.1]	0.48 (1.472)	0.70 [-5.9, 3.7]
LOCF Endpoint	108	67.61 (12.334)	66.55 [41.2, 104.1]	0.48 (1.472)	0.70 [-5.9, 3.7]

- Abbreviations: bid, Twice a day; SD, standard deviation; LOCF, Last Observation Carried Forward

(2) 長期投与（52 週）

体重の Week 36 及び Week 52 のベースラインから変化量を表 2.7.4.4-4 に、すべての評価時点のベースラインからの変化量（平均値±SD）を 2.7.4.7 項付録 Table S-111 に示す。治験期間を通していずれの群でも体重に臨床的に意義のある変動はなかった。体重（kg）のベースラインからの変化量は、Week 36、Week 52、LOCF endpoint の順に 0.68±1.957、0.64±2.401、0.60±2.128 であった。

表 2.7.4.4-4　Summary of Change from Baseline in Weight (kg) to Week 52 in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

Parameter	Observed			Change from baseline	
Treatment Visit	n	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
Weight (kg)					
Placebo/Imeglimin + Insulin (N = 101)					
Baseline	101	66.65 (10.991)	66.30 [43.4, 97.8]		
Week 36	98	67.32 (11.783)	67.70 [43.4, 102.4]	0.56 (1.823)	0.50 [-3.6, 5.8]
LOCF Endpoint	101	67.19 (11.651)	67.20 [43.4, 102.4]	0.54 (1.804)	0.50 [-3.6, 5.8]
Imeglimin/Imeglimin + Insulin (N = 108)					
Baseline	108	67.13 (12.266)	65.40 [41.8, 104.1]		
Week 36	108	67.91 (12.161)	66.55 [41.5, 101.2]	0.78 (2.074)	1.00 [-8.2, 6.5]
Week 52	107	67.82 (12.183)	67.30 [41.7, 101.9]	0.64 (2.401)	0.90 [-6.1, 8.2]
LOCF Endpoint	108	67.79 (12.131)	67.15 [41.7, 101.9]	0.66 (2.399)	0.90 [-6.1, 8.2]
Imeglimin + Insulin Total (N = 209)					
Baseline	209	66.90 (11.642)	66.10 [41.8, 104.1]		
Week 36	206	67.63 (11.957)	67.30 [41.5, 102.4]	0.68 (1.957)	0.80 [-8.2, 6.5]
Week 52	107	67.82 (12.183)	67.30 [41.7, 101.9]	0.64 (2.401)	0.90 [-6.1, 8.2]
LOCF Endpoint	209	67.50 (11.876)	67.20 [41.7, 102.4]	0.60 (2.128)	0.60 [-6.1, 8.2]

- Abbreviations: SD, standard deviation; LOCF, Last Observation Carried Forward
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.

2.7.4.4.3　心電図

治験責任医師又は治験分担医師による心電図チャートの判定結果の推移をシフトテーブルで評価し、ICH E14 ガイドライン等を参考に設定した基準を超える値を顕著な異常値として評価した。

2.7.4.4.3.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

心電図検査で顕著な異常値を示した被験者の割合を表 2.7.4.4-5 に、治験責任医師又は治験分担医師による心電図所見の正異判定のシフトテーブルを 2.7.4.7 項付録 Table S-185 に示す。治験薬投与後に臨床的に意義のある変動がみられた被験者は、Week 24 及び LOCF endopoint で各 1 名（1500 mg bid 群）であった。そのほかは治験期間を通していずれの群で

も心電図所見に臨床的に意義のある変動はなかった。

QTcF が 450 msec 超となった被験者の割合（被験者数、以下同様）はプラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に 6.6%（12/181 名）、20.0%（15/75 名）、10.6%（19/180 名）、20.0%（15/75 名）であった。QTcF が 480 msec 超となった被験者は 0.6%（1/181 名）、1.3%（1/75 名）、1.7%（3/180 名）、0%で、500 msec 超となった被験者はいなかった。QTcF が 30 msec 超増加した被験者の割合は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に 5.0%（9/181 名）、12.0%（9/75 名）、8.3%（15/180 名）、12.0%（9/75 名）であった。QTcF が 60 msec 超増加したのはプラセボ群の被験者のみで、その割合は 0.6%（1/181 名）であった。

ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）6.6%（12/181 名）、1.3%（1/75 名）、6.1%（11/180 名）、10.7%（8/75 名）であった。PR 間隔が 30 msec 以上増加した被験者の割合は、4.4%（8/181 名）、10.7%（8/75 名）、7.2%（13/180 名）、10.7%（8/75 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は、8.3%（15/181 名）、4.0%（3/75 名）、5.6%（10/180 名）、5.3%（4/75 名）であった。

表 2.7.4.4-5　Summary of Markedly Abnormal Post-Baseline Electrocardiogram Parameters in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

Parameter Criteria	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
m	181	75	180	75	330
QTcF interval					
> 450 msec	12 (6.6%)	15 (20.0%)	19 (10.6%)	15 (20.0%)	49 (14.8%)
> 480 msec	1 (0.6%)	1 (1.3%)	3 (1.7%)	0	4 (1.2%)
> 500 msec	0	0	0	0	0
Increase > 30 msec	9 (5.0%)	9 (12.0%)	15 (8.3%)	9 (12.0%)	33 (10.0%)
Increase > 60 msec	1 (0.6%)	0	0	0	0
<= 340 msec	0	0	0	0	0
PR interval					
>= 200 msec	29 (16.0%)	5 (6.7%)	26 (14.4%)	15 (20.0%)	46 (13.9%)
Shift < 200 to >= 200 msec	12 (6.6%)	1 (1.3%)	11 (6.1%)	8 (10.7%)	20 (6.1%)
Increase >= 30 msec	8 (4.4%)	8 (10.7%)	13 (7.2%)	8 (10.7%)	29 (8.8%)
QRS duration					
>= 120 msec	15 (8.3%)	3 (4.0%)	10 (5.6%)	4 (5.3%)	17 (5.2%)

- Abbreviations: bid, Twice a day; QTcF, QT corrected by Fridericia formula
- m is the total number of patients with at least one post-baseline value.
- n and % are respectively the number and percentage of patients meeting the specified criteria at least once post-baseline.
- "Shift" is the shift from baseline to post-baseline.

2.7.4.4.3.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

心電図検査で顕著な異常値を示した被験者の割合を表 2.7.4.4-6 に、治験責任医師又は治験分担医師による心電図所見の正異判定のシフトテーブルを 2.7.4.7 項付録 Table S-193 に示す。

- 単独療法群で治験薬投与後に臨床的に意義のある変動がみられた被験者は、Week 12、Week 40、Week 52 及び LOCF endpoint で各 1 名であった。そのほかは治験期間を通して心電図所見に臨床的に意義のある変動はなかった。QTcF が 450 msec 超となった被験者の割合（被験者数、以下同様）は 6.0%（8/133 名）で、480 msec 超となった被験者はいなかった。QTcF が 30 msec 超増加した被験者の割合は 4.5%（6/133 名）で、60 msec 超増加した被験者の割合は 0.8%（1/133 名）であった。ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は 4.5%（6/133 名）で、PR 間隔が 30 msec 以上増加した被験者の割合は 3.8%（5/133 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は 5.3%（7/133 名）であった。
- SU 併用療法群で治験薬投与後に臨床的に意義のある変動がみられた被験者は、Week 12、Week 24 及び Week 52 で各 1 名、Week 40 及び LOCF endpoint で各 2 名であった。そのほかは治験期間を通して心電図所見に臨床的に意義のある変動はなかった。QTcF が 450 msec 超となった被験者の割合は 8.8%（11/125 名）、480 msec 超となった被験者の割合は 1.6%（2/125 名）、500 msec 超となった被験者の割合は 0.8%（1/125 名）であった。QTcF が 30 msec 超増加した被験者の割合は 4.0%（5/125 名）で、60 msec 超増加した被験者の割合は 0.8%（1/125 名）であった。ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は 2.4%（3/125 名）で、PR 間隔が 30 msec 以上増加した被験者はいなかった。QRS 間隔が 120 msec 以上となった被験者の割合は 8.8%（11/125 名）であった。
- GLIN 併用療法群では、治験期間を通して心電図所見に臨床的に意義のある変動はなかった。QTcF が 450 msec 超となった被験者の割合は 4.7%（3/64 名）、480 msec 超となった被験者の割合は 1.6%（1/64 名）、500 msec 超となった被験者の割合は 1.6%（1/64 名）であった。QTcF が 30 msec 超増加した被験者の割合は 3.1%（2/64 名）で、60 msec 超増加した被験者の割合は 1.6%（1/64 名）であった。ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者はいなかったが、PR 間隔が 30 msec 以上増加した被験者の割合は 3.1%（2/64 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は 3.1%（2/64 名）であった。
- BIG 併用療法群で治験薬投与後に臨床的に意義のある変動がみられた被験者は、Week 52 及び LOCF endpoint で各 1 名であった。そのほかは治験期間を通して心電図所見に臨床的に意義のある変動はなかった。QTcF が 450 msec 超となった被験者の割合は 10.9%（7/64 名）、480 msec 超となった被験者の割合は 1.6%（1/64 名）で、500 msec

超となった被験者はいなかった。QTcF が 30 msec 超増加した被験者の割合は 4.7%（3/64 名）で、60 msec 超増加した被験者はいなかった。ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は 4.7%（3/64 名）で、PR 間隔が 30 msec 以上増加した被験者の割合は 3.1%（2/64 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は 6.3%（4/64 名）であった。

- AGI 併用療法群では、治験期間を通して心電図所見に臨床的に意義のある変動はなかった。QTcF が 450 msec 超となった被験者の割合は 4.7%（3/64 名）、480 msec 超となった被験者の割合は 1.6%（1/64 名）、500 msec 超となった被験者の割合は 1.6%（1/64 名）であった。QTcF が 30 msec 超増加した被験者の割合は 4.7%（3/64 名）で、60 msec 超増加した被験者の割合は 1.6%（1/64 名）であった。ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は 10.9%（7/64 名）で、PR 間隔が 30 msec 以上増加した被験者の割合は 1.6%（1/64 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は 4.7%（3/64 名）であった。
- TZD 併用療法群で治験薬投与後に臨床的に意義のある変動がみられた被験者は、Week 40、Week 52 及び LOCF endopoint で各 1 名であった。そのほかは治験期間を通して心電図所見に臨床的に意義のある変動はなかった。QTcF が 450 msec 超となった被験者の割合は 4.6%（3/65 名）で、480 msec 超となった被験者はいなかった。QTcF が 30 msec 超増加した被験者の割合は 4.6%（3/65 名）で、60 msec 超増加した被験者はいなかった。ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は 7.7%（5/65 名）で、PR 間隔が 30 msec 以上増加した被験者はいなかった。QRS 間隔が 120 msec 以上となった被験者の割合は 6.2%（4/65 名）であった。
- DPP4-I 併用療法群で治験薬投与後に臨床的に意義のある変動がみられた被験者は、Week 40 で 1 名であった。そのほかは治験期間を通して心電図所見に臨床的に意義のある変動はなかった。QTcF が 450 msec 超となった被験者の割合は 14.3%（9/63 名）で、480 msec 超となった被験者の割合は 1.6%（1/63 名）で、500 msec 超となった被験者はいなかった。QTcF が 30 msec 超増加した被験者の割合は 4.8%（3/63 名）で、60 msec 超増加した被験者の割合は 1.6%（1/63 名）であった。ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は 4.8%（3/63 名）で、PR 間隔が 30 msec 以上増加した被験者の割合は 4.8%（3/63 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は 11.1%（7/63 名）であった。
- GLP1-RA 併用療法群で治験薬投与後に臨床的に意義のある変動がみられた被験者は、Week 40 で 1 名であった。そのほかは治験期間を通して心電図所見に臨床的に意義のある変動はなかった。QTcF が 450 msec 超となった被験者の割合は 8.6%（6/70 名）で、480 msec 超及び 500 msec 超となった被験者の割合は 2.9%（2/70 名）であった。QTcF が 30 msec 超増加した被験者の割合は 4.3%（3/70 名）で、60 msec 超増加した被験者の割合は 1.4%（1/70 名）であった。ベースラインの PR 間隔が 200 msec 未満

で治験薬投与後に 200 msec 以上へ変動した被験者の割合は 10.0%（7/70 名）で、PR 間隔が 30 msec 以上増加した被験者の割合は 4.3%（3/70 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は 5.7%（4/70 名）であった。

- SGLT2-I 併用療法群では、治験期間を通して心電図所見に臨床的に意義のある変動はなかった。QTcF が 450 msec 超となった被験者の割合は 12.7%（8/63 名）で、480 msec 超となった被験者の割合は 3.2%（2/63 名）で、500 msec 超となった被験者はいなかった。QTcF が 30 msec 超増加した被験者の割合は 6.3%（4/63 名）で、60 msec 超増加した被験者の割合は 1.6%（1/63 名）であった。ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は 9.5%（6/63 名）で、PR 間隔が 30 msec 以上増加した被験者の割合は 1.6%（1/63 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は 6.3%（4/63 名）であった。

表 2.7.4.4-6　Summary of Markedly Abnormal Post-Baseline Electrocardiogram Parameters in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

Parameter Criteria	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
m	133	125	64	64	64	65	63	70	63	578	711
QTcF interval											
> 450 msec	8 (6.0%)	11 (8.8%)	3 (4.7%)	7 (10.9%)	3 (4.7%)	3 (4.6%)	9 (14.3%)	6 (8.6%)	8 (12.7%)	50 (8.7%)	58 (8.2%)
> 480 msec	0	2 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	0	1 (1.6%)	2 (2.9%)	2 (3.2%)	10 (1.7%)	10 (1.4%)
> 500 msec	0	1 (0.8%)	1 (1.6%)	0	1 (1.6%)	0	0	2 (2.9%)	0	5 (0.9%)	5 (0.7%)
Increase > 30 msec	6 (4.5%)	5 (4.0%)	2 (3.1%)	3 (4.7%)	3 (4.7%)	3 (4.6%)	3 (4.8%)	3 (4.3%)	4 (6.3%)	26 (4.5%)	32 (4.5%)
Increase > 60 msec	1 (0.8%)	1 (0.8%)	1 (1.6%)	0	1 (1.6%)	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	6 (1.0%)	7 (1.0%)
<= 340 msec	0	0	0	0	0	0	0	0	0	0	0
PR interval											
>= 200 msec	18 (13.5%)	16 (12.8%)	3 (4.7%)	9 (14.1%)	24 (37.5%)	14 (21.5%)	7 (11.1%)	13 (18.6%)	9 (14.3%)	95 (16.4%)	113 (15.9%)
Shift < 200 to >= 200 msec	6 (4.5%)	3 (2.4%)	0	3 (4.7%)	7 (10.9%)	5 (7.7%)	3 (4.8%)	7 (10.0%)	6 (9.5%)	34 (5.9%)	40 (5.6%)
Increase >= 30 msec	5 (3.8%)	0	2 (3.1%)	2 (3.1%)	1 (1.6%)	0	3 (4.8%)	3 (4.3%)	1 (1.6%)	12 (2.1%)	17 (2.4%)
QRS duration											
>= 120 msec	7 (5.3%)	11 (8.8%)	2 (3.1%)	4 (6.3%)	3 (4.7%)	4 (6.2%)	7 (11.1%)	4 (5.7%)	4 (6.3%)	39 (6.7%)	46 (6.5%)

- Abbreviations: QTcF, QT corrected by Fridericia formula; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- m is the total number of patients with at least one post-baseline value.
- n and % are respectively the number and percentage of patients meeting the specified criteria at least once post-baseline.
- "Shift" is the shift from baseline to post-baseline.

2.7.4.4.3.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

心電図検査で顕著な異常値を示した被験者の割合を表 2.7.4.4-7 に、治験責任医師又は治験分担医師による心電図所見の正異判定のシフトテーブルを 2.7.4.7 項付録 Table S-201 に示す。治験薬投与後に臨床的に意義のある変動がみられた被験者は、Week 16 及び LOCF endopoint で各 1 名（プラセボ群）であった。そのほかは治験期間を通していずれの群でも心電図所見に臨床的に意義のある変動はなかった。

QTcF が 450 msec 超となった被験者の割合（被験者数、以下同様）は、プラセボ群、イメグリミン群の順に 9.4%（10/106 名）、2.8%（3/108 名）であった。QTcF が 480 msec 超となったのはプラセボ群の被験者のみで、その割合は 0.9%（1/106 名）であった。500 msec 超となった被験者はいなかった。QTcF が 30 msec 超増加した被験者の割合は、プラセボ群、イメグリミン群の順に 2.8%（3/106 名）、2.8%（3/108 名）であった。

ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は、プラセボ群、イメグリミン群の順に（以下同順）0.9%（1/106 名）、1.9%（2/108 名）で、PR 間隔が 30 msec 以上増加した被験者の割合は、0.9%（1/106 名）、0.9%（1/108 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は、6.6%（7/106 名）、7.4%（8/108 名）であった。

表 2.7.4.4-7　Summary of Markedly Abnormal Post-Baseline Electrocardiogram Parameters in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

Parameter Criteria	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
m	106	108
QTcF interval		
> 450 msec	10 (9.4%)	3 (2.8%)
> 480 msec	1 (0.9%)	0
> 500 msec	0	0
Increase > 30 msec	3 (2.8%)	3 (2.8%)
Increase > 60 msec	0	0
<= 340 msec	0	0
PR interval		
>= 200 msec	7 (6.6%)	13 (12.0%)
Shift < 200 to >= 200 msec	1 (0.9%)	2 (1.9%)
Increase >= 30 msec	1 (0.9%)	1 (0.9%)
QRS duration		
>= 120 msec	7 (6.6%)	8 (7.4%)

- Abbreviations: bid, Twice a day; QTcF, QT corrected by Fridericia formula
- m is the total number of patients with at least one post-baseline value.
- n and % are respectively the number and percentage of patients meeting the specified criteria at least once post-baseline.

- "Shift" is the shift from baseline to post-baseline.

(2) 長期投与（52 週）

心電図検査で顕著な異常値を示した被験者の割合を表 2.7.4.4-8 に、治験責任医師又は治験分担医師による心電図所見の正異判定のシフトテーブルを 2.7.4.7 項付録 Table S-209 に示す。治験薬投与後に臨床的に意義のある変動がみられた被験者は、Week 20、Week 36 及び LOCF endopoint で各 1 名であった。そのほかは治験期間を通して心電図所見に臨床的に意義のある変動はなかった。

QTcF が 450 msec 超となった被験者の割合は 8.7%（18/208 名）、480 msec 超となった被験者の割合は 0.5%（1/208 名）で、500 msec 超となった被験者はいなかった。QTcF が 30 msec 超増加した被験者の割合は 2.4%（5/208 名）、60 msec 超増加した被験者の割合は 0.5%（1/208 名）であった。

ベースラインの PR 間隔が 200 msec 未満で治験薬投与後に 200 msec 以上へ変動した被験者の割合は 4.3%（9/208 名）で、PR 間隔が 30 msec 以上増加した被験者の割合は 2.9%（6/208 名）であった。QRS 間隔が 120 msec 以上となった被験者の割合は 7.2%（15/208 名）であった。

表 2.7.4.4-8　Summary of Markedly Abnormal Post-Baseline Electrocardiogram Parameters in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

Parameter Criteria	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
m	100	108	208
QTcF interval			
> 450 msec	8 (8.0%)	10 (9.3%)	18 (8.7%)
> 480 msec	0	1 (0.9%)	1 (0.5%)
> 500 msec	0	0	0
Increase > 30 msec	0	5 (4.6%)	5 (2.4%)
Increase > 60 msec	0	1 (0.9%)	1 (0.5%)
<= 340 msec	0	0	0
PR interval			
>= 200 msec	11 (11.0%)	16 (14.8%)	27 (13.0%)
Shift < 200 to >= 200 msec	4 (4.0%)	5 (4.6%)	9 (4.3%)
Increase >= 30 msec	3 (3.0%)	3 (2.8%)	6 (2.9%)
QRS duration			
>= 120 msec	7 (7.0%)	8 (7.4%)	15 (7.2%)

- Abbreviations: QTcF, QT corrected by Fridericia formula
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group

in the double-blind and open-label periods.
- m is the total number of patients with at least one post-baseline value.
- n and % are respectively the number and percentage of patients meeting the specified criteria at least once post-baseline.
- "Shift" is the shift from baseline to post-baseline.

2.7.4.4.3.4　海外 QT 間隔検討試験：PXL008-016 試験（資料番号：5.3.4.1.01）

本剤の QT/QTc 間隔への影響評価のために、海外で健康被験者を対象にランダム化、プラセボ及び陽性対照、4 群 4 期クロスオーバー試験を実施した。本試験は、本剤 2250 mg（海外での臨床有効用量である 1500 mg bid の定常状態の C_{max} を単回投与で達成できると想定された用量）、本剤 6000 mg（臨床用量を上回る用量、単回投与での最大耐用量）、本剤のプラセボ、モキシフロキサシン 400 mg（陽性対照）をそれぞれ単回経口投与する 4 期で構成された。4 期のうち本剤及びプラセボを投与する期は二重盲検とし、モキシフロキサシンを投与する期は非盲検とした。55 名の被験者が組み入れられ、8 つの投与順序にランダムに割り当てられた。

ECG 解析対象集団は 2250 mg、6000 mg、プラセボ、モキシフロキサシンの順に 51 名、53 名、51 名、50 名であった。本剤 6000 mg に QT/QTc 間隔延長作用はなく、ΔΔQTcF の最大値は 2.9 msec、その両側 90%信頼区間の上限は 5.4 msec で、ICH E14 ガイドラインで規定された閾値（10 msec）未満であった。本剤 6000 mg で QT/QTc 間隔延長作用がみられなかったことから、本剤 2250 mg でも QT/QTc 間隔延長作用はないと考えられた。モキシフロキサシンの ΔΔQTcF の多重性を調整した信頼区間の下限が閾値である 5 msec を上回ったことから、本治験の分析感度が確認された。曝露量–反応関係の解析結果からも、本剤が QT/QTcF 間隔を延長させないことが裏付けられた。QTcF 以外の心電図パラメータの解析、カテゴリカル解析及び T 波の形態的解析でも、本剤が QT/QTc 間隔を延長させないことが示された。

2.7.4.5　特別な患者集団及び状況下における安全性

2.7.4.5.1　内因性要因

本剤の安全性に影響する内因性要因として、年齢、性別、腎機能、肝機能の影響を検討した。また、その他の内因性要因として BMI、ベースラインの HbA1c、2 型糖尿病罹病期間、糖尿病合併症、メタボリックシンドローム区分別の部分集団解析を実施した。

2.7.4.5.1.1　年齢

014 試験、018 試験及び 019 試験で本剤 1000 mg bid の単独療法を受けた被験者の年齢区分別の有害事象の発現割合（3 試験併合）を 2.7.4.7 項付録 Table S-218 に示す。

2.7.4.5.1.1.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

年齢区分別での有害事象の全般的な発現割合を表 2.7.4.5-1 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-162 に示す。いずれの試験も選択基準で年齢を 20 歳以上とした。

014 試験では上限を 75 歳としたため、500 mg bid 群及び 1500 mg bid 群では 75 歳以上の被験者は組み入れられなかった。プラセボ群及び 1000 mg bid 群でも 75 歳以上の被験者は少なかったため、65 歳未満と 65 歳以上の区分で評価した。いずれの群でも有害事象の発現割合に年齢区分で大きな違いはなかった。

表 2.7.4.5-1　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Age in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

TEAE Age	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Number of patients					
< 65 years	106	54	97	47	198
>= 65 years	76	21	83	28	132
< 75 years	169	75	171	75	321
>= 75 years	13	0	9	0	9
Any TEAE					
< 65 years	63 (59.4%)	40 (74.1%)	49 (50.5%)	37 (78.7%)	126 (63.6%)
>= 65 years	36 (47.4%)	11 (52.4%)	44 (53.0%)	18 (64.3%)	73 (55.3%)
< 75 years	93 (55.0%)	51 (68.0%)	86 (50.3%)	55 (73.3%)	192 (59.8%)
>= 75 years	6 (46.2%)	.	7 (77.8%)	.	7 (77.8%)
Treatment-related TEAE					
< 65 years	10 (9.4%)	4 (7.4%)	5 (5.2%)	11 (23.4%)	20 (10.1%)
>= 65 years	3 (3.9%)	0	4 (4.8%)	7 (25.0%)	11 (8.3%)
< 75 years	13 (7.7%)	4 (5.3%)	9 (5.3%)	18 (24.0%)	31 (9.7%)
>= 75 years	0	.	0	.	0
Severe TEAE					
< 65 years	0	0	3 (3.1%)	0	3 (1.5%)
>= 65 years	1 (1.3%)	0	3 (3.6%)	1 (3.6%)	4 (3.0%)
< 75 years	1 (0.6%)	0	5 (2.9%)	1 (1.3%)	6 (1.9%)
>= 75 years	0	.	1 (11.1%)	.	1 (11.1%)
TEAE leading to death					
< 65 years	0	0	0	0	0
>= 65 years	0	0	0	1 (3.6%)	1 (0.8%)
< 75 years	0	0	0	1 (1.3%)	1 (0.3%)
>= 75 years	0	.	0	.	0
Serious TEAE					
< 65 years	1 (0.9%)	0	3 (3.1%)	0	3 (1.5%)
>= 65 years	1 (1.3%)	0	5 (6.0%)	1 (3.6%)	6 (4.5%)
< 75 years	2 (1.2%)	0	6 (3.5%)	1 (1.3%)	7 (2.2%)
>= 75 years	0	.	2 (22.2%)	.	2 (22.2%)

TEAE Age	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
TEAE leading to treatment discontinuation					
< 65 years	8 (7.5%)	2 (3.7%)	3 (3.1%)	3 (6.4%)	8 (4.0%)
>= 65 years	6 (7.9%)	0	3 (3.6%)	2 (7.1%)	5 (3.8%)
< 75 years	13 (7.7%)	2 (2.7%)	5 (2.9%)	5 (6.7%)	12 (3.7%)
>= 75 years	1 (7.7%)	.	1 (11.1%)	.	1 (11.1%)
Hypoglycemia					
< 65 years	2 (1.9%)	4 (7.4%)	5 (5.2%)	4 (8.5%)	13 (6.6%)
>= 65 years	0	1 (4.8%)	0	0	1 (0.8%)
< 75 years	2 (1.2%)	5 (6.7%)	5 (2.9%)	4 (5.3%)	14 (4.4%)
>= 75 years	0	.	0	.	0
Lactic acidosis related TEAEs					
< 65 years	0	0	0	0	0
>= 65 years	0	0	0	0	0
< 75 years	0	0	0	0	0
>= 75 years	0	.	0	.	0
Cardiovascular-related TEAEs					
< 65 years	7 (6.6%)	2 (3.7%)	1 (1.0%)	3 (6.4%)	6 (3.0%)
>= 65 years	0	0	2 (2.4%)	3 (10.7%)	5 (3.8%)
< 75 years	7 (4.1%)	2 (2.7%)	3 (1.8%)	6 (8.0%)	11 (3.4%)
>= 75 years	0	.	0	.	0
Digestive Symptoms					
< 65 years	12 (11.3%)	10 (18.5%)	14 (14.4%)	14 (29.8%)	38 (19.2%)
>= 65 years	8 (10.5%)	1 (4.8%)	12 (14.5%)	10 (35.7%)	23 (17.4%)
< 75 years	20 (11.8%)	11 (14.7%)	25 (14.6%)	24 (32.0%)	60 (18.7%)
>= 75 years	0	.	1 (11.1%)	.	1 (11.1%)
Renal TEAEs					
< 65 years	1 (0.9%)	1 (1.9%)	1 (1.0%)	0	2 (1.0%)
>= 65 years	1 (1.3%)	0	1 (1.2%)	0	1 (0.8%)
< 75 years	2 (1.2%)	1 (1.3%)	2 (1.2%)	0	3 (0.9%)
>= 75 years	0	.	0	.	0
Hepatic TEAEs					
< 65 years	1 (0.9%)	1 (1.9%)	2 (2.1%)	2 (4.3%)	5 (2.5%)
>= 65 years	3 (3.9%)	0	0	1 (3.6%)	1 (0.8%)
< 75 years	4 (2.4%)	1 (1.3%)	2 (1.2%)	3 (4.0%)	6 (1.9%)
>= 75 years	0	.	0	.	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- Percentages are based on "Number of patients".

2.7.4.5.1.1.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

年齢区分別での有害事象の全般的な発現割合を表 2.7.4.5-2 に、有害事象ごとの発現割合

を 2.7.4.7 項付録 Table S-166 に示す。本試験では選択基準で年齢を 20 歳以上とした。いずれの群でも 75 歳以上の被験者は少なかったため、65 歳未満と 65 歳以上の区分で評価した。

- 単独療法群では、有害事象の発現割合に年齢区分で大きな違いはなかった。
- GLIN 併用療法群では、消化器症状の発現割合は年齢区分 65 歳未満、65 歳以上の順に（以下同順）26.2%、4.5%で、下痢の発現割合は 9.5%、0%であった。そのほかの有害事象の発現割合に年齢区分で大きな違いはなかった。
- TZD 併用療法群では、心血管関連事象の発現割合は年齢区分 65 歳未満、65 歳以上の順に（以下同順）6.8%、23.8%であった。洞性徐脈の発現割合は 0%、9.5%、高血圧の発現割合は 2.3%、9.5%であった。そのほかの有害事象の発現割合に年齢区分で大きな違いはなかった。
- SGLT2-I 併用療法群では、消化器症状の発現割合は年齢区分 65 歳未満、65 歳以上の順に（以下同順）15.6%、44.4%であった。悪心の発現割合は 4.4%、11.1%、胃炎の発現割合は 0%、11.1%、腹部膨満の発現割合は 0%、11.1%であった。そのほかの有害事象の発現割合に年齢区分で大きな違いはなかった。
- SU 併用療法群、BIG 併用療法群、AGI 併用療法群、DPP4-I 併用療法群及び GLP1-RA 併用療法群では、有害事象の発現割合に年齢区分で大きな違いはなかった。

表 2.7.4.5-2　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Age in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

TEAE Age	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Number of patients											
< 65 years	86	76	42	47	41	44	28	46	45	369	455
>= 65 years	48	51	22	17	23	21	35	24	18	211	259
< 75 years	127	122	61	61	62	61	58	67	61	553	680
>= 75 years	7	5	3	3	2	4	5	3	2	27	34
Any TEAE											
< 65 years	58 (67.4%)	60 (78.9%)	34 (81.0%)	35 (74.5%)	19 (46.3%)	34 (77.3%)	23 (82.1%)	35 (76.1%)	33 (73.3%)	273 (74.0%)	331 (72.7%)
>= 65 years	40 (83.3%)	42 (82.4%)	20 (90.9%)	13 (76.5%)	14 (60.9%)	16 (76.2%)	27 (77.1%)	21 (87.5%)	15 (83.3%)	168 (79.6%)	208 (80.3%)
< 75 years	92 (72.4%)	99 (81.1%)	51 (83.6%)	46 (75.4%)	31 (50.0%)	47 (77.0%)	47 (81.0%)	53 (79.1%)	46 (75.4%)	420 (75.9%)	512 (75.3%)
>= 75 years	6 (85.7%)	3 (60.0%)	3 (100.0%)	2 (66.7%)	2 (100.0%)	3 (75.0%)	3 (60.0%)	3 (100.0%)	2 (100.0%)	21 (77.8%)	27 (79.4%)
Treatment-related TEAE											
< 65 years	7 (8.1%)	16 (21.1%)	6 (14.3%)	15 (31.9%)	2 (4.9%)	3 (6.8%)	5 (17.9%)	3 (6.5%)	3 (6.7%)	53 (14.4%)	60 (13.2%)
>= 65 years	6 (12.5%)	11 (21.6%)	4 (18.2%)	9 (52.9%)	4 (17.4%)	3 (14.3%)	9 (25.7%)	5 (20.8%)	4 (22.2%)	49 (23.2%)	55 (21.2%)
< 75 years	11 (8.7%)	27 (22.1%)	10 (16.4%)	23 (37.7%)	5 (8.1%)	5 (8.2%)	12 (20.7%)	7 (10.4%)	6 (9.8%)	95 (17.2%)	106 (15.6%)
>= 75 years	2 (28.6%)	0	0	1 (33.3%)	1 (50.0%)	1 (25.0%)	2 (40.0%)	1 (33.3%)	1 (50.0%)	7 (25.9%)	9 (26.5%)
Severe TEAE											
< 65 years	0	2 (2.6%)	0	3 (6.4%)	0	0	1 (3.6%)	1 (2.2%)	1 (2.2%)	8 (2.2%)	8 (1.8%)
>= 65 years	2 (4.2%)	3 (5.9%)	0	1 (5.9%)	1 (4.3%)	1 (4.8%)	0	1 (4.2%)	0	7 (3.3%)	9 (3.5%)
< 75 years	2 (1.6%)	4 (3.3%)	0	4 (6.6%)	1 (1.6%)	0	1 (1.7%)	1 (1.5%)	1 (1.6%)	12 (2.2%)	14 (2.1%)
>= 75 years	0	1 (20.0%)	0	0	0	1 (25.0%)	0	1 (33.3%)	0	3 (11.1%)	3 (8.8%)

TEAE Age	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
TEAE leading to death											
< 65 years	0	0	0	0	0	0	0	0	0	0	0
>= 65 years	1 (2.1%)	0	0	0	0	0	0	0	0	0	1 (0.4%)
< 75 years	1 (0.8%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
>= 75 years	0	0	0	0	0	0	0	0	0	0	0
Serious TEAE											
< 65 years	1 (1.2%)	3 (3.9%)	1 (2.4%)	3 (6.4%)	3 (7.3%)	1 (2.3%)	2 (7.1%)	1 (2.2%)	3 (6.7%)	17 (4.6%)	18 (4.0%)
>= 65 years	3 (6.3%)	8 (15.7%)	0	1 (5.9%)	1 (4.3%)	3 (14.3%)	1 (2.9%)	4 (16.7%)	1 (5.6%)	19 (9.0%)	22 (8.5%)
< 75 years	4 (3.1%)	10 (8.2%)	1 (1.6%)	4 (6.6%)	4 (6.5%)	3 (4.9%)	3 (5.2%)	4 (6.0%)	4 (6.6%)	33 (6.0%)	37 (5.4%)
>= 75 years	0	1 (20.0%)	0	0	0	1 (25.0%)	0	1 (33.3%)	0	3 (11.1%)	3 (8.8%)
TEAE leading to treatment discontinuation											
< 65 years	2 (2.3%)	7 (9.2%)	1 (2.4%)	4 (8.5%)	1 (2.4%)	2 (4.5%)	3 (10.7%)	9 (19.6%)	1 (2.2%)	28 (7.6%)	30 (6.6%)
>= 65 years	1 (2.1%)	2 (3.9%)	0	3 (17.6%)	1 (4.3%)	2 (9.5%)	2 (5.7%)	6 (25.0%)	0	16 (7.6%)	17 (6.6%)
< 75 years	3 (2.4%)	9 (7.4%)	1 (1.6%)	7 (11.5%)	1 (1.6%)	3 (4.9%)	4 (6.9%)	14 (20.9%)	1 (1.6%)	40 (7.2%)	43 (6.3%)
>= 75 years	0	0	0	0	1 (50.0%)	1 (25.0%)	1 (20.0%)	1 (33.3%)	0	4 (14.8%)	4 (11.8%)
Hypoglycemia											
< 65 years	3 (3.5%)	12 (15.8%)	5 (11.9%)	3 (6.4%)	2 (4.9%)	2 (4.5%)	2 (7.1%)	2 (4.3%)	1 (2.2%)	29 (7.9%)	32 (7.0%)
>= 65 years	2 (4.2%)	9 (17.6%)	4 (18.2%)	3 (17.6%)	0	0	3 (8.6%)	0	3 (16.7%)	22 (10.4%)	24 (9.3%)
< 75 years	5 (3.9%)	21 (17.2%)	8 (13.1%)	5 (8.2%)	2 (3.2%)	2 (3.3%)	5 (8.6%)	2 (3.0%)	3 (4.9%)	48 (8.7%)	53 (7.8%)
>= 75 years	0	0	1 (33.3%)	1 (33.3%)	0	0	0	0	1 (50.0%)	3 (11.1%)	3 (8.8%)
Lactic acidosis related TEAEs											
< 65 years	0	1 (1.3%)	0	0	0	0	0	0	0	1 (0.3%)	1 (0.2%)
>= 65 years	0	1 (2.0%)	0	0	0	0	0	0	0	1 (0.5%)	1 (0.4%)
< 75 years	0	2 (1.6%)	0	0	0	0	0	0	0	2 (0.4%)	2 (0.3%)
>= 75 years	0	0	0	0	0	0	0	0	0	0	0

TEAE Age	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Cardiovascular-related TEAEs											
< 65 years	2 (2.3%)	4 (5.3%)	1 (2.4%)	4 (8.5%)	3 (7.3%)	3 (6.8%)	0	2 (4.3%)	3 (6.7%)	20 (5.4%)	22 (4.8%)
>= 65 years	2 (4.2%)	7 (13.7%)	2 (9.1%)	2 (11.8%)	3 (13.0%)	5 (23.8%)	3 (8.6%)	3 (12.5%)	1 (5.6%)	26 (12.3%)	28 (10.8%)
< 75 years	4 (3.1%)	11 (9.0%)	3 (4.9%)	5 (8.2%)	6 (9.7%)	7 (11.5%)	3 (5.2%)	3 (4.5%)	4 (6.6%)	42 (7.6%)	46 (6.8%)
>= 75 years	0	0	0	1 (33.3%)	0	1 (25.0%)	0	2 (66.7%)	0	4 (14.8%)	4 (11.8%)
Digestive Symptoms											
< 65 years	17 (19.8%)	16 (21.1%)	11 (26.2%)	18 (38.3%)	1 (2.4%)	8 (18.2%)	8 (28.6%)	8 (17.4%)	7 (15.6%)	77 (20.9%)	94 (20.7%)
>= 65 years	13 (27.1%)	12 (23.5%)	1 (4.5%)	8 (47.1%)	4 (17.4%)	2 (9.5%)	13 (37.1%)	7 (29.2%)	8 (44.4%)	55 (26.1%)	68 (26.3%)
< 75 years	27 (21.3%)	28 (23.0%)	12 (19.7%)	25 (41.0%)	4 (6.5%)	9 (14.8%)	20 (34.5%)	14 (20.9%)	14 (23.0%)	126 (22.8%)	153 (22.5%)
>= 75 years	3 (42.9%)	0	0	1 (33.3%)	1 (50.0%)	1 (25.0%)	1 (20.0%)	1 (33.3%)	1 (50.0%)	6 (22.2%)	9 (26.5%)
Renal TEAEs											
< 65 years	0	0	1 (2.4%)	1 (2.1%)	1 (2.4%)	3 (6.8%)	1 (3.6%)	3 (6.5%)	2 (4.4%)	12 (3.3%)	12 (2.6%)
>= 65 years	1 (2.1%)	2 (3.9%)	0	0	2 (8.7%)	0	2 (5.7%)	1 (4.2%)	1 (5.6%)	8 (3.8%)	9 (3.5%)
< 75 years	1 (0.8%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	3 (4.8%)	3 (4.9%)	3 (5.2%)	4 (6.0%)	3 (4.9%)	20 (3.6%)	21 (3.1%)
>= 75 years	0	0	0	0	0	0	0	0	0	0	0
Hepatic TEAEs											
< 65 years	0	2 (2.6%)	0	0	0	2 (4.5%)	1 (3.6%)	2 (4.3%)	3 (6.7%)	10 (2.7%)	10 (2.2%)
>= 65 years	0	1 (2.0%)	1 (4.5%)	0	1 (4.3%)	1 (4.8%)	0	0	0	4 (1.9%)	4 (1.5%)
< 75 years	0	3 (2.5%)	0	0	1 (1.6%)	3 (4.9%)	1 (1.7%)	2 (3.0%)	3 (4.9%)	13 (2.4%)	13 (1.9%)
>= 75 years	0	0	1 (33.3%)	0	0	0	0	0	0	1 (3.7%)	1 (2.9%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- Percentages are based on "Number of patients".

2.7.4.5.1.1.3　インスリン製剤併用療法：020 試験

本試験では選択基準で年齢を 20 歳以上とした。75 歳以上の被験者は少なかったため、65 歳未満と 65 歳以上の区分で評価した。

(1) 二重盲検治療（16 週）

年齢区分別での有害事象の全般的な発現割合を表 2.7.4.5-3 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-170 に示す。いずれの群でも有害事象の発現割合に年齢区分で大きな違いはなかった。

表 2.7.4.5-3　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Age in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

TEAE Age	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Number of patients		
< 65 years	76	68
>= 65 years	31	40
< 75 years	104	101
>= 75 years	3	7
Any TEAE		
< 65 years	36 (47.4%)	33 (48.5%)
>= 65 years	15 (48.4%)	24 (60.0%)
< 75 years	49 (47.1%)	52 (51.5%)
>= 75 years	2 (66.7%)	5 (71.4%)
Treatment-related TEAE		
< 65 years	8 (10.5%)	8 (11.8%)
>= 65 years	5 (16.1%)	8 (20.0%)
< 75 years	12 (11.5%)	16 (15.8%)
>= 75 years	1 (33.3%)	0
Severe TEAE		
< 65 years	1 (1.3%)	0
>= 65 years	1 (3.2%)	0
< 75 years	2 (1.9%)	0
>= 75 years	0	0
TEAE leading to death		
< 65 years	0	0
>= 65 years	0	0
< 75 years	0	0
>= 75 years	0	0

TEAE Age	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Serious TEAE		
< 65 years	1 (1.3%)	1 (1.5%)
>= 65 years	2 (6.5%)	0
< 75 years	3 (2.9%)	1 (1.0%)
>= 75 years	0	0
TEAE leading to treatment discontinuation		
< 65 years	3 (3.9%)	0
>= 65 years	1 (3.2%)	1 (2.5%)
< 75 years	4 (3.8%)	1 (1.0%)
>= 75 years	0	0
Hypoglycemia		
< 65 years	11 (14.5%)	12 (17.6%)
>= 65 years	6 (19.4%)	11 (27.5%)
< 75 years	15 (14.4%)	20 (19.8%)
>= 75 years	2 (66.7%)	3 (42.9%)
Lactic acidosis related TEAEs		
< 65 years	0	0
>= 65 years	0	0
< 75 years	0	0
>= 75 years	0	0
Cardiovascular-related TEAEs		
< 65 years	1 (1.3%)	3 (4.4%)
>= 65 years	0	1 (2.5%)
< 75 years	1 (1.0%)	4 (4.0%)
>= 75 years	0	0
Digestive Symptoms		
< 65 years	4 (5.3%)	4 (5.9%)
>= 65 years	3 (9.7%)	6 (15.0%)
< 75 years	7 (6.7%)	9 (8.9%)
>= 75 years	0	1 (14.3%)
Renal TEAEs		
< 65 years	0	1 (1.5%)
>= 65 years	0	0
< 75 years	0	1 (1.0%)
>= 75 years	0	0
Hepatic TEAEs		
< 65 years	0	0
>= 65 years	0	0
< 75 years	0	0
>= 75 years	0	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- Percentages are based on "Number of patients".

(2) 長期投与（52 週）

年齢区分別での有害事象の全般的な発現割合を表 2.7.4.5-4 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-174 に示す。有害事象の発現割合に年齢区分で大きな違いはなかった。

表 2.7.4.5-4　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Age in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

TEAE Age	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Number of patients			
< 65 years	72	68	140
>= 65 years	29	40	69
< 75 years	98	101	199
>= 75 years	3	7	10
Any TEAE			
< 65 years	54 (75.0%)	57 (83.8%)	111 (79.3%)
>= 65 years	23 (79.3%)	35 (87.5%)	58 (84.1%)
< 75 years	75 (76.5%)	85 (84.2%)	160 (80.4%)
>= 75 years	2 (66.7%)	7 (100.0%)	9 (90.0%)
Treatment-related TEAE			
< 65 years	9 (12.5%)	18 (26.5%)	27 (19.3%)
>= 65 years	7 (24.1%)	10 (25.0%)	17 (24.6%)
< 75 years	15 (15.3%)	28 (27.7%)	43 (21.6%)
>= 75 years	1 (33.3%)	0	1 (10.0%)
Severe TEAE			
< 65 years	0	1 (1.5%)	1 (0.7%)
>= 65 years	3 (10.3%)	0	3 (4.3%)
< 75 years	2 (2.0%)	1 (1.0%)	3 (1.5%)
>= 75 years	1 (33.3%)	0	1 (10.0%)
TEAE leading to death			
< 65 years	0	0	0
>= 65 years	1 (3.4%)	0	1 (1.4%)
< 75 years	1 (1.0%)	0	1 (0.5%)
>= 75 years	0	0	0
Serious TEAE			
< 65 years	1 (1.4%)	6 (8.8%)	7 (5.0%)
>= 65 years	5 (17.2%)	0	5 (7.2%)
< 75 years	5 (5.1%)	6 (5.9%)	11 (5.5%)
>= 75 years	1 (33.3%)	0	1 (10.0%)

TEAE Age	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
TEAE leading to treatment discontinuation			
< 65 years	1 (1.4%)	3 (4.4%)	4 (2.9%)
>= 65 years	2 (6.9%)	2 (5.0%)	4 (5.8%)
< 75 years	3 (3.1%)	5 (5.0%)	8 (4.0%)
>= 75 years	0	0	0
Hypoglycemia			
< 65 years	23 (31.9%)	23 (33.8%)	46 (32.9%)
>= 65 years	13 (44.8%)	16 (40.0%)	29 (42.0%)
< 75 years	35 (35.7%)	34 (33.7%)	69 (34.7%)
>= 75 years	1 (33.3%)	5 (71.4%)	6 (60.0%)
Lactic acidosis related TEAEs			
< 65 years	0	1 (1.5%)	1 (0.7%)
>= 65 years	0	0	0
< 75 years	0	1 (1.0%)	1 (0.5%)
>= 75 years	0	0	0
Cardiovascular-related TEAEs			
< 65 years	3 (4.2%)	5 (7.4%)	8 (5.7%)
>= 65 years	4 (13.8%)	3 (7.5%)	7 (10.1%)
< 75 years	6 (6.1%)	8 (7.9%)	14 (7.0%)
>= 75 years	1 (33.3%)	0	1 (10.0%)
Digestive Symptoms			
< 65 years	8 (11.1%)	10 (14.7%)	18 (12.9%)
>= 65 years	2 (6.9%)	10 (25.0%)	12 (17.4%)
< 75 years	10 (10.2%)	18 (17.8%)	28 (14.1%)
>= 75 years	0	2 (28.6%)	2 (20.0%)
Renal TEAEs			
< 65 years	0	1 (1.5%)	1 (0.7%)
>= 65 years	1 (3.4%)	0	1 (1.4%)
< 75 years	1 (1.0%)	1 (1.0%)	2 (1.0%)
>= 75 years	0	0	0
Hepatic TEAEs			
< 65 years	1 (1.4%)	2 (2.9%)	3 (2.1%)
>= 65 years	1 (3.4%)	1 (2.5%)	2 (2.9%)
< 75 years	1 (1.0%)	3 (3.0%)	4 (2.0%)
>= 75 years	1 (33.3%)	0	1 (10.0%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Percentages are based on "Number of patients".

2.7.4.5.1.2　性別

2.7.4.5.1.2.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

性別での有害事象の全般的な発現割合を表 2.7.4.5-5 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-163 に示す。消化器症状の発現割合は男性、女性の順に（以下同順）プラセボ群で 7.1%、20.0%、500 mg bid 群で 16.3%、11.5%、1000 mg bid 群で 11.6%、23.8%、1500 mg bid 群で 24.1%、52.4%であった。下痢の発現割合はプラセボ群で 0.8%、0%、500 mg bid 群で 4.1%、3.8%、1000 mg bid 群で 1.4%、7.1%、1500 mg bid 群で 5.6%、14.3%、悪心の発現割合はプラセボ群で 0%、1.8%、500 mg bid 群で 0%、3.8%、1000 mg bid 群で 0.7%、0%、1500 mg bid 群で 3.7%、14.3%であった。そのほかの有害事象の発現割合に性別で大きな違いはなかった。

表 2.7.4.5-5 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Sex in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

TEAE Sex	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Number of patients					
Male	127	49	138	54	241
Female	55	26	42	21	89
Any TEAE					
Male	60 (47.2%)	32 (65.3%)	64 (46.4%)	38 (70.4%)	134 (55.6%)
Female	39 (70.9%)	19 (73.1%)	29 (69.0%)	17 (81.0%)	65 (73.0%)
Treatment-related TEAE					
Male	11 (8.7%)	2 (4.1%)	6 (4.3%)	11 (20.4%)	19 (7.9%)
Female	2 (3.6%)	2 (7.7%)	3 (7.1%)	7 (33.3%)	12 (13.5%)
Severe TEAE					
Male	0	0	3 (2.2%)	1 (1.9%)	4 (1.7%)
Female	1 (1.8%)	0	3 (7.1%)	0	3 (3.4%)
TEAE leading to death					
Male	0	0	0	1 (1.9%)	1 (0.4%)
Female	0	0	0	0	0
Serious TEAE					
Male	1 (0.8%)	0	4 (2.9%)	1 (1.9%)	5 (2.1%)
Female	1 (1.8%)	0	4 (9.5%)	0	4 (4.5%)
TEAE leading to treatment discontinuation					
Male	9 (7.1%)	1 (2.0%)	4 (2.9%)	2 (3.7%)	7 (2.9%)
Female	5 (9.1%)	1 (3.8%)	2 (4.8%)	3 (14.3%)	6 (6.7%)
Hypoglycemia					
Male	2 (1.6%)	4 (8.2%)	5 (3.6%)	4 (7.4%)	13 (5.4%)
Female	0	1 (3.8%)	0	0	1 (1.1%)

TEAE Sex	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Lactic acidosis related TEAEs					
Male	0	0	0	0	0
Female	0	0	0	0	0
Cardiovascular-related TEAEs					
Male	6 (4.7%)	0	1 (0.7%)	4 (7.4%)	5 (2.1%)
Female	1 (1.8%)	2 (7.7%)	2 (4.8%)	2 (9.5%)	6 (6.7%)
Digestive Symptoms					
Male	9 (7.1%)	8 (16.3%)	16 (11.6%)	13 (24.1%)	37 (15.4%)
Female	11 (20.0%)	3 (11.5%)	10 (23.8%)	11 (52.4%)	24 (27.0%)
Renal TEAEs					
Male	2 (1.6%)	0	2 (1.4%)	0	2 (0.8%)
Female	0	1 (3.8%)	0	0	1 (1.1%)
Hepatic TEAEs					
Male	4 (3.1%)	0	2 (1.4%)	1 (1.9%)	3 (1.2%)
Female	0	1 (3.8%)	0	2 (9.5%)	3 (3.4%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- Percentages are based on "Number of patients".

2.7.4.5.1.2.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

性別での有害事象の全般的な発現割合を表 2.7.4.5-6 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-167 に示す。

- 単独療法群では、有害事象の発現割合に性別で大きな違いはなかった。
- BIG 併用療法群では、治験薬の投与中止に至った有害事象の発現割合は男性、女性の順に 6.5%、22.2%であった。そのほかの有害事象の発現割合に性別で大きな違いはなかった。
- TZD 併用療法群では、治験薬の投与中止に至った有害事象の発現割合は男性、女性の順に（以下同順）3.7%、18.2%であった。また、消化器症状の発現割合は 11.1%、36.4%であった。下痢及び嘔吐の発現割合は 0%、18.2%、悪心及び便秘の発現割合は 0%、9.1%であった。そのほかの有害事象の発現割合に性別で大きな違いはなかった。
- SU 併用療法群、GLIN 併用療法群、AGI 併用療法群、DPP4-I 併用療法群、GLP1-RA 併用療法群及び SGLT2-I 併用療法群では、有害事象の発現割合に性別で大きな違いはなかった。

表 2.7.4.5-6　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Sex in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

TEAE Sex	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Number of patients											
Male	106	101	43	46	48	54	39	44	45	420	526
Female	28	26	21	18	16	11	24	26	18	160	188
Any TEAE											
Male	74 (69.8%)	83 (82.2%)	35 (81.4%)	32 (69.6%)	23 (47.9%)	40 (74.1%)	28 (71.8%)	33 (75.0%)	36 (80.0%)	310 (73.8%)	384 (73.0%)
Female	24 (85.7%)	19 (73.1%)	19 (90.5%)	16 (88.9%)	10 (62.5%)	10 (90.9%)	22 (91.7%)	23 (88.5%)	12 (66.7%)	131 (81.9%)	155 (82.4%)
Treatment-related TEAE											
Male	8 (7.5%)	21 (20.8%)	7 (16.3%)	15 (32.6%)	5 (10.4%)	3 (5.6%)	9 (23.1%)	3 (6.8%)	6 (13.3%)	69 (16.4%)	77 (14.6%)
Female	5 (17.9%)	6 (23.1%)	3 (14.3%)	9 (50.0%)	1 (6.3%)	3 (27.3%)	5 (20.8%)	5 (19.2%)	1 (5.6%)	33 (20.6%)	38 (20.2%)
Severe TEAE											
Male	2 (1.9%)	4 (4.0%)	0	4 (8.7%)	1 (2.1%)	1 (1.9%)	1 (2.6%)	2 (4.5%)	1 (2.2%)	14 (3.3%)	16 (3.0%)
Female	0	1 (3.8%)	0	0	0	0	0	0	0	1 (0.6%)	1 (0.5%)
TEAE leading to death											
Male	1 (0.9%)	0	0	0	0	0	0	0	0	0	1 (0.2%)
Female	0	0	0	0	0	0	0	0	0	0	0
Serious TEAE											
Male	4 (3.8%)	7 (6.9%)	1 (2.3%)	4 (8.7%)	3 (6.3%)	4 (7.4%)	1 (2.6%)	4 (9.1%)	3 (6.7%)	27 (6.4%)	31 (5.9%)
Female	0	4 (15.4%)	0	0	1 (6.3%)	0	2 (8.3%)	1 (3.8%)	1 (5.6%)	9 (5.6%)	9 (4.8%)
TEAE leading to treatment discontinuation											
Male	2 (1.9%)	6 (5.9%)	1 (2.3%)	3 (6.5%)	1 (2.1%)	2 (3.7%)	4 (10.3%)	8 (18.2%)	1 (2.2%)	26 (6.2%)	28 (5.3%)
Female	1 (3.6%)	3 (11.5%)	0	4 (22.2%)	1 (6.3%)	2 (18.2%)	1 (4.2%)	7 (26.9%)	0	18 (11.3%)	19 (10.1%)

TEAE Sex	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Hypoglycemia											
Male	5 (4.7%)	16 (15.8%)	5 (11.6%)	4 (8.7%)	2 (4.2%)	2 (3.7%)	3 (7.7%)	2 (4.5%)	2 (4.4%)	36 (8.6%)	41 (7.8%)
Female	0	5 (19.2%)	4 (19.0%)	2 (11.1%)	0	0	2 (8.3%)	0	2 (11.1%)	15 (9.4%)	15 (8.0%)
Lactic acidosis related TEAEs											
Male	0	2 (2.0%)	0	0	0	0	0	0	0	2 (0.5%)	2 (0.4%)
Female	0	0	0	0	0	0	0	0	0	0	0
Cardiovascular-related TEAEs											
Male	4 (3.8%)	10 (9.9%)	2 (4.7%)	4 (8.7%)	5 (10.4%)	8 (14.8%)	1 (2.6%)	4 (9.1%)	3 (6.7%)	37 (8.8%)	41 (7.8%)
Female	0	1 (3.8%)	1 (4.8%)	2 (11.1%)	1 (6.3%)	0	2 (8.3%)	1 (3.8%)	1 (5.6%)	9 (5.6%)	9 (4.8%)
Digestive Symptoms											
Male	19 (17.9%)	21 (20.8%)	6 (14.0%)	16 (34.8%)	3 (6.3%)	6 (11.1%)	10 (25.6%)	6 (13.6%)	12 (26.7%)	80 (19.0%)	99 (18.8%)
Female	11 (39.3%)	7 (26.9%)	6 (28.6%)	10 (55.6%)	2 (12.5%)	4 (36.4%)	11 (45.8%)	9 (34.6%)	3 (16.7%)	52 (32.5%)	63 (33.5%)
Renal TEAEs											
Male	1 (0.9%)	2 (2.0%)	1 (2.3%)	1 (2.2%)	3 (6.3%)	3 (5.6%)	1 (2.6%)	2 (4.5%)	3 (6.7%)	16 (3.8%)	17 (3.2%)
Female	0	0	0	0	0	0	2 (8.3%)	2 (7.7%)	0	4 (2.5%)	4 (2.1%)
Hepatic TEAEs											
Male	0	2 (2.0%)	1 (2.3%)	0	1 (2.1%)	3 (5.6%)	1 (2.6%)	1 (2.3%)	3 (6.7%)	12 (2.9%)	12 (2.3%)
Female	0	1 (3.8%)	0	0	0	0	0	1 (3.8%)	0	2 (1.3%)	2 (1.1%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- Percentages are based on "Number of patients".

2.7.4.5.1.2.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

性別での有害事象の全般的な発現割合を表 2.7.4.5-7 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-171 に示す。いずれの群でも有害事象の発現割合に性別で大きな違いはなかった。

表 2.7.4.5-7　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Sex in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

TEAE Sex	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Number of patients		
Male	69	66
Female	38	42
Any TEAE		
Male	31 (44.9%)	33 (50.0%)
Female	20 (52.6%)	24 (57.1%)
Treatment-related TEAE		
Male	9 (13.0%)	8 (12.1%)
Female	4 (10.5%)	8 (19.0%)
Severe TEAE		
Male	1 (1.4%)	0
Female	1 (2.6%)	0
TEAE leading to death		
Male	0	0
Female	0	0
Serious TEAE		
Male	1 (1.4%)	1 (1.5%)
Female	2 (5.3%)	0
TEAE leading to treatment discontinuation		
Male	4 (5.8%)	0
Female	0	1 (2.4%)
Hypoglycemia		
Male	11 (15.9%)	11 (16.7%)
Female	6 (15.8%)	12 (28.6%)
Lactic acidosis related TEAEs		
Male	0	0
Female	0	0
Cardiovascular-related TEAEs		
Male	0	3 (4.5%)
Female	1 (2.6%)	1 (2.4%)

TEAE Sex	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Digestive Symptoms		
Male	4 (5.8%)	6 (9.1%)
Female	3 (7.9%)	4 (9.5%)
Renal TEAEs		
Male	0	1 (1.5%)
Female	0	0
Hepatic TEAEs		
Male	0	0
Female	0	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- Percentages are based on "Number of patients".

(2) 長期投与（52 週）

性別での有害事象の全般的な発現割合を表 2.7.4.5-8 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-175 に示す。有害事象の発現割合に性別で大きな違いはなかった。

表 2.7.4.5-8　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Sex in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

TEAE Sex	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Number of patients			
Male	64	66	130
Female	37	42	79
Any TEAE			
Male	50 (78.1%)	53 (80.3%)	103 (79.2%)
Female	27 (73.0%)	39 (92.9%)	66 (83.5%)
Treatment-related TEAE			
Male	13 (20.3%)	15 (22.7%)	28 (21.5%)
Female	3 (8.1%)	13 (31.0%)	16 (20.3%)
Severe TEAE			
Male	2 (3.1%)	1 (1.5%)	3 (2.3%)
Female	1 (2.7%)	0	1 (1.3%)
TEAE leading to death			
Male	1 (1.6%)	0	1 (0.8%)
Female	0	0	0
Serious TEAE			
Male	3 (4.7%)	6 (9.1%)	9 (6.9%)
Female	3 (8.1%)	0	3 (3.8%)

TEAE Sex	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
TEAE leading to treatment discontinuation			
Male	1 (1.6%)	1 (1.5%)	2 (1.5%)
Female	2 (5.4%)	4 (9.5%)	6 (7.6%)
Hypoglycemia			
Male	24 (37.5%)	22 (33.3%)	46 (35.4%)
Female	12 (32.4%)	17 (40.5%)	29 (36.7%)
Lactic acidosis related TEAEs			
Male	0	1 (1.5%)	1 (0.8%)
Female	0	0	0
Cardiovascular-related TEAEs			
Male	4 (6.3%)	6 (9.1%)	10 (7.7%)
Female	3 (8.1%)	2 (4.8%)	5 (6.3%)
Digestive Symptoms			
Male	5 (7.8%)	10 (15.2%)	15 (11.5%)
Female	5 (13.5%)	10 (23.8%)	15 (19.0%)
Renal TEAEs			
Male	1 (1.6%)	1 (1.5%)	2 (1.5%)
Female	0	0	0
Hepatic TEAEs			
Male	1 (1.6%)	2 (3.0%)	3 (2.3%)
Female	1 (2.7%)	1 (2.4%)	2 (2.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Percentages are based on "Number of patients".

2.7.4.5.1.3　腎機能

ベースラインの腎機能区分（CKD 1、CKD 2、CKD 3a）別で有害事象の発現割合を比較した。014 試験、018 試験及び 019 試験で本剤 1000 mg bid の単独療法を受けた被験者の腎機能区分別の有害事象の発現割合（3 試験併合）を 2.7.4.7 項付録 Table S-219 に示す。

2.7.4.5.1.3.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

ベースラインの腎機能区分別での有害事象の全般的な発現割合を表 2.7.4.5-9 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-164 に示す。いずれの試験でも、選択基準で eGRF（mL/min/1.73m^2）をスクリーニング時に 50 以上（CKD 1、CKD 2、CKD 3a の一部）、ランダム化前来院時に 45 以上（CKD 1、CKD 2、CKD 3a）としていた。いずれの群でも有害事象の発現割合に腎機能区分別で大きな違いはなかった。

表 2.7.4.5-9　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Renal Function at Baseline in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

TEAE Renal function	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Number of patients					
CKD Stage 1	16	9	21	14	44
CKD Stage 2	137	56	131	52	239
CKD Stage 3a	29	10	28	9	47
Any TEAE					
CKD Stage 1	11 (68.8%)	5 (55.6%)	10 (47.6%)	12 (85.7%)	27 (61.4%)
CKD Stage 2	71 (51.8%)	39 (69.6%)	68 (51.9%)	36 (69.2%)	143 (59.8%)
CKD Stage 3a	17 (58.6%)	7 (70.0%)	15 (53.6%)	7 (77.8%)	29 (61.7%)
Treatment-related TEAE					
CKD Stage 1	2 (12.5%)	0	0	5 (35.7%)	5 (11.4%)
CKD Stage 2	10 (7.3%)	3 (5.4%)	8 (6.1%)	12 (23.1%)	23 (9.6%)
CKD Stage 3a	1 (3.4%)	1 (10.0%)	1 (3.6%)	1 (11.1%)	3 (6.4%)
Severe TEAE					
CKD Stage 1	0	0	0	0	0
CKD Stage 2	1 (0.7%)	0	6 (4.6%)	1 (1.9%)	7 (2.9%)
CKD Stage 3a	0	0	0	0	0
TEAE leading to death					
CKD Stage 1	0	0	0	0	0
CKD Stage 2	0	0	0	1 (1.9%)	1 (0.4%)
CKD Stage 3a	0	0	0	0	0
Serious TEAE					
CKD Stage 1	0	0	0	0	0
CKD Stage 2	2 (1.5%)	0	8 (6.1%)	1 (1.9%)	9 (3.8%)
CKD Stage 3a	0	0	0	0	0
TEAE leading to treatment discontinuation					
CKD Stage 1	1 (6.3%)	0	0	1 (7.1%)	1 (2.3%)
CKD Stage 2	10 (7.3%)	2 (3.6%)	6 (4.6%)	4 (7.7%)	12 (5.0%)
CKD Stage 3a	3 (10.3%)	0	0	0	0
Hypoglycemia					
CKD Stage 1	0	1 (11.1%)	0	1 (7.1%)	2 (4.5%)
CKD Stage 2	1 (0.7%)	3 (5.4%)	3 (2.3%)	3 (5.8%)	9 (3.8%)
CKD Stage 3a	1 (3.4%)	1 (10.0%)	2 (7.1%)	0	3 (6.4%)
Lactic acidosis related TEAEs					
CKD Stage 1	0	0	0	0	0
CKD Stage 2	0	0	0	0	0
CKD Stage 3a	0	0	0	0	0

TEAE Renal function	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Cardiovascular-related TEAEs					
CKD Stage 1	2 (12.5%)	0	1 (4.8%)	0	1 (2.3%)
CKD Stage 2	3 (2.2%)	2 (3.6%)	1 (0.8%)	5 (9.6%)	8 (3.3%)
CKD Stage 3a	2 (6.9%)	0	1 (3.6%)	1 (11.1%)	2 (4.3%)
Digestive Symptoms					
CKD Stage 1	6 (37.5%)	0	4 (19.0%)	3 (21.4%)	7 (15.9%)
CKD Stage 2	11 (8.0%)	9 (16.1%)	19 (14.5%)	17 (32.7%)	45 (18.8%)
CKD Stage 3a	3 (10.3%)	2 (20.0%)	3 (10.7%)	4 (44.4%)	9 (19.1%)
Renal TEAEs					
CKD Stage 1	0	0	0	0	0
CKD Stage 2	1 (0.7%)	1 (1.8%)	2 (1.5%)	0	3 (1.3%)
CKD Stage 3a	1 (3.4%)	0	0	0	0
Hepatic TEAEs					
CKD Stage 1	0	0	0	0	0
CKD Stage 2	4 (2.9%)	0	2 (1.5%)	3 (5.8%)	5 (2.1%)
CKD Stage 3a	0	1 (10.0%)	0	0	1 (2.1%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- Percentages are based on "Number of patients".

2.7.4.5.1.3.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

ベースラインの腎機能区分別での有害事象の全般的な発現割合を表 2.7.4.5-10 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-168 に示す。本試験では、選択基準でスクリーニング時の eGRF（mL/min/1.73m^2）を単独療法では 50 以上（CKD 1、CKD 2、CKD 3a の一部）、併用療法では 60 以上（CKD 1、CKD 2）としていた。すべての併用療法群で、ベースラインまでに CKD 3a となった被験者が複数名（2～9 名）みられた。

- 単独療法群では、有害事象の発現割合に腎機能区分別（CKD 1、CKD 2、CKD 3a）で大きな違いはなかった。
- SU 併用療法群では、治験薬の投与中止に至った有害事象の発現割合は CKD 1、CKD 2 の順に 22.7%、4.2%であった。そのほかの有害事象の発現割合に腎機能区分別（CKD 1、CKD 2）で大きな違いはなかった。ベースラインの腎機能区分が CKD 3a であった被験者で、心血管関連事象が 3 名、低血糖が 2 名、重度の有害事象、重篤な有害事象、消化器症状及び腎機能関連事象が各 1 名に発現した。
- GLIN 併用療法群では、有害事象の発現割合に腎機能区分別（CKD 1、CKD 2）で大きな違いはなかった。ベースラインの腎機能区分が CKD 3a であった被験者で、低血糖が 1 名に発現した。

- BIG 併用療法群では、低血糖の発現割合は CKD 1、CKD 2 の順に 22.2%、4.8%であった。そのほかの有害事象の発現割合に腎機能区分別（CKD 1、CKD 2）で大きな違いはなかった。ベースラインの腎機能区分が CKD 3a であった被験者で、消化器症状が 3 名、治験薬の投与中止に至った有害事象が 1 名に発現した。
- AGI 併用療法群では、有害事象の発現割合に腎機能区分別（CKD 1、CKD 2）で大きな違いはなかった。ベースラインの腎機能区分が CKD 3a であった被験者で、腎機能関連事象が 1 名に発現した。
- TZD 併用療法群では、有害事象の発現割合に腎機能区分別（CKD 1、CKD 2）で大きな違いはなかった。ベースラインの腎機能区分が CKD 3a であった被験者で、消化器症状が 2 名、重篤な有害事象及び治験薬の投与中止に至った有害事象が各 1 名に発現した。
- DPP4-I 併用療法群では、有害事象の発現割合に腎機能区分別（CKD 1、CKD 2）で大きな違いはなかった。ベースラインの腎機能区分が CKD 3a であった被験者で、消化器症状が 3 名、低血糖及び心血管関連事象が各 1 名に発現した。
- GLP1-RA 併用療法群では、有害事象の発現割合に腎機能区分別（CKD 1、CKD 2）で大きな違いはなかった。ベースラインの腎機能区分が CKD 3a であった被験者で、消化器症状が 1 名に発現した。
- SGLT2-I 併用療法群では、有害事象の発現割合に腎機能区分別（CKD 1、CKD 2）で大きな違いはなかった。ベースラインの腎機能区分が CKD 3a であった被験者で、低血糖及び消化器症状が各 1 名に発現した。

表 2.7.4.5-10　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Renal Function at Baseline in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

TEAE Renal function	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Number of patients											
CKD Stage 1	24	22	12	18	13	16	9	16	21	127	151
CKD Stage 2	91	96	50	42	49	44	47	51	40	419	510
CKD Stage 3a	19	9	2	4	2	5	7	3	2	34	53
Any TEAE											
CKD Stage 1	16 (66.7%)	20 (90.9%)	9 (75.0%)	15 (83.3%)	6 (46.2%)	13 (81.3%)	7 (77.8%)	15 (93.8%)	17 (81.0%)	102 (80.3%)	118 (78.1%)
CKD Stage 2	68 (74.7%)	75 (78.1%)	43 (86.0%)	30 (71.4%)	25 (51.0%)	34 (77.3%)	37 (78.7%)	39 (76.5%)	30 (75.0%)	313 (74.7%)	381 (74.7%)
CKD Stage 3a	14 (73.7%)	7 (77.8%)	2 (100.0%)	3 (75.0%)	2 (100.0%)	3 (60.0%)	6 (85.7%)	2 (66.7%)	1 (50.0%)	26 (76.5%)	40 (75.5%)
Treatment-related TEAE											
CKD Stage 1	3 (12.5%)	6 (27.3%)	2 (16.7%)	7 (38.9%)	1 (7.7%)	1 (6.3%)	1 (11.1%)	3 (18.8%)	2 (9.5%)	23 (18.1%)	26 (17.2%)
CKD Stage 2	9 (9.9%)	18 (18.8%)	7 (14.0%)	14 (33.3%)	5 (10.2%)	4 (9.1%)	12 (25.5%)	4 (7.8%)	4 (10.0%)	68 (16.2%)	77 (15.1%)
CKD Stage 3a	1 (5.3%)	3 (33.3%)	1 (50.0%)	3 (75.0%)	0	1 (20.0%)	1 (14.3%)	1 (33.3%)	1 (50.0%)	11 (32.4%)	12 (22.6%)
Severe TEAE											
CKD Stage 1	0	2 (9.1%)	0	0	0	0	0	0	0	2 (1.6%)	2 (1.3%)
CKD Stage 2	1 (1.1%)	2 (2.1%)	0	4 (9.5%)	1 (2.0%)	1 (2.3%)	1 (2.1%)	2 (3.9%)	1 (2.5%)	12 (2.9%)	13 (2.5%)
CKD Stage 3a	1 (5.3%)	1 (11.1%)	0	0	0	0	0	0	0	1 (2.9%)	2 (3.8%)
TEAE leading to death											
CKD Stage 1	0	0	0	0	0	0	0	0	0	0	0
CKD Stage 2	1 (1.1%)	0	0	0	0	0	0	0	0	0	1 (0.2%)
CKD Stage 3a	0	0	0	0	0	0	0	0	0	0	0

TEAE Renal function	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Serious TEAE											
CKD Stage 1	1 (4.2%)	4 (18.2%)	0	0	1 (7.7%)	0	0	1 (6.3%)	0	6 (4.7%)	7 (4.6%)
CKD Stage 2	2 (2.2%)	6 (6.3%)	1 (2.0%)	4 (9.5%)	3 (6.1%)	3 (6.8%)	3 (6.4%)	4 (7.8%)	4 (10.0%)	28 (6.7%)	30 (5.9%)
CKD Stage 3a	1 (5.3%)	1 (11.1%)	0	0	0	1 (20.0%)	0	0	0	2 (5.9%)	3 (5.7%)
TEAE leading to treatment discontinuation											
CKD Stage 1	0	5 (22.7%)	0	2 (11.1%)	1 (7.7%)	1 (6.3%)	0	3 (18.8%)	0	12 (9.4%)	12 (7.9%)
CKD Stage 2	3 (3.3%)	4 (4.2%)	1 (2.0%)	4 (9.5%)	1 (2.0%)	2 (4.5%)	5 (10.6%)	12 (23.5%)	1 (2.5%)	30 (7.2%)	33 (6.5%)
CKD Stage 3a	0	0	0	1 (25.0%)	0	1 (20.0%)	0	0	0	2 (5.9%)	2 (3.8%)
Hypoglycemia											
CKD Stage 1	2 (8.3%)	7 (31.8%)	1 (8.3%)	4 (22.2%)	1 (7.7%)	1 (6.3%)	0	1 (6.3%)	0	15 (11.8%)	17 (11.3%)
CKD Stage 2	2 (2.2%)	12 (12.5%)	7 (14.0%)	2 (4.8%)	1 (2.0%)	1 (2.3%)	4 (8.5%)	1 (2.0%)	3 (7.5%)	31 (7.4%)	33 (6.5%)
CKD Stage 3a	1 (5.3%)	2 (22.2%)	1 (50.0%)	0	0	0	1 (14.3%)	0	1 (50.0%)	5 (14.7%)	6 (11.3%)
Lactic acidosis related TEAEs											
CKD Stage 1	0	0	0	0	0	0	0	0	0	0	0
CKD Stage 2	0	2 (2.1%)	0	0	0	0	0	0	0	2 (0.5%)	2 (0.4%)
CKD Stage 3a	0	0	0	0	0	0	0	0	0	0	0
Cardiovascular-related TEAEs											
CKD Stage 1	1 (4.2%)	1 (4.5%)	0	1 (5.6%)	1 (7.7%)	1 (6.3%)	0	1 (6.3%)	1 (4.8%)	6 (4.7%)	7 (4.6%)
CKD Stage 2	2 (2.2%)	7 (7.3%)	3 (6.0%)	5 (11.9%)	5 (10.2%)	7 (15.9%)	2 (4.3%)	4 (7.8%)	3 (7.5%)	36 (8.6%)	38 (7.5%)
CKD Stage 3a	1 (5.3%)	3 (33.3%)	0	0	0	0	1 (14.3%)	0	0	4 (11.8%)	5 (9.4%)
Digestive Symptoms											
CKD Stage 1	6 (25.0%)	7 (31.8%)	3 (25.0%)	6 (33.3%)	1 (7.7%)	4 (25.0%)	3 (33.3%)	3 (18.8%)	6 (28.6%)	33 (26.0%)	39 (25.8%)
CKD Stage 2	18 (19.8%)	20 (20.8%)	9 (18.0%)	17 (40.5%)	4 (8.2%)	4 (9.1%)	15 (31.9%)	11 (21.6%)	8 (20.0%)	88 (21.0%)	106 (20.8%)
CKD Stage 3a	6 (31.6%)	1 (11.1%)	0	3 (75.0%)	0	2 (40.0%)	3 (42.9%)	1 (33.3%)	1 (50.0%)	11 (32.4%)	17 (32.1%)

TEAE Renal function	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Renal TEAEs											
CKD Stage 1	0	0	0	0	0	2 (12.5%)	0	0	2 (9.5%)	4 (3.1%)	4 (2.6%)
CKD Stage 2	1 (1.1%)	1 (1.0%)	1 (2.0%)	1 (2.4%)	2 (4.1%)	1 (2.3%)	3 (6.4%)	4 (7.8%)	1 (2.5%)	14 (3.3%)	15 (2.9%)
CKD Stage 3a	0	1 (11.1%)	0	0	1 (50.0%)	0	0	0	0	2 (5.9%)	2 (3.8%)
Hepatic TEAEs											
CKD Stage 1	0	0	0	0	0	2 (12.5%)	1 (11.1%)	0	1 (4.8%)	4 (3.1%)	4 (2.6%)
CKD Stage 2	0	3 (3.1%)	1 (2.0%)	0	1 (2.0%)	1 (2.3%)	0	2 (3.9%)	2 (5.0%)	10 (2.4%)	10 (2.0%)
CKD Stage 3a	0	0	0	0	0	0	0	0	0	0	0

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- Percentages are based on "Number of patients".

2.7.4.5.1.3.3　インスリン製剤併用療法：020 試験

本試験では、選択基準でスクリーニング時及びランダム化前来院時の eGRF（mL/min/1.73m^2）を 60 以上（CKD 1、CKD 2）としていたため CKD 3a の被験者はいなかった。

(1) 二重盲検治療（16 週）

ベースラインの腎機能区分別での有害事象の全般的な発現割合を表 2.7.4.5-11 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-172 に示す。消化器症状の有害事象の発現割合は CKD 1、CKD 2 の順に（以下同順）プラセボ群で 7.1%、6.5%、イメグリミン群で 25.0%、6.5%であった。また、悪心の発現割合はプラセボ群で 7.1%、1.1%、イメグリミン群で 12.5%、0%であった。いずれの群でもそのほかの有害事象の発現割合に腎機能区分別で大きな違いはなかった。

表 2.7.4.5-11　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Renal Function at Baseline in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

TEAE Renal function	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Number of patients		
CKD Stage 1	14	16
CKD Stage 2	93	92
Any TEAE		
CKD Stage 1	7 (50.0%)	9 (56.3%)
CKD Stage 2	44 (47.3%)	48 (52.2%)
Treatment-related TEAE		
CKD Stage 1	1 (7.1%)	2 (12.5%)
CKD Stage 2	12 (12.9%)	14 (15.2%)
Severe TEAE		
CKD Stage 1	0	0
CKD Stage 2	2 (2.2%)	0
TEAE leading to death		
CKD Stage 1	0	0
CKD Stage 2	0	0
Serious TEAE		
CKD Stage 1	0	0
CKD Stage 2	3 (3.2%)	1 (1.1%)
TEAE leading to treatment discontinuation		
CKD Stage 1	0	1 (6.3%)
CKD Stage 2	4 (4.3%)	0

TEAE Renal function	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Hypoglycemia		
CKD Stage 1	1 (7.1%)	4 (25.0%)
CKD Stage 2	16 (17.2%)	19 (20.7%)
Lactic acidosis related TEAEs		
CKD Stage 1	0	0
CKD Stage 2	0	0
Cardiovascular-related TEAEs		
CKD Stage 1	0	1 (6.3%)
CKD Stage 2	1 (1.1%)	3 (3.3%)
Digestive Symptoms		
CKD Stage 1	1 (7.1%)	4 (25.0%)
CKD Stage 2	6 (6.5%)	6 (6.5%)
Renal TEAEs		
CKD Stage 1	0	0
CKD Stage 2	0	1 (1.1%)
Hepatic TEAEs		
CKD Stage 1	0	0
CKD Stage 2	0	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2.
- Percentages are based on "Number of patients".

(2) 長期投与（52 週）

ベースラインの腎機能区分別での有害事象の全般的な発現割合を表 2.7.4.5-12 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-176 に示す。有害事象の発現割合に腎機能区分別で大きな違いはなかった。

表 2.7.4.5-12　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Renal Function at Baseline in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

TEAE Renal function	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Number of patients			
CKD Stage 1	13	16	29
CKD Stage 2	88	92	180

TEAE Renal function	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any TEAE			
CKD Stage 1	11 (84.6%)	13 (81.3%)	24 (82.8%)
CKD Stage 2	66 (75.0%)	79 (85.9%)	145 (80.6%)
Treatment-related TEAE			
CKD Stage 1	3 (23.1%)	3 (18.8%)	6 (20.7%)
CKD Stage 2	13 (14.8%)	25 (27.2%)	38 (21.1%)
Severe TEAE			
CKD Stage 1	0	1 (6.3%)	1 (3.4%)
CKD Stage 2	3 (3.4%)	0	3 (1.7%)
TEAE leading to death			
CKD Stage 1	0	0	0
CKD Stage 2	1 (1.1%)	0	1 (0.6%)
Serious TEAE			
CKD Stage 1	0	2 (12.5%)	2 (6.9%)
CKD Stage 2	6 (6.8%)	4 (4.3%)	10 (5.6%)
TEAE leading to treatment discontinuation			
CKD Stage 1	0	2 (12.5%)	2 (6.9%)
CKD Stage 2	3 (3.4%)	3 (3.3%)	6 (3.3%)
Hypoglycemia			
CKD Stage 1	7 (53.8%)	6 (37.5%)	13 (44.8%)
CKD Stage 2	29 (33.0%)	33 (35.9%)	62 (34.4%)
Lactic acidosis related TEAEs			
CKD Stage 1	0	0	0
CKD Stage 2	0	1 (1.1%)	1 (0.6%)
Cardiovascular-related TEAEs			
CKD Stage 1	2 (15.4%)	2 (12.5%)	4 (13.8%)
CKD Stage 2	5 (5.7%)	6 (6.5%)	11 (6.1%)
Digestive Symptoms			
CKD Stage 1	2 (15.4%)	5 (31.3%)	7 (24.1%)
CKD Stage 2	8 (9.1%)	15 (16.3%)	23 (12.8%)
Renal TEAEs			
CKD Stage 1	0	0	0
CKD Stage 2	1 (1.1%)	1 (1.1%)	2 (1.1%)
Hepatic TEAEs			
CKD Stage 1	0	2 (12.5%)	2 (6.9%)
CKD Stage 2	2 (2.3%)	1 (1.1%)	3 (1.7%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group

in the double-blind and open-label periods.
- Percentages are based on "Number of patients".

2.7.4.5.1.3.4　海外腎機能障害影響検討試験：RVT-1501-1002 試験（資料番号：5.3.3.3.03）

中等度又は重度の慢性腎臓病を合併する 2 型糖尿病患者での本剤の安全性、忍容性及び薬物動態を評価するため、海外でランダム化、二重盲検、プラセボ対照並行群間比較試験を実施した。本試験では、スクリーニング期の腎機能区分が CKD 3b 又は CKD 4 の患者を対象とした。被験者は、本剤 500 mg を 1 日 2 回（500 mg bid）又はプラセボを 1 日 2 回投与する 500 mg bid コホート、本剤 1500 mg を 1 日 1 回（1500 mg qd）又はプラセボを 1 日 1 回投与する 1500 mg qd コホート、本剤 1000 mg を 1 日 2 回（1000 mg bid）又はプラセボを 1 日 2 回投与する 1000 mg bid コホートのいずれかにランダムに割り当てられ、28 日間、治験薬を投与された。500 mg bid コホートでは 2 名（CKD 3b：1 名、CKD 4：1 名）にプラセボ、13 名（CKD 3b：8 名、CKD 4：5 名）に本剤が、1500 mg qd コホートでは 5 名（CKD 3b：3 名、CKD 4：2 名）にプラセボ、12 名（CKD 3b：7 名、CKD 4：5 名）に本剤が、1000 mg bid コホートでは、4 名（CKD 3b：2 名、CKD 4：2 名）にプラセボ、13 名（CKD 3b：6 名、CKD 4：7 名）に本剤が投与された。

有害事象の発現割合［発現被験者数（以下同様）］は、プラセボ群で CKD 3b、CKD 4 の順に（以下同順）66.7%（4/6 名）、40.0%（2/5 名）、500 mg bid 群で 25.0%（2/8 名）、20.0%（1/5 名）、1500 mg qd 群で 57.1%（4/7 名）、60.0%（3/5 名）、1000 mg bid 群で 66.7%（4/6 名）、57.1%（4/7 名）であった。有害事象はいずれも軽度又は中等度であった。死亡した被験者はなく、重篤な有害事象は発現しなかった。1000 mg bid コホートの 1 名（CKD 4）が悪心及び嘔吐（共に軽度）を発現し、治験を中止した。1000 mg bid コホートの 1 名（CKD 3b）で高乳酸血症がみられた。また、各コホートの複数の被験者で空腹時に低血糖がみられた。臨床検査値、バイタルサイン及び心電図に臨床的に意義のある変化はみられなかった。

2.7.4.5.1.3.5　国内腎機能障害患者 PK 試験：DD401102 試験（資料番号：5.3.3.3.01）

本剤を単回経口投与したときの薬物動態に及ぼす腎機能障害の影響を検討するため、国内で腎機能障害患者及び腎機能正常者を対象に無対照、非盲検試験を実施した。eGFR（mL/min/1.73 m^2）が 90 以上の被験者を腎機能正常者と定義し、6 名を組み入れた。軽度腎機能障害は CKD 2、中等度腎機能障害は CKD 3a 及び CKD 3b、重度腎機能障害は CKD 4 の患者と定義し、各 6 名を組み入れた。腎機能正常者、軽度腎機能障害患者及び中等度腎機能障害患者には本剤 1000 mg を、重度腎機能障害患者には本剤 500 mg を単回投与した。

腎機能正常者及び腎機能障害患者共に有害事象は発現しなかった。また、臨床検査値、バイタルサイン及び心電図に臨床的に意義のある変化はみられなかった。

2.7.4.5.1.4　肝機能

ベースラインの肝機能パラメータ区分（異常あり、異常なし）別で有害事象の発現割合を

比較した。肝機能パラメータ区分の基準を表 2.7.4.5-13 に示す。基準のうち 1 つ以上に該当する被験者を異常あり（Yes）、いずれにも該当しない被験者を異常なし（No）と分類した。

表 2.7.4.5-13　肝機能パラメータ区分の基準

検査項目名	基準
総ビリルビン	1.6 mg/dL 以上
AST	基準値上限の 1.25 倍以上 50 IU 以上
ALT	基準値上限の 1.25 倍以上 50 IU 以上
アルカリホスファターゼ	基準値上限の 1.25 倍以上
γ-GTP	基準値上限の 1.5 倍以上

「医薬品等の副作用の重篤度分類基準について」（平成 4 年 6 月 29 日付け薬安第 80 号厚生省薬務局安全課長通知）の肝臓のグレード 1 の基準を参考に設定した。

2.7.4.5.1.4.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

ベースラインの肝機能パラメータ区分別の有害事象の全般的な発現割合を表 2.7.4.5-14 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-165 に示す。014 試験では、AST 又は ALT が基準値上限の 3 倍以上の肝機能障害を有する患者を除外した。018 試験では、スクリーニング時及びランダム化前来院時の AST 又は ALT が基準値上限の 3 倍以上、あるいは総ビリルビンが 2 mg/dL 以上のいずれかの高値を伴う重度の肝疾患患者を除外した。

消化器症状の発現割合は、肝機能パラメータ異常あり、なしの順に（以下同順）プラセボ群で 3.2%、12.6%、500 mg bid 群で 28.6%、11.5%、1000 mg bid 群で 8.3%、15.4%、1500 mg bid 群で 28.6%、32.8%であった。また、下痢の発現割合は、プラセボ群で 0%、0.7%、500 mg bid 群で 21.4%、0%、1000 mg bid 群で 0%、3.2%、1500 mg bid 群で 7.1%、8.2%であった。いずれの群でもそのほかの有害事象の発現割合にベースラインの肝機能パラメータ区分別で大きな違いはなかった。

表 2.7.4.5-14　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Hepatic Parameter Abnormality in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

TEAE Hepatic parameter abnormality	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Number of patients					
Yes	31	14	24	14	52
No	151	61	156	61	278

TEAE Hepatic parameter abnormality	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any TEAE					
Yes	14 (45.2%)	9 (64.3%)	14 (58.3%)	12 (85.7%)	35 (67.3%)
No	85 (56.3%)	42 (68.9%)	79 (50.6%)	43 (70.5%)	164 (59.0%)
Treatment-related TEAE					
Yes	2 (6.5%)	1 (7.1%)	1 (4.2%)	4 (28.6%)	6 (11.5%)
No	11 (7.3%)	3 (4.9%)	8 (5.1%)	14 (23.0%)	25 (9.0%)
Severe TEAE					
Yes	0	0	1 (4.2%)	0	1 (1.9%)
No	1 (0.7%)	0	5 (3.2%)	1 (1.6%)	6 (2.2%)
TEAE leading to death					
Yes	0	0	0	0	0
No	0	0	0	1 (1.6%)	1 (0.4%)
Serious TEAE					
Yes	0	0	0	0	0
No	2 (1.3%)	0	8 (5.1%)	1 (1.6%)	9 (3.2%)
TEAE leading to treatment discontinuation					
Yes	2 (6.5%)	0	0	1 (7.1%)	1 (1.9%)
No	12 (7.9%)	2 (3.3%)	6 (3.8%)	4 (6.6%)	12 (4.3%)
Hypoglycemia					
Yes	0	1 (7.1%)	1 (4.2%)	2 (14.3%)	4 (7.7%)
No	2 (1.3%)	4 (6.6%)	4 (2.6%)	2 (3.3%)	10 (3.6%)
Lactic acidosis related TEAEs					
Yes	0	0	0	0	0
No	0	0	0	0	0
Cardiovascular-related TEAEs					
Yes	1 (3.2%)	1 (7.1%)	0	1 (7.1%)	2 (3.8%)
No	6 (4.0%)	1 (1.6%)	3 (1.9%)	5 (8.2%)	9 (3.2%)
Digestive Symptoms					
Yes	1 (3.2%)	4 (28.6%)	2 (8.3%)	4 (28.6%)	10 (19.2%)
No	19 (12.6%)	7 (11.5%)	24 (15.4%)	20 (32.8%)	51 (18.3%)
Renal TEAEs					
Yes	0	0	0	0	0
No	2 (1.3%)	1 (1.6%)	2 (1.3%)	0	3 (1.1%)
Hepatic TEAEs					
Yes	2 (6.5%)	0	2 (8.3%)	1 (7.1%)	3 (5.8%)
No	2 (1.3%)	1 (1.6%)	0	2 (3.3%)	3 (1.1%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- Percentages are based on "Number of patients".

2.7.4.5.1.4.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

ベースラインの肝機能パラメータ区分別の有害事象の全般的な発現割合を表 2.7.4.5-15 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-169 に示す。本試験では、スクリーニング時の AST 又は ALT が基準値上限の 3 倍以上、あるいは総ビリルビンが 2 mg/dL 以上のいずれかの高値を伴う重度の肝疾患患者を除外した。

- 単独療法群では、有害事象の発現割合にベースラインの肝機能パラメータ区分別で大きな違いはなかった。
- TZD 併用療法群では、消化器症状の発現割合は肝機能パラメータ異常あり、なしの順に 0%、17.9%であった。そのほかの有害事象の発現割合にベースラインの肝機能パラメータ区分別で大きな違いはなかった。
- SU 併用療法群、GLIN 併用療法群、BIG 併用療法群、AGI 併用療法群、DPP4-I 併用療法群、GLP1-RA 併用療法群及び SGLT2-I 併用療法群では、有害事象の発現割合にベースラインの肝機能パラメータ区分別で大きな違いはなかった。

表 2.7.4.5-15　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Hepatic Parameter Abnormality in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

TEAE Hepatic parameter abnormality	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Number of patients											
Yes	18	16	11	10	9	9	12	20	13	100	118
No	116	111	53	54	55	56	51	50	50	480	596
Any TEAE											
Yes	10 (55.6%)	12 (75.0%)	9 (81.8%)	7 (70.0%)	5 (55.6%)	9 (100.0%)	11 (91.7%)	13 (65.0%)	12 (92.3%)	78 (78.0%)	88 (74.6%)
No	88 (75.9%)	90 (81.1%)	45 (84.9%)	41 (75.9%)	28 (50.9%)	41 (73.2%)	39 (76.5%)	43 (86.0%)	36 (72.0%)	363 (75.6%)	451 (75.7%)
Treatment-related TEAE											
Yes	2 (11.1%)	2 (12.5%)	3 (27.3%)	4 (40.0%)	1 (11.1%)	1 (11.1%)	2 (16.7%)	3 (15.0%)	2 (15.4%)	18 (18.0%)	20 (16.9%)
No	11 (9.5%)	25 (22.5%)	7 (13.2%)	20 (37.0%)	5 (9.1%)	5 (8.9%)	12 (23.5%)	5 (10.0%)	5 (10.0%)	84 (17.5%)	95 (15.9%)
Severe TEAE											
Yes	0	0	0	1 (10.0%)	0	0	0	0	1 (7.7%)	2 (2.0%)	2 (1.7%)
No	2 (1.7%)	5 (4.5%)	0	3 (5.6%)	1 (1.8%)	1 (1.8%)	1 (2.0%)	2 (4.0%)	0	13 (2.7%)	15 (2.5%)
TEAE leading to death											
Yes	0	0	0	0	0	0	0	0	0	0	0
No	1 (0.9%)	0	0	0	0	0	0	0	0	0	1 (0.2%)
Serious TEAE											
Yes	0	1 (6.3%)	0	1 (10.0%)	1 (11.1%)	1 (11.1%)	0	1 (5.0%)	1 (7.7%)	6 (6.0%)	6 (5.1%)
No	4 (3.4%)	10 (9.0%)	1 (1.9%)	3 (5.6%)	3 (5.5%)	3 (5.4%)	3 (5.9%)	4 (8.0%)	3 (6.0%)	30 (6.3%)	34 (5.7%)
TEAE leading to treatment discontinuation											
Yes	0	1 (6.3%)	0	0	0	1 (11.1%)	0	5 (25.0%)	0	7 (7.0%)	7 (5.9%)
No	3 (2.6%)	8 (7.2%)	1 (1.9%)	7 (13.0%)	2 (3.6%)	3 (5.4%)	5 (9.8%)	10 (20.0%)	1 (2.0%)	37 (7.7%)	40 (6.7%)

TEAE Hepatic parameter abnormality	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Hypoglycemia											
Yes	0	2 (12.5%)	2 (18.2%)	2 (20.0%)	1 (11.1%)	1 (11.1%)	2 (16.7%)	1 (5.0%)	0	11 (11.0%)	11 (9.3%)
No	5 (4.3%)	19 (17.1%)	7 (13.2%)	4 (7.4%)	1 (1.8%)	1 (1.8%)	3 (5.9%)	1 (2.0%)	4 (8.0%)	40 (8.3%)	45 (7.6%)
Lactic acidosis related TEAEs											
Yes	0	1 (6.3%)	0	0	0	0	0	0	0	1 (1.0%)	1 (0.8%)
No	0	1 (0.9%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Cardiovascular-related TEAEs											
Yes	0	3 (18.8%)	0	1 (10.0%)	2 (22.2%)	2 (22.2%)	1 (8.3%)	0	2 (15.4%)	11 (11.0%)	11 (9.3%)
No	4 (3.4%)	8 (7.2%)	3 (5.7%)	5 (9.3%)	4 (7.3%)	6 (10.7%)	2 (3.9%)	5 (10.0%)	2 (4.0%)	35 (7.3%)	39 (6.5%)
Digestive Symptoms											
Yes	3 (16.7%)	5 (31.3%)	2 (18.2%)	5 (50.0%)	0	0	2 (16.7%)	5 (25.0%)	4 (30.8%)	23 (23.0%)	26 (22.0%)
No	27 (23.3%)	23 (20.7%)	10 (18.9%)	21 (38.9%)	5 (9.1%)	10 (17.9%)	19 (37.3%)	10 (20.0%)	11 (22.0%)	109 (22.7%)	136 (22.8%)
Renal TEAEs											
Yes	0	1 (6.3%)	0	0	0	1 (11.1%)	0	0	1 (7.7%)	3 (3.0%)	3 (2.5%)
No	1 (0.9%)	1 (0.9%)	1 (1.9%)	1 (1.9%)	3 (5.5%)	2 (3.6%)	3 (5.9%)	4 (8.0%)	2 (4.0%)	17 (3.5%)	18 (3.0%)
Hepatic TEAEs											
Yes	0	1 (6.3%)	0	0	0	1 (11.1%)	0	1 (5.0%)	3 (23.1%)	6 (6.0%)	6 (5.1%)
No	0	2 (1.8%)	1 (1.9%)	0	1 (1.8%)	2 (3.6%)	1 (2.0%)	1 (2.0%)	0	8 (1.7%)	8 (1.3%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- Percentages are based on "Number of patients".

2.7.4.5.1.4.3　インスリン製剤併用療法：020 試験

本試験では、スクリーニング時及びランダム化前来院時の AST 又は ALT が基準値上限の 3 倍以上、あるいは総ビリルビンが 2 mg/dL 以上のいずれかの高値を伴う重度の肝疾患患者を除外した。

(1) 二重盲検治療（16 週）

ベースラインの肝機能パラメータ区分別の有害事象の全般的な発現割合を表 2.7.4.5-16 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-173 に示す。いずれの群でも有害事象の発現割合にベースラインの肝機能パラメータ区分別で大きな違いはなかった。

表 2.7.4.5-16　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Hepatic Parameter Abnormality in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

TEAE Hepatic parameter abnormality	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Number of patients		
Yes	15	17
No	92	91
Any TEAE		
Yes	7 (46.7%)	10 (58.8%)
No	44 (47.8%)	47 (51.6%)
Treatment-related TEAE		
Yes	2 (13.3%)	2 (11.8%)
No	11 (12.0%)	14 (15.4%)
Severe TEAE		
Yes	1 (6.7%)	0
No	1 (1.1%)	0
TEAE leading to death		
Yes	0	0
No	0	0
Serious TEAE		
Yes	1 (6.7%)	0
No	2 (2.2%)	1 (1.1%)
TEAE leading to treatment discontinuation		
Yes	1 (6.7%)	0
No	3 (3.3%)	1 (1.1%)
Hypoglycemia		
Yes	1 (6.7%)	4 (23.5%)
No	16 (17.4%)	19 (20.9%)

TEAE Hepatic parameter abnormality	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Lactic acidosis related TEAEs		
Yes	0	0
No	0	0
Cardiovascular-related TEAEs		
Yes	0	0
No	1 (1.1%)	4 (4.4%)
Digestive Symptoms		
Yes	1 (6.7%)	1 (5.9%)
No	6 (6.5%)	9 (9.9%)
Renal TEAEs		
Yes	0	0
No	0	1 (1.1%)
Hepatic TEAEs		
Yes	0	0
No	0	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- Percentages are based on "Number of patients".

(2) 長期投与（52 週）

ベースラインの肝機能パラメータ区分別の有害事象の全般的な発現割合を表 2.7.4.5-17 に、有害事象ごとの発現割合を 2.7.4.7 項付録 Table S-177 に示す。有害事象の発現割合にベースラインの肝機能パラメータ区分別で大きな違いはなかった。

表 2.7.4.5-17　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Hepatic Parameter Abnormality in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

TEAE Hepatic parameter abnormality	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Number of patients			
Yes	14	17	31
No	87	91	178
Any TEAE			
Yes	12 (85.7%)	14 (82.4%)	26 (83.9%)
No	65 (74.7%)	78 (85.7%)	143 (80.3%)

TEAE Hepatic parameter abnormality	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Treatment-related TEAE			
Yes	4 (28.6%)	4 (23.5%)	8 (25.8%)
No	12 (13.8%)	24 (26.4%)	36 (20.2%)
Severe TEAE			
Yes	1 (7.1%)	0	1 (3.2%)
No	2 (2.3%)	1 (1.1%)	3 (1.7%)
TEAE leading to death			
Yes	0	0	0
No	1 (1.1%)	0	1 (0.6%)
Serious TEAE			
Yes	1 (7.1%)	1 (5.9%)	2 (6.5%)
No	5 (5.7%)	5 (5.5%)	10 (5.6%)
TEAE leading to treatment discontinuation			
Yes	1 (7.1%)	1 (5.9%)	2 (6.5%)
No	2 (2.3%)	4 (4.4%)	6 (3.4%)
Hypoglycemia			
Yes	7 (50.0%)	5 (29.4%)	12 (38.7%)
No	29 (33.3%)	34 (37.4%)	63 (35.4%)
Lactic acidosis related TEAEs			
Yes	0	1 (5.9%)	1 (3.2%)
No	0	0	0
Cardiovascular-related TEAEs			
Yes	1 (7.1%)	0	1 (3.2%)
No	6 (6.9%)	8 (8.8%)	14 (7.9%)
Digestive Symptoms			
Yes	0	2 (11.8%)	2 (6.5%)
No	10 (11.5%)	18 (19.8%)	28 (15.7%)
Renal TEAEs			
Yes	0	0	0
No	1 (1.1%)	1 (1.1%)	2 (1.1%)
Hepatic TEAEs			
Yes	0	1 (5.9%)	1 (3.2%)
No	2 (2.3%)	2 (2.2%)	4 (2.2%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Percentages are based on "Number of patients".

2.7.4.5.1.4.4　海外肝機能障害患者 PK 試験：PXL008-024 試験（資料番号：5.3.3.3.02）

本剤を単回経口投与したときの薬物動態に及ぼす中等度の肝機能障害の影響を検討するため、海外で中等度肝機能障害患者及び肝機能正常者を対象とした第 1 相、単施設、非盲検、並行群間試験を実施した。肝機能障害の評価には Child-Pugh（CP）スコアを使用し、CP スコアが 7～9 ポイントの被験者を中等度肝機能障害患者として組み入れた。また、組み入れられた中等度肝機能障害患者と年齢、性別及び BMI によって 1 対 1 でマッチングされた肝機能正常者を組み入れた。中等度肝機能障害患者及び肝機能正常者は各 7 名組み入れられ、本剤 1000 mg を単回投与された。

有害事象の発現割合（発現被験者数、以下同様）は全体で 28.6%（4/14 名）で、中等度肝機能障害患者で 42.9%（3/7 名）、肝機能正常者で 14.3%（1/7 名）であった。すべての有害事象が本剤との因果関係ありと判断されたが、いずれも軽度で治験終了時までに回復した。有害事象ごとの発現割合を 2.7.6.7 項に示す。2 名以上で発現した有害事象はなく、重篤な有害事象は発現しなかった。臨床検査値、バイタルサイン、心電図パラメータ又は診察所見では、臨床的に意義のある変動又は所見は認められなかった。

2.7.4.5.1.5　その他の内因性要因

ベースラインのその他の内因性要因（BMI、HbA1c、2 型糖尿病罹病期間、糖尿病合併症、メタボリックシンドローム）の区分別で、有害事象の発現割合の部分集団解析を行った。

2.7.4.5.1.5.1　BMI

ベースラインの BMI 区分（25 kg/m^2 未満、25 kg/m^2 以上、25 以上 30 kg/m^2 未満、30 kg/m^2 以上）別の、有害事象、副作用、重度の有害事象、死亡に至った有害事象、重篤な有害事象、治験薬投与中止に至った有害事象、注目すべき有害事象の発現割合の部分集団解析結果を 2.7.4.7 項付録 Table S-530、Table S-540、Table S-550、Table S-560 に示す。

単独療法［二重盲検試験併合（24 週）：014 試験・018 試験］

いずれの群でも有害事象の発現状況に BMI 区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-530）。

単独及び血糖降下薬との併用療法［長期投与（52 週）：019 試験］（2.7.4.7 項付録 Table S-540）

- 単独療法群では有害事象の発現状況に BMI 区分別で大きな違いはなかった。
- SU 併用療法群では、治験薬の投与中止に至った有害事象の発現割合は BMI（kg/m^2）区分 25 未満、25～30 未満、30 以上の順に 3.1%、2.3%、31.6%であった。また、低血糖の発現割合は BMI 区分 25 未満、25 以上の順に 24.6%、8.1%であった。その他の有害事象の発現状況に BMI 区分別で大きな違いはなかった。

- GLIN 併用療法群では、低血糖の発現割合は BMI（kg/m^2）区分 25 未満、25～30 未満、30 以上の順に 20.0%、0%、18.2%であった。その他の有害事象の発現状況に BMI 区分別で大きな違いはなかった。
- BIG 併用療法群では、治験薬の投与中止に至った有害事象の発現割合は BMI（kg/m^2）区分 25 未満、25 以上の順に 22.7%、4.8%であった。その他の有害事象の発現状況に BMI 区分別で大きな違いはなかった。
- TZD 併用療法群では、消化器症状の発現割合は BMI（kg/m^2）区分 25 未満、25～30 未満、30 以上の順に 8.3%、16.0%、25.0%であった。その他の有害事象の発現状況に BMI 区分別で大きな違いはなかった。
- DPP4-I 併用療法群では、BMI（kg/m^2）区分 30 以上の被験者が少なく他の区分と比較するのは困難であったが、BMI 区分 25 以上と 25 未満では有害事象の発現状況に大きな違いはなかった。
- AGI 併用療法群、GLP1-RA 併用療法群及び SGLT2-I 併用療法群では、有害事象の発現状況に BMI 区分別で大きな違いはなかった。

インスリン製剤併用療法［二重盲検治療（16 週）、長期投与（52 週）：020 試験］

- 二重盲検治療では、低血糖の発現割合は BMI（kg/m^2）区分 25 未満、25 以上の順にプラセボ群で 23.3%、6.4%、イメグリミン群で 21.4%、21.2%であった。その他の有害事象の発現状況に BMI 区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-550）。
- 長期投与では、低血糖の発現割合が BMI（kg/m^2）区分 25 未満、25～30 未満、30 以上の順に 41.2%、35.1%、5.6%であった。その他の有害事象の発現状況に BMI 区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-560）。

2.7.4.5.1.5.2　HbA1c

ベースラインの HbA1c 区分（8.0%未満、8.0%以上、8.0 以上 9.0%未満、9.0%以上）別の、有害事象、副作用、重度の有害事象、死亡に至った有害事象、重篤な有害事象、治験薬投与中止に至った有害事象、注目すべき有害事象の発現割合の部分集団解析結果を 2.7.4.7 項付録 Table S-531、Table S-541、Table S-551、Table S-561 に示す。

単独療法［二重盲検試験併合（24 週）：014 試験・018 試験］

1500 mg bid 群では HbA1c（%）区分 9.0 以上の被験者が少なく、他の区分と比較するのは困難であった。治験薬投与中止に至った有害事象の発現割合は HbA1c（%）区分 8.0 未満、8.0～9.0 未満、9.0 以上の順に（以下同順）プラセボ群で 1.9%、10.2%、37.5%、500 mg bid 群で 0%、0%、25.0%、1000 mg bid 群で 4.7%、0%、4.3%、1500 mg bid 群で 4.8%、10.0%、0%であった。消化器症状の発現割合は、プラセボ群で 10.3%、10.2%、18.8%、500 mg bid 群で 21.3%、5.0%、0%、1000 mg bid 群で 16.8%、6.0%、21.7%、1500 mg bid 群で 35.7%、30.0%、0%であった。その他の有害事象の発現状況に HbA1c 区分別で大きな違いはなかった（2.7.4.7

項付録 Table S-531）。

単独及び血糖降下薬との併用療法［長期投与（52 週）：019 試験］（2.7.4.7 項付録 Table S-541）

- 単独療法群では、治験薬投与中止に至った有害事象の発現割合は HbA1c（%）区分 8.0 未満、8.0～9.0 未満、9.0 以上の順に 0%、0%、27.3%であった。その他の有害事象の発現状況に HbA1c 区分別で大きな違いはなかった。
- SU 併用療法群では、低血糖の発現割合は HbA1c（%）区分 8.0 未満、8.0～9.0 未満、9.0 以上の順に 24.2%、19.2%、7.1%であった。その他の有害事象の発現状況に HbA1c 区分別で大きな違いはなかった。
- GLIN 併用療法群では、副作用の発現割合は HbA1c（%）区分 8.0 未満、8.0～9.0 未満、9.0 以上の順に（以下同順）8.7%、27.3%、10.5%であった。また、低血糖の発現割合は、21.7%、13.6%、5.3%であった。その他の有害事象の発現状況に HbA1c 区分別で大きな違いはなかった。
- AGI 併用療法群では、有害事象の発現割合は HbA1c（%）区分 8.0 未満、8.0～9.0 未満、9.0 以上の順に 75.0%、48.4%、23.1%であった。また、心血管関連事象の発現割合は、20.0%、6.5%、0%であった。その他の有害事象の発現状況に HbA1c 区分別で大きな違いはなかった。
- DPP4-I 併用療法群では、消化器症状の発現割合は HbA1c（%）区分 8.0 未満、8.0～9.0 未満、9.0 以上の順に 33.3%、42.9%、9.1%であった。その他の有害事象の発現状況に HbA1c 区分別で大きな違いはなかった。
- GLP1-RA 併用療法群では、治験薬投与中止に至った有害事象の発現割合は HbA1c（%）区分 8.0 未満、8.0～9.0 未満、9.0 以上の順に 11.8%、7.7%、40.7%であった。その他の有害事象の発現状況に HbA1c 区分別で大きな違いはなかった。
- BIG 併用療法群、TZD 併用療法群及び SGLT2-I 併用療法群では、有害事象の発現状況に HbA1c 区分別で大きな違いはなかった。

インスリン製剤併用療法［二重盲検治療（16 週）、長期投与（52 週）：020 試験］

- 二重盲検治療では、低血糖の発現割合は HbA1c（%）区分 8.0 未満、8.0～9.0 未満、9.0 以上の順にプラセボ群で 31.3%、18.2%、8.5%、イメグリミン群で 18.8%、22.6%、20.5%であった。その他の有害事象の発現状況に HbA1c 区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-551）。
- 長期投与では、有害事象の発現状況に HbA1c 区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-561）。

2.7.4.5.1.5.3　2 型糖尿病罹病期間

2 型糖尿病罹病期間区分（5 年未満、5 年以上）別の有害事象、副作用、重度の有害事象、

死亡に至った有害事象、重篤な有害事象、治験薬投与中止に至った有害事象、注目すべき有害事象の発現割合の部分集団解析結果を 2.7.4.7 項付録 Table S-532、Table S-542、Table S-552、Table S-562 に示す。

単独療法［二重盲検試験併合（24 週）：014 試験・018 試験］

いずれの群でも有害事象の発現状況に 2 型糖尿病罹病期間区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-532）。

単独及び血糖降下薬との併用療法［長期投与（52 週）：019 試験］（2.7.4.7 項付録 Table S-542）

- 単独療法群では、有害事象の発現状況に 2 型糖尿病罹病期間区分別で大きな違いはなかった。
- TZD 併用療法群では、消化器症状の発現割合は 2 型糖尿病罹病期間区分 5 年未満、5 年以上の順に 5.0%、20.0%であった。その他の有害事象の発現状況に 2 型糖尿病罹病期間区分別で大きな違いはなかった。
- SU 併用療法群、GLIN 併用療法群、BIG 併用療法群、AGI 併用療法群、DPP4-I 併用療法群、GLP1-RA 併用療法群及び SGLT2-I 併用療法群では、有害事象の発現状況に 2 型糖尿病罹病期間区分別で大きな違いはなかった。

インスリン製剤併用療法［二重盲検治療（16 週）、長期投与（52 週）：020 試験］

二重盲検治療、長期投与ともに有害事象の発現状況に 2 型糖尿病罹病期間区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-552 及び Table S-562）。

2.7.4.5.1.5.4　糖尿病合併症

糖尿病合併症区分（あり、なし）別の有害事象、副作用、重度の有害事象、死亡に至った有害事象、重篤な有害事象、治験薬投与中止に至った有害事象、注目すべき有害事象の発現割合の部分集団解析結果を 2.7.4.7 項付録 Table S-533、Table S-543、Table S-553、Table S-563 に示す。MedDRA HLGT「糖尿病合併症」に含まれる PT に該当する合併症のある被験者をあり（Yes）、ない被験者をなし（No）に分類した。

単独療法［二重盲検試験併合（24 週）：014 試験・018 試験］

有害事象の発現割合は糖尿病合併症区分あり、なしの順にプラセボ群で 54.8%、54.3%、500 mg bid 群で 64.7%、69.0%、1000 mg bid 群で 58.1%、50.3%、1500 mg bid 群で 93.3%、68.3%であった。いずれの群でもその他の有害事象の発現状況に糖尿病合併症区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-533）。

単独及び血糖降下薬との併用療法［長期投与（52 週）：019 試験］（2.7.4.7 項付録 Table S-543）

- 単独療法群では、有害事象の発現状況に糖尿病合併症区分別で大きな違いはなかった。
- GLP1-RA 併用療法群では、消化器症状の発現割合は糖尿病合併症区分あり、なしの順に 34.4%、10.5%であった。その他の有害事象の発現状況に糖尿病合併症区分別で大きな違いはなかった。
- SU 併用療法群、GLIN 併用療法群、BIG 併用療法群、AGI 併用療法群、TZD 併用療法群、DPP4-I 併用療法群及び SGLT2-I 併用療法群では、有害事象の発現状況に糖尿病合併症区分別で大きな違いはなかった。

インスリン製剤併用療法［二重盲検治療（16 週）、長期投与（52 週）：020 試験］

二重盲検治療、長期投与ともに有害事象の発現状況に糖尿病合併症区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-553 及び Table S-563）。

2.7.4.5.1.5.5　メタボリックシンドローム

ベースラインのメタボリックシンドローム区分（該当、非該当）別の、有害事象、副作用、重度の有害事象、死亡に至った有害事象、重篤な有害事象、治験薬投与中止に至った有害事象、注目すべき有害事象の発現割合の部分集団解析解析結果を 2.7.4.7 項付録 Table S-534、Table S-544、Table S-554、Table S-564 に示す。ベースラインでメタボリックシンドローム区分の基準（表 2.7.4.5-18）（1）に該当し、基準（2）のうち 2 つ以上に該当する被験者を該当（Yes）、それ以外の被験者を非該当（No）と分類した。

表 2.7.4.5-18　メタボリックシンドローム区分の基準

（1）	ウエスト周囲径： 男性 85 cm 以上／女性 90 cm 以上
（2）	血圧： 収縮期血圧 130 mmHg 以上又は拡張期血圧 85 mmHg 以上
	空腹時高血糖： 空腹時グルコース 110 mg/dL 以上
	高トリグリセライド血症、低 HDL コレステロール血症： トリグリセリド 150 mg/dL 以上又は HDL コレステロール 40 mg/dL 未満

メタボリックシンドロームの定義と診断基準[文献 4)]を参考に設定した。

単独療法［二重盲検試験併合（24 週）：014 試験・018 試験］

いずれの群でも有害事象の発現状況にメタボリックシンドローム区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-534）。

単独及び血糖降下薬との併用療法［長期投与（52 週）：019 試験］（2.7.4.7 項付録 Table S-544）

- 単独療法群では、有害事象の発現状況にメタボリックシンドローム区分別で大きな違いはなかった。
- DPP4-I 併用療法群では、消化器症状の発現割合はメタボリックシンドローム区分該当、非該当の順に 20.0%、42.1%であった。その他の有害事象の発現状況にメタボリックシンドローム区分別で大きな違いはなかった。
- SU 併用療法群、GLIN 併用療法群、BIG 併用療法群、AGI 併用療法群、TZD 併用療法群、GLP1-RA 併用療法群及び SGLT2-I 併用療法群では、有害事象の発現状況にメタボリックシンドローム区分別で大きな違いはなかった。

インスリン製剤併用療法［二重盲検治療（16 週）、長期投与（52 週）：020 試験］

二重盲検治療、長期投与ともに有害事象の発現状況にメタボリックシンドローム区分別で大きな違いはなかった（2.7.4.7 項付録 Table S-554 及び Table S-564）。

2.7.4.5.2　外因性要因

2.7.4.5.2.1　食事

2.7.4.5.2.1.1　国内食事の影響検討試験：DD401101 試験（資料番号：5.3.1.1.01）

本剤を食後及び空腹時に単回経口投与したときの薬物動態に及ぼす食事の影響を検討するために、国内で健康男性被験者を対象に非盲検、無作為化、2 用法 2 期クロスオーバー試験を実施した。食後投与及び空腹時投与共に有害事象は発現しなかった。また、臨床検査値、バイタルサイン及び心電図に臨床的に意義のある変化はみられなかった。

2.7.4.5.2.2　前治療

2.7.4.5.2.2.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

前治療歴区分（なし、あり）別の有害事象の全般的な発現割合を表 2.7.4.5-19 に示す。いずれの試験でも、薬物治療の経験がない（一度も治療経験がない又はスクリーニング 12 週間前から治療を受けていない）又はスクリーニングまでに 12 週間以上経口血糖降下薬の単独療法を受けている患者を選択した。いずれの群でも前治療歴区分別での有害事象の発現割合に大きな違いはなかった。

表 2.7.4.5-19　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Previous Treatment Status in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

TEAE Previous treatment status	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Number of patients					
Treatment naive	111	33	109	29	171
Previously treated	71	42	71	46	159
Any TEAE					
Treatment naive	52 (46.8%)	21 (63.6%)	48 (44.0%)	23 (79.3%)	92 (53.8%)
Previously treated	47 (66.2%)	30 (71.4%)	45 (63.4%)	32 (69.6%)	107 (67.3%)
Treatment-related TEAE					
Treatment naive	9 (8.1%)	0	6 (5.5%)	7 (24.1%)	13 (7.6%)
Previously treated	4 (5.6%)	4 (9.5%)	3 (4.2%)	11 (23.9%)	18 (11.3%)
Severe TEAE					
Treatment naive	0	0	4 (3.7%)	0	4 (2.3%)
Previously treated	1 (1.4%)	0	2 (2.8%)	1 (2.2%)	3 (1.9%)
TEAE leading to death					
Treatment naive	0	0	0	0	0
Previously treated	0	0	0	1 (2.2%)	1 (0.6%)
Serious TEAE					
Treatment naive	0	0	4 (3.7%)	0	4 (2.3%)
Previously treated	2 (2.8%)	0	4 (5.6%)	1 (2.2%)	5 (3.1%)
TEAE leading to treatment discontinuation					
Treatment naive	6 (5.4%)	0	3 (2.8%)	1 (3.4%)	4 (2.3%)
Previously treated	8 (11.3%)	2 (4.8%)	3 (4.2%)	4 (8.7%)	9 (5.7%)
Hypoglycemia					
Treatment naive	2 (1.8%)	2 (6.1%)	5 (4.6%)	1 (3.4%)	8 (4.7%)
Previously treated	0	3 (7.1%)	0	3 (6.5%)	6 (3.8%)
Lactic acidosis related TEAEs					
Treatment naive	0	0	0	0	0
Previously treated	0	0	0	0	0
Cardiovascular-related TEAEs					
Treatment naive	7 (6.3%)	2 (6.1%)	3 (2.8%)	4 (13.8%)	9 (5.3%)
Previously treated	0	0	0	2 (4.3%)	2 (1.3%)
Digestive Symptoms					
Treatment naive	8 (7.2%)	4 (12.1%)	11 (10.1%)	9 (31.0%)	24 (14.0%)
Previously treated	12 (16.9%)	7 (16.7%)	15 (21.1%)	15 (32.6%)	37 (23.3%)
Renal TEAEs					
Treatment naive	2 (1.8%)	0	2 (1.8%)	0	2 (1.2%)
Previously treated	0	1 (2.4%)	0	0	1 (0.6%)

TEAE Previous treatment status	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Hepatic TEAEs					
Treatment naive	3 (2.7%)	0	1 (0.9%)	3 (10.3%)	4 (2.3%)
Previously treated	1 (1.4%)	1 (2.4%)	1 (1.4%)	0	2 (1.3%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- Percentages are based on "Number of patients".

2.7.4.5.2.2.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

単独療法群では 12 週間以上の食事・運動療法で血糖コントロール不十分な患者を、併用療法群では 12 週間以上の食事・運動療法と血糖降下薬単独療法で血糖コントロール不十分な患者を選択した。そのため、単独療法群では全被験者が前治療歴なし、併用療法群では全被験者が前治療歴ありで（2.4.7.4 項付録 Table S-539）、治療群ごとの前治療歴区分別での有害事象の全般的な発現割合を評価しなかった。

2.7.4.5.2.2.3　インスリン製剤併用療法：020 試験

本試験では、食事・運動療法とインスリン単独療法で血糖コントロール不十分な患者又はインスリンと経口血糖降下薬 1 剤の併用療法で血糖コントロール不十分な患者を選択した。

(1) 二重盲検治療（16 週）

前治療歴区分（インスリン単独療法、インスリン及び経口血糖降下薬 1 剤の併用療法）別の有害事象の全般的な発現割合を表 2.7.4.5-20 に示す。いずれの群でも前治療歴区分別での有害事象の発現状況に大きな違いはなかった。

表 2.7.4.5-20　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Previous Treatment Status in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

TEAE Previous treatment status	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Number of patients		
Insulin monotherapy	86	87
Insulin in combination with 1 OHA	21	21
Any TEAE		
Insulin monotherapy	41 (47.7%)	45 (51.7%)
Insulin in combination with 1 OHA	10 (47.6%)	12 (57.1%)
Treatment-related TEAE		
Insulin monotherapy	10 (11.6%)	13 (14.9%)
Insulin in combination with 1 OHA	3 (14.3%)	3 (14.3%)

TEAE Previous treatment status	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Severe TEAE		
Insulin monotherapy	2 (2.3%)	0
Insulin in combination with 1 OHA	0	0
TEAE leading to death		
Insulin monotherapy	0	0
Insulin in combination with 1 OHA	0	0
Serious TEAE		
Insulin monotherapy	3 (3.5%)	1 (1.1%)
Insulin in combination with 1 OHA	0	0
TEAE leading to treatment discontinuation		
Insulin monotherapy	1 (1.2%)	1 (1.1%)
Insulin in combination with 1 OHA	3 (14.3%)	0
Hypoglycemia		
Insulin monotherapy	14 (16.3%)	18 (20.7%)
Insulin in combination with 1 OHA	3 (14.3%)	5 (23.8%)
Lactic acidosis related TEAEs		
Insulin monotherapy	0	0
Insulin in combination with 1 OHA	0	0
Cardiovascular-related TEAEs		
Insulin monotherapy	1 (1.2%)	4 (4.6%)
Insulin in combination with 1 OHA	0	0
Digestive Symptoms		
Insulin monotherapy	7 (8.1%)	8 (9.2%)
Insulin in combination with 1 OHA	0	2 (9.5%)
Renal TEAEs		
Insulin monotherapy	0	1 (1.1%)
Insulin in combination with 1 OHA	0	0
Hepatic TEAEs		
Insulin monotherapy	0	0
Insulin in combination with 1 OHA	0	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- Percentages are based on "Number of patients".

(2) 長期投与（52 週）

前治療歴区分（インスリン単独療法、インスリン及び経口血糖降下薬 1 剤の併用療法）別の有害事象の全般的な発現割合を表 2.7.4.5-21 に示す。前治療歴区分別での有害事象の発現状況に大きな違いはなかった。

表 2.7.4.5-21　Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Previous Treatment Status in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

TEAE Previous treatment status	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Number of patients			
Insulin monotherapy	83	87	170
Insulin in combination with 1 OHA	18	21	39
Any TEAE			
Insulin monotherapy	64 (77.1%)	74 (85.1%)	138 (81.2%)
Insulin in combination with 1 OHA	13 (72.2%)	18 (85.7%)	31 (79.5%)
Treatment-related TEAE			
Insulin monotherapy	14 (16.9%)	24 (27.6%)	38 (22.4%)
Insulin in combination with 1 OHA	2 (11.1%)	4 (19.0%)	6 (15.4%)
Severe TEAE			
Insulin monotherapy	3 (3.6%)	1 (1.1%)	4 (2.4%)
Insulin in combination with 1 OHA	0	0	0
TEAE leading to death			
Insulin monotherapy	1 (1.2%)	0	1 (0.6%)
Insulin in combination with 1 OHA	0	0	0
Serious TEAE			
Insulin monotherapy	5 (6.0%)	5 (5.7%)	10 (5.9%)
Insulin in combination with 1 OHA	1 (5.6%)	1 (4.8%)	2 (5.1%)
TEAE leading to treatment discontinuation			
Insulin monotherapy	3 (3.6%)	5 (5.7%)	8 (4.7%)
Insulin in combination with 1 OHA	0	0	0
Hypoglycemia			
Insulin monotherapy	31 (37.3%)	31 (35.6%)	62 (36.5%)
Insulin in combination with 1 OHA	5 (27.8%)	8 (38.1%)	13 (33.3%)
Lactic acidosis related TEAEs			
Insulin monotherapy	0	0	0
Insulin in combination with 1 OHA	0	1 (4.8%)	1 (2.6%)
Cardiovascular-related TEAEs			
Insulin monotherapy	7 (8.4%)	7 (8.0%)	14 (8.2%)
Insulin in combination with 1 OHA	0	1 (4.8%)	1 (2.6%)
Digestive Symptoms			
Insulin monotherapy	9 (10.8%)	17 (19.5%)	26 (15.3%)
Insulin in combination with 1 OHA	1 (5.6%)	3 (14.3%)	4 (10.3%)
Renal TEAEs			
Insulin monotherapy	1 (1.2%)	1 (1.1%)	2 (1.2%)
Insulin in combination with 1 OHA	0	0	0

TEAE Previous treatment status	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Hepatic TEAEs			
Insulin monotherapy	1 (1.2%)	3 (3.4%)	4 (2.4%)
Insulin in combination with 1 OHA	1 (5.6%)	0	1 (2.6%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Percentages are based on "Number of patients".

2.7.4.5.3　薬物相互作用

本剤は経口投与後、一部は代謝（酸化的芳香族化、N-脱メチル化）を受けるが、大部分は未変化体のまま尿中に排泄される（2.6.4.5.1 項）。海外の薬物相互作用試験では、メトホルミン、シタグリプチン及びシメチジンとの相互作用を検討した。その結果、シメチジンの併用で本剤の薬物動態は臨床的に意義のある影響を受けず、メトホルミン、シタグリプチンの併用で本剤はそれぞれの薬剤の薬物動態に臨床的に意義のある影響を与えなかった（2.7.2.2.2.4.2 項）。本項では、海外の薬物相互作用試験で薬物相互作用による安全性への影響を検討した。

2.7.4.5.3.1　外国人を対象としたメトホルミンとの薬物相互作用試験：PXL008-001 試験（資料番号：5.3.3.4.01）

PXL008-001 試験は、健康男性被験者を対象にメトホルミンと本剤の反復併用投与がメトホルミンの薬物動態パラメータに及ぼす影響を評価する単盲検、one-sequence 試験である。導入期にメトホルミン 850 mg 及び本剤のプラセボを 1 日 2 回、6 日間投与し、その後の上乗せ期にメトホルミン 850 mg 及び本剤 1500 mg を 1 日 2 回、6 日間投与した。

有害事象の発現割合［発現被験者数、発現件数（以下同様）］は、全体で 50.0%（8/16 名、27 件）、メトホルミン単独投与時で 31.3%（5/16 名、9 件）、メトホルミン及び本剤の併用投与時で 46.7%（7/15 名、18 件）であった。すべての有害事象は治験薬との因果関係ありと判断され、いずれも悪心、下痢及び嘔吐などの消化器系の事象であった。多くみられた有害事象とその発現割合は全体で、悪心が 37.5%（6/16 名、11 件）、下痢が 37.5%（6/16 名、6 件）、嘔吐が 12.5%（2/16 名、4 件）であった。有害事象はいずれも軽度又は中等度であった。死亡した被験者はなく、重篤な有害事象及び中止に至った有害事象は発現しなかった。臨床検査値、バイタルサイン及び心電図に臨床的に意義のある変化はみられなかった。

2.7.4.5.3.2　外国人を対象としたシタグリプチンとの薬物相互作用試験：PXL008-003 試験（資料番号：5.3.3.4.02）

PXL008-003 試験は、健康男性被験者を対象にシタグリプチンと本剤の反復併用投与がシタグリプチンの薬物動態パラメータに及ぼす影響を評価する単盲検、one-sequence 試験である。導入期にシタグリプチン 100 mg を 1 日 1 回（朝食時）、本剤のプラセボを 1 日 2 回（朝食時及び夕食時）、6 日間投与し、その後の上乗せ期にはシタグリプチン 100 mg を 1 日 1 回（朝食時）、本剤 1500 mg を 1 日 2 回（朝食時及び夕食時）、6 日間投与した。

有害事象の発現割合［発現被験者数、発現件数（以下同様）］は、全体で 87.5%（14/16 名、49 件）、シタグリプチンの単独投与時で 56.3%（9/16 名、20 件）、シタグリプチン及び本剤の併用投与時で 68.8%（11/16 名、29 件）であった。2 名以上に発現した有害事象とその発現割合は全体で、頭痛が 56.3%（9/16 名、17 件）、鼻咽頭炎が 25.0%（4/16 名、4 件）、悪心が 18.8%（3/16 名、8 件）、下痢及び頻尿がそれぞれ 18.8%（3/16 名、3 件）、嘔吐及び食欲減退がそれぞれ 12.5%（2/16 名、2 件）であった。このうち悪心、嘔吐及び食欲減退はシタグリプチン及び本剤の併用投与時にのみみられ、頻尿はシタグリプチンの単独投与時にのみみられた。有害事象はいずれも軽度又は中等度であった。死亡した被験者はなく、重篤な有害事象及び中止に至った有害事象は発現しなかった。臨床検査値、バイタルサイン及び心電図に臨床的に意義のある変化はみられなかった。

2.7.4.5.3.3　外国人を対象としたシメチジンとの薬物相互作用試験：PXL008-023 試験（資料番号：5.3.3.4.03）

PXL008-023 試験は、健康被験者を対象にシメチジンの反復経口投与が本剤の単回経口投与時の薬物動態に及ぼす影響を評価する非盲検、one-sequence 試験である。Day 1 に本剤 1500 mg を単独で単回経口投与、Day 5～10 にシメチジン 400 mg を 1 日 2 回 6 日間投与、Day 8 に本剤 1500 mg（2 回目）をシメチジンの朝投与と同時に単回経口投与した。

有害事象の発現割合［発現被験者数、発現件数（以下同様）］は、本剤の単独投与時に 12.5%（2/16 名、4 件）、シメチジン及び本剤の併用投与時に 12.5%（2/16 名、3 件）であった。SOC 別で最も多くみられた有害事象は胃腸障害で、発現割合は本剤の単独投与時に 12.5%［2/16 名、3 件（上腹部痛並びに同一被験者で発現した腹痛及び悪心）］、シメチジン及び本剤の併用投与時に 6.3%［1/16 名、1 件（心窩部不快感）］であった。心窩部不快感を除いて、胃腸障害の有害事象はいずれも治験薬との因果関係ありと判断された。そのほかに眼痛、頭痛及びカテーテル留置部位疼痛が各 1 件報告された。このうち頭痛のみが治験責任医師により治験薬との因果関係ありと判断された。有害事象はいずれも軽度又は中等度であった。死亡した被験者はなく、重篤な有害事象及び中止に至った有害事象は発現しなかった。臨床検査値、バイタルサイン及び 12 誘導心電図に臨床的に意義のある変化はみられなかった。

2.7.4.5.4　妊娠及び授乳時の使用

014 試験、018 試験、019 試験及び 020 試験では、妊娠可能な場合は避妊に同意する被験

者を選択し、妊婦又は授乳中の女性を除外した。臨床試験中に妊娠した被験者はいなかった。また、ラットを用いた非臨床試験で、[^{14}C]で標識した本剤の乳汁中への移行が認められた（2.6.4.6.4 項）。

2.7.4.5.5　過量投与

014 試験、018 試験、019 試験及び 020 試験では、本剤の 1 回投与量、又は 1 日投与量が 6000 mg を超える場合を過量投与と定義した。いずれの試験でも過量投与された被験者はいなかった。

2.7.4.5.6　薬物乱用

014 試験、018 試験、019 試験及び 020 試験では、本剤への依存性の評価は行わなかった。

2.7.4.5.7　離脱症状及び反跳現象

014 試験、018 試験、019 試験及び 020 試験では、投与終了後の離脱症状や反跳現象の評価は行わなかった。

2.7.4.5.8　自動車運転及び機械操作に対する影響又は精神機能の障害

低血糖は、その症状として眠気、めまい、集中力低下、見当識低下、霧視、不安感等が発現する可能性があり[文献 5)]、自動車運転及び機械操作に影響すると考えられる。014 試験、018 試験、019 試験及び 020 試験での低血糖の発現状況を 2.7.4.2.1.6.2.1 項に示した。

2.7.4.6　市販後データ

2020 年 7 月末時点で本剤の承認を取得している国又は地域はないため、市販後データは存在しない。

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5) 日本糖尿病学会. 糖尿病診療ガイドライン 2019. 東京: 南江堂; 2019. P329-345.【5.4.28】

2.7.4.7　付録

付録一覧

見出し	表番号	表番号及びタイトル
表 2.7.4.7 1　注目すべき有害事象として集計した PT 一覧（MedDRA/J ver.20.1）	表 2.7.4.7-1	表 2.7.4.7-1　注目すべき有害事象として集計した PT 一覧（MedDRA/J ver.20.1）
t-s-008-demog-24wdb	Table S-008	Table S-008 Summary of Demographic and Baseline Characteristics in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-009-demog-019lt	Table S-009	Table S-009 Summary of Demographic and Baseline Characteristics in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-010-demog-020db	Table S-010	Table S-010 Summary of Demographic and Baseline Characteristics in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-011-demog-020lt	Table S-011	Table S-011 Summary of Demographic and Baseline Characteristics in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-024-aesoc-24wdb	Table S-024	Table S-024 Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-025-aesoc-24wdb	Table S-025	Table S-025 Summary of Treatment Emergent Adverse Events Related to Treatment by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-031-aeint-019lt	Table S-031	Table S-031 Summary of Treatment Emergent Lactic Acidosis-related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-032-aeint-019lt	Table S-032	Table S-032 Summary of Cardiovascular Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-053-aeint-020lt	Table S-053	Table S-053 Summary of Treatment Emergent Lactic Acidosis-related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-057-aesoc-020lt	Table S-057	Table S-057 Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-058-aesoc-020lt	Table S-058	Table S-058 Summary of Treatment Emergent Adverse Events Related to Treatment by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-061-aesev-24wdb	Table S-061	Table S-061 Summary of Treatment Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

見出し	表番号	表番号及びタイトル
t-s-063-aesev-019lt	Table S-063	Table S-063 Summary of Treatment Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-065-aesev-020db	Table S-065	Table S-065 Summary of Treatment Emergent Adverse Events by Maximum Severity , System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-067-aesev-020lt	Table S-067	Table S-067 Summary of Treatment Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-068-aeons-24wdb	Table S-068	Table S-068 Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Timing of Initial Onset, System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-069-aeons-24wdb	Table S-069	Table S-069 Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Timing of Every Onset, System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-072-aeons-019lt	Table S-072	Table S-072 Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Timing of Initial Onset, System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-073-aeons-019lt	Table S-073	Table S-073 Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Timing of Every Onset, System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-076-aeons-020db	Table S-076	Table S-076 Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Timing of Initial Onset, System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
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t-s-080-aeons-020lt	Table S-080	Table S-080 Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Timing of Initial Onset, System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
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t-s-094-labot-020db	Table S-094	Table S-094 Summary of Markedly Abnormal Post-Baseline Laboratory Values in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

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t-s-095-labot-020lt	Table S-095	Table S-095 Summary of Markedly Abnormal Post-Baseline Laboratory Values in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
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t-s-101-labot-019lt	Table S-101	Table S-101 Summary of Change from Baseline in eGFR (mL/min/1.73m2) to Week 52 in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
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t-s-107-vsign-020db	Table S-107	Table S-107 Summary of Change from Baseline in Weight (kg) at All Visits in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
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t-s-111-vsign-020lt	Table S-111	Table S-111 Summary of Change from Baseline in Weight (kg) at All Visits in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-160-aesoc-other	Table S-160	Table S-160 Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term in All Patients Treated Imeglimin (PXL008-014, PXL008-018, PXL008-019, PXL008-020; Safety Population, Long-term Safety Population)
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t-s-167-subae-019lt	Table S-167	Table S-167 Subgroup Analysis of Treatment Emergent Adverse Events by Sex, System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
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t-s-171-subae-020db	Table S-171	Table S-171 Subgroup Analysis of Treatment Emergent Adverse Events by Sex, System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-172-subae-020db	Table S-172	Table S-172 Subgroup Analysis of Treatment Emergent Adverse Events by Renal Function, System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
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t-s-180-labot-24wdb	Table S-180	Table S-180 Shift of Laboratory Findings of Urinalysis in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
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t-s-196-labot-020db	Table S-196	Table S-196 Shift of Laboratory Findings of Urinalysis in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
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t-s-199-labot-020db	Table S-199	Table S-199 Shift of Laboratory Findings of UACR (Albuminuria) in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
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t-s-201-ecgqt-020db	Table S-201	Table S-201 Shift of ECG Findings in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
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t-s-204-labot-020lt	Table S-204	Table S-204 Shift of Laboratory Findings of Urinalysis in Long-term Period (PXL008-020; Long-term Safety Population)
t-s-205-labot-020lt	Table S-205	Table S-205 Shift of Laboratory Findings of Coagulation in Long-term Period (PXL008-020; Long-term Safety Population)
t-s-207-labot-020lt	Table S-207	Table S-207 Shift of Laboratory Findings of UACR (Albuminuria) in Long-term Period (PXL008-020; Long-term Safety Population)
t-s-208-labot-020lt	Table S-208	Table S-208 Shift of Laboratory Findings of Lactate Concentration in Long-term Period (PXL008-020; Long-term Safety Population)
t-s-209-ecgqt-020lt	Table S-209	Table S-209 Shift of ECG Findings in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-214-dispo-24wdb	Table S-214	Table S-214 Summary of Analysis Population in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-215-dispo-019lt	Table S-215	Table S-215 Summary of Analysis Population in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-216-dispo-020db	Table S-216	Table S-216 Summary of Analysis Population in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-217-dispo-020lt	Table S-217	Table S-217 Summary of Analysis Population in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-218-subae-other	Table S-218	Table S-218 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Age in All Patients Treated Imeglimin 1000 mg bid Monotherapy (PXL008-014, PXL008-018, PXL008-019; Safety Population, Long-term Safety Population)
t-s-219-subae-other	Table S-219	Table S-219 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Renal Function at Baseline in All Patients Treated Imeglimin 1000 mg bid Monotherapy (PXL008-014, PXL008-018, PXL008-019; Safety Population, Long-term Safety Population)
t-s-232-labot-24wdb	Table S-232	Table S-232 Summary of Change from Baseline in Plasma Lactate Concentration (mmol/L) at All Visits in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-530-subae-24wdb	Table S-530	Table S-530 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by BMI in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-531-subae-24wdb	Table S-531	Table S-531 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by HbA1c at baseline in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

見出し	表番号	表番号及びタイトル
t-s-532-subae-24wdb	Table S-532	Table S-532 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Duration of type 2 diabetes in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-533-subae-24wdb	Table S-533	Table S-533 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Complication of diabetes in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-534-subae-24wdb	Table S-534	Table S-534 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Metabolic syndrome in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-539-subae-019lt	Table S-539	Table S-539 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Previous Treatment Status in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-540-subae-019lt	Table S-540	Table S-540 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by BMI in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-541-subae-019lt	Table S-541	Table S-541 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by HbA1c at baseline in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-542-subae-019lt	Table S-542	Table S-542 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Duration of type 2 diabetes in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-543-subae-019lt	Table S-543	Table S-543 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Complication of diabetes in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-544-subae-019lt	Table S-544	Table S-544 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Metabolic syndrome in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-550-subae-020db	Table S-550	Table S-550 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by BMI in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-551-subae-020db	Table S-551	Table S-551 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by HbA1c at baseline in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-552-subae-020db	Table S-552	Table S-552 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Duration of type 2 diabetes in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-553-subae-020db	Table S-553	Table S-553 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Complication of diabetes in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

見出し	表番号	表番号及びタイトル
t-s-554-subae-020db	Table S-554	Table S-554 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Metabolic syndrome in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-560-subae-020lt	Table S-560	Table S-560 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by BMI in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-561-subae-020lt	Table S-561	Table S-561 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by HbA1c at baseline in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-562-subae-020lt	Table S-562	Table S-562 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Duration of type 2 diabetes in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-563-subae-020lt	Table S-563	Table S-563 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Complication of diabetes in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-564-subae-020lt	Table S-564	Table S-564 Subgroup Analysis of Overall Frequency of Treatment Emergent Adverse Events by Metabolic syndrome in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-565-vsign-24wdb	Table S-565	Table S-565 Summary of Change from Baseline in Vital Signs to Week 24 in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-566-vsign-24wdb	Table S-566	Table S-566 Summary of Change from Baseline in Vital Signs at All Visits in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)
t-s-567-vsign-019lt	Table S-567	Table S-567 Summary of Change from Baseline in Vital Signs to Week 52 in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-568-vsign-019lt	Table S-568	Table S-568 Summary of Change from Baseline in Vital Signs at All Visits in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)
t-s-569-vsign-020db	Table S-569	Table S-569 Summary of Change from Baseline in Vital Signs to Week 16 in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-570-vsign-020db	Table S-570	Table S-570 Summary of Change from Baseline in Vital Signs at All Visits in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)
t-s-571-vsign-020lt	Table S-571	Table S-571 Summary of Change from Baseline in Vital Signs to Week 52 in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-572-vsign-020lt	Table S-572	Table S-572 Summary of Change from Baseline in Vital Signs at All Visits in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)
t-s-573-expos-other	Table S-573	Table S-573 Overall Study Treatment Exposure in All Patients Treated Imeglimin (PXL008-014, PXL008-018, PXL008-019, PXL008-020; Safety Population, Long-term Safety Population)

表 2.7.4.7-1　注目すべき有害事象として集計した PT 一覧（MedDRA/J ver.20.1）

PT コード	PT_日本語	PT_英語
低血糖		
10020993	低血糖	Hypoglycaemia
乳酸アシドーシス関連事象		
10005635	血中乳酸増加	Blood lactic acid increased
10020660	高乳酸血症	Hyperlactacidaemia
10023676	乳酸アシドーシス	Lactic acidosis
10000457	酸塩基平衡異常	Acid base balance abnormal
10000486	アシドーシス	Acidosis
10002523	アニオンギャップ異常	Anion gap abnormal
10002528	アニオンギャップ増加	Anion gap increased
10005358	血中重炭酸塩異常	Blood bicarbonate abnormal
10005359	血中重炭酸塩減少	Blood bicarbonate decreased
10005539	血液ガス異常	Blood gases abnormal
10005633	血中乳酸異常	Blood lactic acid abnormal
10005705	血液ｐＨ異常	Blood pH abnormal
10005706	血液ｐＨ低下	Blood pH decreased
10079539	二酸化炭素結合能異常	Carbon dioxide combining power abnormal
10079540	二酸化炭素結合能減少	Carbon dioxide combining power decreased
10049037	アシドーシス性昏睡	Coma acidotic
10023499	クスマウル大呼吸	Kussmaul respiration
10027417	代謝性アシドーシス	Metabolic acidosis
10058982	炭酸ガス分圧異常	PCO2 abnormal
10034181	炭酸ガス分圧低下	PCO2 decreased
10060086	尿中乳酸増加	Urine lactic acid increased
心血管関連事象		
10057375	バリント症候群	Balint's syndrome
10077607	脳底動脈瘤	Basilar artery aneurysm
10007686	頚動脈瘤	Carotid artery aneurysm
10050403	頚動脈解離	Carotid artery dissection
10077079	脳血管内動脈瘤修復	Cerebral endovascular aneurysm repair
10075401	脳再潅流障害	Cerebral reperfusion injury
10075249	脳室穿破	Cerebral ventricular rupture
10049165	脳血管発作予防	Cerebrovascular accident prophylaxis
10054749	シャルコ・ブシャール微小動脈瘤	Charcot-Bouchard microaneurysms
10071359	先天性不全片麻痺	Congenital hemiparesis
10071326	ＣＳＦビリルビン陽性	CSF bilirubin positive
10078388	遅発性虚血性神経脱落症状	Delayed ischaemic neurological deficit
10077170	片側感覚消失	Hemianaesthesia
10077171	片側身体失認	Hemiasomatognosia
10078746	片側錯感覚	Hemiparaesthesia
10019465	不全片麻痺	Hemiparesis

PT コード	PT_日本語	PT_英語
10019468	片麻痺	Hemiplegia
10022736	脳内動脈瘤手術	Intra-cerebral aneurysm operation
10022758	頭蓋内動脈瘤	Intracranial aneurysm
10070606	脳卒中後うつ病	Post stroke depression
10079859	出血後水頭症	Posthaemorrhagic hydrocephalus
10077889	ガレン大静脈瘤	Vein of Galen aneurysmal malformation
10077498	椎骨動脈瘤	Vertebral artery aneurysm
10071716	椎骨動脈解離	Vertebral artery dissection
10048663	失認症	Agnosia
10052906	脳血管造影異常	Angiogram cerebral abnormal
10002948	失語症	Aphasia
10067967	脳損傷	Brain injury
10064012	中枢痛症候群	Central pain syndrome
10070728	脳ヘモジデリン沈着	Cerebral haemosiderin deposition
10075562	ＣＳＦ赤血球陽性	CSF red blood cell count positive
10013033	両麻痺	Diplegia
10013887	構語障害	Dysarthria
10071355	内頚動脈屈曲	Internal carotid artery kinking
10073565	頭蓋内動脈解離	Intracranial artery dissection
10072882	修正ランキンスコア減少	Modified Rankin score decreased
10072881	修正ランキンスコア増加	Modified Rankin score increased
10027925	不全単麻痺	Monoparesis
10027926	単麻痺	Monoplegia
10065531	ＮＩＨ脳卒中スケール異常	NIH stroke scale abnormal
10065529	ＮＩＨ脳卒中スケールスコア減少	NIH stroke scale score decreased
10065528	ＮＩＨ脳卒中スケールスコア増加	NIH stroke scale score increased
10033799	麻痺	Paralysis
10033885	不全対麻痺	Paraparesis
10033892	対麻痺	Paraplegia
10033985	不全麻痺	Paresis
10049680	四肢不全麻痺	Quadriparesis
10037714	四肢麻痺	Quadriplegia
10075037	右半球症候群	Right hemisphere deficit syndrome
10070564	脳表ヘモジデリン沈着症	Superficial siderosis of central nervous system
10077168	視覚性失認	Visual agnosia
10066856	視覚正中線偏位症候群	Visual midline shift syndrome
10077031	大脳基底核血腫	Basal ganglia haematoma
10067057	大脳基底核出血	Basal ganglia haemorrhage
10071043	大脳基底核卒中	Basal ganglia stroke
10075736	脳底動脈穿孔	Basilar artery perforation
10073230	脳幹血腫	Brain stem haematoma
10006145	脳幹出血	Brain stem haemorrhage

PT コード	PT_日本語	PT_英語
10071205	脳幹微小出血	Brain stem microhaemorrhage
10068644	脳幹卒中	Brain stem stroke
10051328	頚動脈瘤破裂	Carotid aneurysm rupture
10075728	頚動脈穿孔	Carotid artery perforation
10072043	中枢神経系出血	Central nervous system haemorrhage
10061038	小脳血腫	Cerebellar haematoma
10008030	小脳出血	Cerebellar haemorrhage
10071206	小脳微小出血	Cerebellar microhaemorrhage
10079062	小脳卒中	Cerebellar stroke
10075394	脳動脈瘤穿孔	Cerebral aneurysm perforation
10008076	梅毒性脳動脈瘤破裂	Cerebral aneurysm ruptured syphilitic
10008086	出血性脳動静脈奇形	Cerebral arteriovenous malformation haemorrhagic
10075734	大脳動脈穿孔	Cerebral artery perforation
10053942	脳血腫	Cerebral haematoma
10008111	脳出血	Cerebral haemorrhage
10050157	胎児脳出血	Cerebral haemorrhage foetal
10008112	新生児脳出血	Cerebral haemorrhage neonatal
10067277	脳微小出血	Cerebral microhaemorrhage
10008190	脳血管発作	Cerebrovascular accident
10008196	脳血管障害	Cerebrovascular disorder
10073681	硬膜外出血	Epidural haemorrhage
10078254	脳実質外出血	Extra-axial haemorrhage
10015769	硬膜外血腫	Extradural haematoma
10018985	頭蓋内出血	Haemorrhage intracranial
10019005	出血性脳梗塞	Haemorrhagic cerebral infarction
10019016	出血性卒中	Haemorrhagic stroke
10055677	卒中の出血性変化	Haemorrhagic transformation stroke
10062025	脳内血腫除去術	Intracerebral haematoma evacuation
10059491	頭蓋内血腫	Intracranial haematoma
10022775	頭蓋内腫瘍出血	Intracranial tumour haemorrhage
10022840	脳室内出血	Intraventricular haemorrhage
10022841	新生児脳室内出血	Intraventricular haemorrhage neonatal
10052593	髄膜出血	Meningorrhagia
10073945	周産期脳卒中	Perinatal stroke
10076706	新生児脳室周囲出血	Periventricular haemorrhage neonatal
10049760	下垂体出血	Pituitary haemorrhage
10058940	被殻出血	Putamen haemorrhage
10039330	破裂性脳動脈瘤	Ruptured cerebral aneurysm
10076051	脊髄血腫	Spinal cord haematoma
10048992	脊髄出血	Spinal cord haemorrhage
10050162	脊髄硬膜外血腫	Spinal epidural haematoma

PT コード	PT_日本語	PT_英語
10049236	脊髄硬膜外出血	Spinal epidural haemorrhage
10073564	脊髄くも膜下出血	Spinal subarachnoid haemorrhage
10050164	脊髄硬膜下血腫	Spinal subdural haematoma
10073563	脊髄硬膜下出血	Spinal subdural haemorrhage
10059613	進行性脳卒中	Stroke in evolution
10076701	くも膜下血腫	Subarachnoid haematoma
10042316	くも膜下出血	Subarachnoid haemorrhage
10042317	新生児くも膜下出血	Subarachnoid haemorrhage neonatal
10042361	硬膜下血腫	Subdural haematoma
10042363	硬膜下血腫除去	Subdural haematoma evacuation
10042364	硬膜下出血	Subdural haemorrhage
10042365	新生児硬膜下出血	Subdural haemorrhage neonatal
10058939	視床出血	Thalamus haemorrhage
10075735	椎骨動脈穿孔	Vertebral artery perforation
10001903	一過性黒内障	Amaurosis fugax
10069020	大脳基底核梗塞	Basal ganglia infarction
10048963	脳底動脈閉塞	Basilar artery occlusion
10004163	脳底動脈狭窄	Basilar artery stenosis
10063093	脳底動脈血栓症	Basilar artery thrombosis
10075449	腕頭動脈硬化症	Brachiocephalic arteriosclerosis
10069694	腕頭動脈閉塞	Brachiocephalic artery occlusion
10075450	腕頭動脈狭窄	Brachiocephalic artery stenosis
10006127	脳低酸素症	Brain hypoxia
10074422	脳幹塞栓症	Brain stem embolism
10006147	脳幹梗塞	Brain stem infarction
10006148	脳幹部虚血	Brain stem ischaemia
10062573	脳幹血栓症	Brain stem thrombosis
10067744	内包性前兆症候群	Capsular warning syndrome
10071260	頚動脈形成	Carotid angioplasty
10007684	頚動脈塞栓	Carotid arterial embolus
10067116	頚動脈硬化症	Carotid arteriosclerosis
10053003	頚動脈バイパス	Carotid artery bypass
10078214	頚動脈石灰化	Carotid artery calcification
10061744	頚動脈疾患	Carotid artery disease
10064949	頚動脈不全	Carotid artery insufficiency
10048964	頚動脈閉塞	Carotid artery occlusion
10072558	頚動脈再狭窄	Carotid artery restenosis
10007687	頚動脈狭窄	Carotid artery stenosis
10066102	頚動脈ステント挿入	Carotid artery stent insertion
10069952	頚動脈ステント除去	Carotid artery stent removal
10007688	頚動脈血栓症	Carotid artery thrombosis
10007692	頚動脈内膜剥離術	Carotid endarterectomy

PT コード	PT_日本語	PT_英語
10072559	頚動脈血行再建	Carotid revascularisation
10053633	小脳動脈閉塞	Cerebellar artery occlusion
10008023	小脳動脈血栓症	Cerebellar artery thrombosis
10067167	小脳塞栓症	Cerebellar embolism
10008034	小脳梗塞	Cerebellar infarction
10068621	小脳虚血	Cerebellar ischaemia
10065559	脳動脈硬化症	Cerebral arteriosclerosis
10008088	大脳動脈塞栓症	Cerebral artery embolism
10008089	大脳動脈閉塞	Cerebral artery occlusion
10075423	大脳動脈再狭窄	Cerebral artery restenosis
10063648	大脳動脈狭窄	Cerebral artery stenosis
10008092	大脳動脈血栓症	Cerebral artery thrombosis
10070813	脳ガス塞栓症	Cerebral gas embolism
10008118	脳梗塞	Cerebral infarction
10008119	胎児脳梗塞	Cerebral infarction foetal
10008120	脳虚血	Cerebral ischaemia
10078311	脳微小塞栓症	Cerebral microembolism
10071508	脳血行再建	Cerebral revascularisation
10070671	敗血症性脳梗塞	Cerebral septic infarct
10070878	虚血性脳小血管疾患	Cerebral small vessel ischaemic disease
10008132	脳血栓症	Cerebral thrombosis
10076895	脳血管閉塞	Cerebral vascular occlusion
10059109	脳血管収縮	Cerebral vasoconstriction
10008138	大脳静脈血栓症	Cerebral venous thrombosis
10058842	脳血管不全	Cerebrovascular insufficiency
10061751	脳血管狭窄	Cerebrovascular stenosis
10060839	塞栓性脳梗塞	Embolic cerebral infarction
10014498	塞栓性脳卒中	Embolic stroke
10070511	低酸素性虚血性脳症	Hypoxic-ischaemic encephalopathy
10070754	内耳梗塞	Inner ear infarction
10060840	虚血性脳梗塞	Ischaemic cerebral infarction
10061256	虚血性脳卒中	Ischaemic stroke
10051078	ラクナ梗塞	Lacunar infarction
10076994	ラクナ脳卒中	Lacunar stroke
10024033	外側髄症候群	Lateral medullary syndrome
10056237	片頭痛性梗塞	Migrainous infarction
10067462	ミラール・ギュブレ症候群	Millard-Gubler syndrome
10028047	もやもや病	Moyamoya disease
10078202	心停止後症候群	Post cardiac arrest syndrome
10066591	処置後脳卒中	Post procedural stroke
10077033	脳実質外動脈硬化症	Precerebral arteriosclerosis
10036511	脳実質外動脈閉塞	Precerebral artery occlusion

PT コード	PT_日本語	PT_英語
10073240	可逆性脳血管収縮症候群	Reversible cerebral vasoconstriction syndrome
10050496	回復性虚血性神経脱落症候	Reversible ischaemic neurological deficit
10049440	脊髄動脈塞栓症	Spinal artery embolism
10071316	脊髄動脈血栓症	Spinal artery thrombosis
10042335	鎖骨下動脈スチール症候群	Subclavian steal syndrome
10064961	視床梗塞	Thalamic infarction
10067347	血栓性脳梗塞	Thrombotic cerebral infarction
10043647	血栓性脳卒中	Thrombotic stroke
10044390	一過性脳虚血発作	Transient ischaemic attack
10063661	血管性脳症	Vascular encephalopathy
10077143	血管ステント閉塞	Vascular stent occlusion
10077145	血管ステント再狭窄	Vascular stent restenosis
10077144	血管ステント狭窄	Vascular stent stenosis
10048965	椎骨動脈閉塞	Vertebral artery occlusion
10047330	椎骨動脈狭窄	Vertebral artery stenosis
10057777	椎骨動脈血栓症	Vertebral artery thrombosis
10047334	椎骨脳底動脈不全	Vertebrobasilar insufficiency
10008087	脳動脈炎	Cerebral arteritis
10075633	脳毛細血管拡張症	Cerebral capillary telangiectasia
10008097	脳循環不全	Cerebral circulatory failure
10076929	脳うっ血	Cerebral congestion
10065384	脳低潅流	Cerebral hypoperfusion
10074462	硬膜動静脈瘻	Dural arteriovenous fistula
10061251	頭蓋内静脈洞血栓症	Intracranial venous sinus thrombosis
10042567	上矢状洞血栓症	Superior sagittal sinus thrombosis
10044457	横静脈洞血栓症	Transverse sinus thrombosis
10047119	脳血管炎	Vasculitis cerebral
10072599	アミロイド関連画像異常	Amyloid related imaging abnormalities
10057361	血液脳関門欠損	Blood brain barrier defect
10080308	頚動脈延長拡張症	Carotid artery dolichoectasia
10068044	脳アミロイド血管障害	Cerebral amyloid angiopathy
10067466	脳微小血管症	Cerebral microangiopathy
10056371	脳血管動静脈奇形	Cerebrovascular arteriovenous malformation
10062327	先天性脳血管異常	Congenital cerebrovascular anomaly
10053601	胎児脳血管障害	Foetal cerebrovascular disorder
10077000	高血圧性脳血管疾患	Hypertensive cerebrovascular disease
10078822	原発性家族性脳石灰化	Primary familial brain calcification
10053841	スネドン症候群	Sneddon's syndrome
10061369	脊髄血管障害	Spinal vascular disorder
10041603	先天性脊椎血管異常	Spinal vessel congenital anomaly
10071573	スザック症候群	Susac's syndrome
10071505	椎骨脳底動脈伸展拡張症	Vertebrobasilar dolichoectasia

PT コード	PT_日本語	PT_英語
10051592	急性冠動脈症候群	Acute coronary syndrome
10000891	急性心筋梗塞	Acute myocardial infarction
10002388	不安定狭心症	Angina unstable
10005472	血中クレアチンホスホキナーゼＭＢ異常	Blood creatine phosphokinase MB abnormal
10005474	血中クレアチンホスホキナーゼＭＢ増加	Blood creatine phosphokinase MB increased
10011084	冠動脈塞栓症	Coronary artery embolism
10011086	冠動脈閉塞	Coronary artery occlusion
10053261	冠動脈再閉塞	Coronary artery reocclusion
10011091	冠動脈血栓症	Coronary artery thrombosis
10059025	冠動脈バイパス血栓症	Coronary bypass thrombosis
10075162	冠血管グラフト閉塞	Coronary vascular graft occlusion
10069167	コーニス症候群	Kounis syndrome
10028596	心筋梗塞	Myocardial infarction
10028602	心筋壊死	Myocardial necrosis
10051624	心筋再潅流障害	Myocardial reperfusion injury
10072186	気絶心筋	Myocardial stunning
10033697	乳頭筋梗塞	Papillary muscle infarction
10079319	周術期心筋梗塞	Periprocedural myocardial infarction
10066592	処置後心筋梗塞	Post procedural myocardial infarction
10058144	梗塞後狭心症	Postinfarction angina
10049768	無症候性心筋梗塞	Silent myocardial infarction
10058268	トロポニンＩ増加	Troponin I increased
10058267	トロポニン増加	Troponin increased
10058269	トロポニンＴ増加	Troponin T increased
10005468	血中クレアチンホスホキナーゼ異常	Blood creatine phosphokinase abnormal
10005470	血中クレアチンホスホキナーゼ増加	Blood creatine phosphokinase increased
10076898	心室瘢痕	Cardiac ventricular scarring
10072252	心電図の電気的無活動領域	ECG electrically inactive area
10075299	心筋梗塞の心電図所見	ECG signs of myocardial infarction
10051177	心電図異常Ｑ波	Electrocardiogram Q wave abnormal
10014390	心電図ＳＴ部分異常	Electrocardiogram ST segment abnormal
10014392	心電図ＳＴ部分上昇	Electrocardiogram ST segment elevation
10049225	心電図ＳＴ－Ｔ部分上昇	Electrocardiogram ST-T segment elevation
10062314	心電図Ｕ波逆転	Electrocardiogram U wave inversion
10061216	梗塞	Infarction
10075211	心筋壊死マーカー上昇	Myocardial necrosis marker increased
10061501	心筋血流スキャン異常	Scan myocardial perfusion abnormal
10049060	移植血管閉塞	Vascular graft occlusion
10063934	血管ステント血栓症	Vascular stent thrombosis
10002383	狭心症	Angina pectoris
10076419	狭心症相当症状	Anginal equivalent
10003211	冠動脈硬化症	Arteriosclerosis coronary artery

PT コード	PT_日本語	PT_英語
10003225	冠動脈攣縮	Arteriospasm coronary
10050329	冠動脈形成	Coronary angioplasty
10052086	冠動脈ステント挿入	Coronary arterial stent insertion
10011077	冠動脈バイパス	Coronary artery bypass
10079589	冠動脈圧迫	Coronary artery compression
10011078	冠動脈疾患	Coronary artery disease
10048631	冠動脈解離	Coronary artery dissection
10052895	冠動脈不全	Coronary artery insufficiency
10056489	冠動脈再狭窄	Coronary artery restenosis
10011089	冠動脈狭窄	Coronary artery stenosis
10011090	冠動脈手術	Coronary artery surgery
10076627	冠血管近距離照射療法	Coronary brachytherapy
10077824	冠動脈バイパス狭窄	Coronary bypass stenosis
10011101	冠動脈内膜剥離術	Coronary endarterectomy
10068534	冠動脈ノーリフロー現象	Coronary no-reflow phenomenon
10011105	冠動脈入口部狭窄	Coronary ostial stenosis
10049887	冠動脈血行再建	Coronary revascularisation
10077334	冠血管グラフト狭窄	Coronary vascular graft stenosis
10013428	解離性冠動脈瘤	Dissecting coronary artery aneurysm
10058317	心筋虚血の心電図所見	ECG signs of myocardial ischaemia
10067876	体外カウンターパルセーション	External counterpulsation
10055803	冠動脈出血	Haemorrhage coronary artery
10048858	虚血性心筋症	Ischaemic cardiomyopathy
10077864	虚血性僧帽弁逆流	Ischaemic mitral regurgitation
10072685	微小血管性冠動脈疾患	Microvascular coronary artery disease
10078980	心筋低酸素症	Myocardial hypoxia
10028600	心筋虚血	Myocardial ischaemia
10065608	経皮的冠インターベンション	Percutaneous coronary intervention
10036759	プリンツメタル狭心症	Prinzmetal angina
10066286	ストレス心筋症	Stress cardiomyopathy
10064994	鎖骨下冠動脈スチール症候群	Subclavian coronary steal syndrome
10058145	心内膜下虚血	Subendocardial ischaemia
10003201	冠血管造影異常	Arteriogram coronary abnormal
10055014	心臓負荷試験異常	Cardiac stress test abnormal
10074359	心肺運動試験異常	Cardiopulmonary exercise test abnormal
10060806	冠動脈コンピュータ断層撮影異常	Computerised tomogram coronary artery abnormal
10014391	心電図ＳＴ部分下降	Electrocardiogram ST segment depression
10052333	心電図ＳＴ－Ｔ部分異常	Electrocardiogram ST-T segment abnormal
10049224	心電図ＳＴ－Ｔ部分下降	Electrocardiogram ST-T segment depression
10050380	心電図異常Ｔ波	Electrocardiogram T wave abnormal
10014395	心電図Ｔ波逆転	Electrocardiogram T wave inversion

PT コード	PT_日本語	PT_英語
10015645	運動負荷心電図異常	Exercise electrocardiogram abnormal
10015653	運動試験異常	Exercise test abnormal
10077146	血管形成後再狭窄	Post angioplasty restenosis
10070746	負荷心エコー像異常	Stress echocardiogram abnormal
10079016	壁運動スコア指数異常	Wall motion score index abnormal
10063081	急性左室不全	Acute left ventricular failure
10001029	急性肺水腫	Acute pulmonary oedema
10063082	急性右室不全	Acute right ventricular failure
10007522	心臓性喘息	Cardiac asthma
10007554	心不全	Cardiac failure
10007556	急性心不全	Cardiac failure acute
10007558	慢性心不全	Cardiac failure chronic
10007559	うっ血性心不全	Cardiac failure congestive
10007560	高拍出性心不全	Cardiac failure high output
10007625	心原性ショック	Cardiogenic shock
10051093	心肺不全	Cardiopulmonary failure
10068230	心腎症候群	Cardiorenal syndrome
10063083	慢性左室不全	Chronic left ventricular failure
10063084	慢性右室不全	Chronic right ventricular failure
10010968	肺性心	Cor pulmonale
10010969	急性肺性心	Cor pulmonale acute
10010970	慢性肺性心	Cor pulmonale chronic
10050528	駆出率減少	Ejection fraction decreased
10019645	肝臓うっ血	Hepatic congestion
10051448	肝頚静脈逆流	Hepatojugular reflux
10024119	左室不全	Left ventricular failure
10024899	低心拍出量症候群	Low cardiac output syndrome
10049780	新生児心不全	Neonatal cardiac failure
10073708	閉塞性ショック	Obstructive shock
10037423	肺水腫	Pulmonary oedema
10050459	新生児肺水腫	Pulmonary oedema neonatal
10076203	放射線関連心不全	Radiation associated cardiac failure
10075337	右室駆出率低下	Right ventricular ejection fraction decreased
10039163	右室不全	Right ventricular failure
10060953	心室不全	Ventricular failure
10072066	人工心臓植込み	Artificial heart implant
10053410	心房性ナトリウム利尿ペプチド異常	Atrial natriuretic peptide abnormal
10053412	心房性ナトリウム利尿ペプチド増加	Atrial natriuretic peptide increased
10077819	前屈呼吸困難	Bendopnoea
10053408	脳性ナトリウム利尿ペプチド異常	Brain natriuretic peptide abnormal
10053405	脳性ナトリウム利尿ペプチド増加	Brain natriuretic peptide increased
10054936	心臓性肝硬変	Cardiac cirrhosis

PT コード	PT_日本語	PT_英語
10077454	心筋収縮調整療法	Cardiac contractility modulation therapy
10079751	心機能障害	Cardiac dysfunction
10007577	心指数減少	Cardiac index decreased
10007595	心拍出量低下	Cardiac output decreased
10059862	心臓再同調療法	Cardiac resynchronisation therapy
10053447	心室造影異常	Cardiac ventriculogram abnormal
10053499	左室造影異常	Cardiac ventriculogram left abnormal
10053444	右室造影異常	Cardiac ventriculogram right abnormal
10007632	心拡大	Cardiomegaly
10049874	心肺機能窮迫	Cardio-respiratory distress
10007646	心胸郭比増加	Cardiothoracic ratio increased
10007980	中心静脈圧上昇	Central venous pressure increased
10052337	拡張機能障害	Diastolic dysfunction
10013012	心室拡張	Dilatation ventricular
10013974	発作性夜間呼吸困難	Dyspnoea paroxysmal nocturnal
10019314	心臓移植	Heart transplant
10069112	肝静脈拡張	Hepatic vein dilatation
10079904	心内圧上昇	Intracardiac pressure increased
10059865	頚静脈拡張	Jugular vein distension
10050043	左室拡張	Left ventricular dilatation
10049694	左室機能不全	Left ventricular dysfunction
10050581	左室拡大	Left ventricular enlargement
10075565	下気道うっ血	Lower respiratory tract congestion
10069140	心筋抑制	Myocardial depression
10049235	夜間呼吸困難	Nocturnal dyspnoea
10071660	脳性ナトリウム利尿ペプチド前駆体N端フラグメント異常	N-terminal prohormone brain natriuretic peptide abnormal
10071662	脳性ナトリウム利尿ペプチド前駆体N端フラグメント増加	N-terminal prohormone brain natriuretic peptide increased
10030095	浮腫	Oedema
10080039	水疱性浮腫	Oedema blister
10049632	心疾患による浮腫	Oedema due to cardiac disease
10061317	新生児浮腫	Oedema neonatal
10030124	末梢性浮腫	Oedema peripheral
10031123	起坐呼吸	Orthopnoea
10049779	新生児末梢性浮腫	Peripheral oedema neonatal
10048959	末梢腫脹	Peripheral swelling
10077783	脳性ナトリウム利尿ペプチド前駆体異常	Prohormone brain natriuretic peptide abnormal
10077781	脳性ナトリウム利尿ペプチド前駆体増加	Prohormone brain natriuretic peptide increased
10037368	肺うっ血	Pulmonary congestion
10079613	右室拡張期虚脱	Right ventricular diastolic collapse
10074222	右室拡張	Right ventricular dilatation

PT コード	PT_日本語	PT_英語
10058597	右室機能不全	Right ventricular dysfunction
10050582	右室拡大	Right ventricular enlargement
10042246	一回拍出量減少	Stroke volume decreased
10078218	外科的心室再建	Surgical ventricular restoration
10071436	収縮機能障害	Systolic dysfunction
10047236	静脈圧上昇	Venous pressure increased
10047238	頚静脈圧異常	Venous pressure jugular abnormal
10047240	頚静脈圧上昇	Venous pressure jugular increased
10052371	心室補助人工心臓挿入	Ventricular assist device insertion
10059056	心室機能不全	Ventricular dysfunction
10071186	心室同期不全	Ventricular dyssynchrony
10068627	変時性応答不全	Chronotropic incompetence
10052464	心電図再分極異常	Electrocardiogram repolarisation abnormality
10067652	心電図ＲＲ間隔延長	Electrocardiogram RR interval prolonged
10057913	心電図Ｕ波陽性	Electrocardiogram U wave present
10055032	心電図Ｕ波異常	Electrocardiogram U-wave abnormality
10049418	心突然死	Sudden cardiac death
10076999	ベツォルト・ヤーリッシュ反射	Bezold-Jarisch reflex
10006093	徐脈	Bradycardia
10007515	心停止	Cardiac arrest
10049993	心臓死	Cardiac death
10053450	心電図テレメトリー異常	Cardiac telemetry abnormal
10007617	心肺停止	Cardio-respiratory arrest
10078310	中枢性徐脈	Central bradycardia
10014363	心電図異常	Electrocardiogram abnormal
10014369	外来心電図異常	Electrocardiogram ambulatory abnormal
10061116	心電図変化	Electrocardiogram change
10019300	心拍数異常	Heart rate abnormal
10019301	心拍数減少	Heart rate decreased
10019303	心拍数増加	Heart rate increased
10024855	意識消失	Loss of consciousness
10033557	動悸	Palpitations
10067207	リバウンド頻脈	Rebound tachycardia
10079117	呼吸性洞性不整脈振幅異常	Respiratory sinus arrhythmia magnitude abnormal
10079116	呼吸性洞性不整脈振幅減少	Respiratory sinus arrhythmia magnitude decreased
10079115	呼吸性洞性不整脈振幅増加	Respiratory sinus arrhythmia magnitude increased
10042434	突然死	Sudden death
10042772	失神	Syncope
10043071	頻脈	Tachycardia
10043079	発作性頻脈	Tachycardia paroxysmal

PT コード	PT_日本語	PT_英語
10049765	徐脈性不整脈	Bradyarrhythmia
10047284	心室無収縮	Ventricular asystole
10067618	心臓副伝導路	Accessory cardiac pathway
10001115	アダムス・ストークス症候群	Adams-Stokes syndrome
10054015	死戦調律	Agonal rhythm
10064191	心房内伝導時間遅延	Atrial conduction time prolongation
10003671	房室ブロック	Atrioventricular block
10003673	完全房室ブロック	Atrioventricular block complete
10003674	第一度房室ブロック	Atrioventricular block first degree
10003677	第二度房室ブロック	Atrioventricular block second degree
10068180	房室伝導時間短縮	Atrioventricular conduction time shortened
10069571	房室解離	Atrioventricular dissociation
10057393	二束ブロック	Bifascicular block
10059027	ブルガダ症候群	Brugada syndrome
10006578	脚ブロック	Bundle branch block
10006579	両側性脚ブロック	Bundle branch block bilateral
10006580	左脚ブロック	Bundle branch block left
10006582	右脚ブロック	Bundle branch block right
10010276	伝導障害	Conduction disorder
10012118	心室内伝導障害	Defect conduction intraventricular
10014372	心電図δ波異常	Electrocardiogram delta waves abnormal
10053656	心電図ＰＱ間隔延長	Electrocardiogram PQ interval prolonged
10075328	心電図ＰＱ間隔短縮	Electrocardiogram PQ interval shortened
10053657	心電図ＰＲ延長	Electrocardiogram PR prolongation
10014374	心電図ＰＲ短縮	Electrocardiogram PR shortened
10014380	心電図ＱＲＳ群延長	Electrocardiogram QRS complex prolonged
10014387	心電図ＱＴ延長	Electrocardiogram QT prolonged
10071710	ルネーグル病	Lenegre's disease
10024803	ＱＴ延長症候群	Long QT syndrome
10077503	発作性房室ブロック	Paroxysmal atrioventricular block
10040736	洞房ブロック	Sinoatrial block
10044644	三束ブロック	Trifascicular block
10048015	ウォルフ・パーキンソン・ホワイト症候群	Wolff-Parkinson-White syndrome
10029458	結節性不整脈	Nodal arrhythmia
10029470	結節性調律	Nodal rhythm
10040738	洞停止	Sinus arrest
10040739	洞性不整脈	Sinus arrhythmia
10040741	洞性徐脈	Sinus bradycardia
10075889	洞結節機能不全	Sinus node dysfunction
10047818	移動性ペースメーカー	Wandering pacemaker
10003119	不整脈	Arrhythmia
10058155	交互脈	Heart alternation

PT コード	PT_日本語	PT_英語
10019304	心拍数不整	Heart rate irregular
10053486	ペースメーカー原性不整脈	Pacemaker generated arrhythmia
10051994	ペースメーカー症候群	Pacemaker syndrome
10050106	発作性不整脈	Paroxysmal arrhythmia
10058151	無脈性電気活動	Pulseless electrical activity
10058156	再潅流性不整脈	Reperfusion arrhythmia
10047997	離脱性不整脈	Withdrawal arrhythmia
10003130	上室性不整脈	Arrhythmia supraventricular
10003658	心房細動	Atrial fibrillation
10003662	心房粗動	Atrial flutter
10071666	心房副収縮	Atrial parasystole
10003668	心房頻脈	Atrial tachycardia
10074640	接合部異所性頻脈	Junctional ectopic tachycardia
10040752	洞性頻脈	Sinus tachycardia
10042602	上室性期外収縮	Supraventricular extrasystoles
10065342	上室性頻脈性不整脈	Supraventricular tachyarrhythmia
10042604	上室性頻脈	Supraventricular tachycardia
10057526	心電図Ｐ波逆転	ECG P wave inverted
10050384	心電図異常Ｐ波	Electrocardiogram P wave abnormal
10071187	逆行性Ｐ波	Retrograde p-waves
10002611	房室興奮の異常	Anomalous atrioventricular excitation
10061592	心細動	Cardiac fibrillation
10052840	心粗動	Cardiac flutter
10015856	期外収縮	Extrasystoles
10049447	頻脈性不整脈	Tachyarrhythmia
10049003	促進型心室固有調律	Accelerated idioventricular rhythm
10033929	副収縮	Parasystole
10039111	心室固有調律	Rhythm idioventricular
10044066	トルサード　ド　ポアント	Torsade de pointes
10047281	心室性不整脈	Ventricular arrhythmia
10047289	心室性期外収縮	Ventricular extrasystoles
10047290	心室細動	Ventricular fibrillation
10047294	心室粗動	Ventricular flutter
10058184	心室性副収縮	Ventricular parasystole
10049761	心室早期興奮	Ventricular pre-excitation
10065341	心室性頻脈性不整脈	Ventricular tachyarrhythmia
10047302	心室性頻脈	Ventricular tachycardia
10003124	新生児不整脈	Arrhythmia neonatal
10058093	不整脈原性右室異形成症	Arrhythmogenic right ventricular dysplasia
10077893	房室結節分散	Atrioventricular node dispersion
10016847	胎児不整脈	Foetal arrhythmia
10061158	胎児心拍障害	Foetal heart rate disorder

PT コード	PT_日本語	PT_英語
10077575	胎児頻脈性不整脈	Foetal tachyarrhythmia
10019263	先天性心ブロック	Heart block congenital
10057926	先天性ＱＴ延長症候群	Long QT syndrome congenital
10024984	ラウン・ギャノン・レバイン症候群	Lown-Ganong-Levine syndrome
10049291	先天性ウォルフ・パーキンソン・ホワイト症候群	Wolff-Parkinson-White syndrome congenital
10074638	胎児心拍数基線細変動障害	Baseline foetal heart rate variability disorder
10006094	胎児徐脈	Bradycardia foetal
10056471	新生児徐脈	Bradycardia neonatal
10007516	新生児心停止	Cardiac arrest neonatal
10007618	新生児心肺停止	Cardio-respiratory arrest neonatal
10074642	胎児一過性頻脈異常	Foetal heart rate acceleration abnormality
10074636	胎児一過性徐脈異常	Foetal heart rate deceleration abnormality
10049775	新生児頻脈	Neonatal tachycardia
10074641	胎児機能不全心拍パターン	Nonreassuring foetal heart rate pattern
10043074	胎児頻脈	Tachycardia foetal
10007513	心臓瘤	Cardiac aneurysm
10002900	大動脈壊死	Aortic necrosis
10002906	大動脈狭窄	Aortic stenosis
10003175	動脈攣縮	Arterial spasm
10003210	動脈硬化症	Arteriosclerosis
10003212	メンケベルグ動脈硬化症	Arteriosclerosis Moenckeberg-type
10009243	顎筋跛行	Claudication of jaw muscles
10019013	出血性梗塞	Haemorrhagic infarction
10022562	間欠性跛行	Intermittent claudication
10024242	ルリッシュ症候群	Leriche syndrome
10028862	虚血性壊死	Necrosis ischaemic
10028872	動脈壊死	Necrosis of artery
10034568	末梢冷感	Peripheral coldness
10034576	末梢性虚血	Peripheral ischaemia
10036155	末梢循環不良	Poor peripheral circulation
10037912	レイノー現象	Raynaud's phenomenon
10042569	上大静脈症候群	Superior vena cava syndrome
10047139	血管収縮	Vasoconstriction
10047163	血管痙攣	Vasospasm
10048671	静脈狭窄	Venous stenosis
10049927	乾性壊疽	Dry gangrene
10050180	鎖骨下動脈狭窄	Subclavian artery stenosis
10052760	静脈硬化症	Phlebosclerosis
10053648	血管閉塞	Vascular occlusion
10054044	糖尿病性微小血管症	Diabetic microangiopathy
10054794	線維筋性形成異常	Fibromuscular dysplasia

PT コード	PT_日本語	PT_英語
10054880	血行不全	Vascular insufficiency
10057469	血管狭窄	Vascular stenosis
10057525	末梢動脈閉塞	Peripheral artery occlusion
10058178	大動脈閉塞	Aortic occlusion
10058987	下大静脈閉塞	Inferior vena caval occlusion
10058988	上大静脈閉塞	Superior vena cava occlusion
10058990	静脈閉塞	Venous occlusion
10058992	腸骨静脈閉塞	Iliac vein occlusion
10059385	四肢壊死	Extremity necrosis
10060965	動脈狭窄	Arterial stenosis
10061216	梗塞	Infarction
10061255	虚血	Ischaemia
10061815	糖尿病性血管障害	Diabetic vascular disorder
10062542	動脈不全	Arterial insufficiency
10062585	末梢動脈閉塞性疾患	Peripheral arterial occlusive disease
10062599	動脈閉塞性疾患	Arterial occlusive disease
10062610	虚血性四肢痛	Ischaemic limb pain
10063547	糖尿病性大血管障害	Diabetic macroangiopathy
10063900	スチール症候群	Steal syndrome
10064601	腸骨動脈閉塞	Iliac artery occlusion
10064771	上大静脈狭窄	Superior vena cava stenosis
10064849	外因性腸骨静脈圧迫	Extrinsic iliac vein compression
10065558	大動脈硬化症	Aortic arteriosclerosis
10068057	循環不全性充血	Dependent rubor
10069018	腕頭静脈狭窄	Brachiocephalic vein stenosis
10069694	腕頭動脈閉塞	Brachiocephalic artery occlusion
10069695	鎖骨下動脈閉塞	Subclavian artery occlusion
10069696	腹腔動脈閉塞	Coeliac artery occlusion
10069727	マイ・トゥルナー症候群	May-Thurner syndrome
10070911	下大静脈症候群	Inferior vena cava syndrome
10070995	血管圧迫	Vascular compression
10071642	膝窩動脈捕捉症候群	Popliteal artery entrapment syndrome
10072563	末梢動脈狭窄	Peripheral artery stenosis
10074639	下大静脈狭窄	Inferior vena cava stenosis
10075049	末梢静脈疾患	Peripheral venous disease
10075449	腕頭動脈硬化症	Brachiocephalic arteriosclerosis
10075450	腕頭動脈狭窄	Brachiocephalic artery stenosis
10076246	自然切断	Spontaneous amputation
10076604	アテローム動脈硬化性プラーク破裂	Atherosclerotic plaque rupture
10076713	鎖骨下静脈狭窄	Subclavian vein stenosis
10076837	腕頭静脈閉塞	Brachiocephalic vein occlusion
10077115	腸骨動脈疾患	Iliac artery disease

PT コード	PT_日本語	PT_英語
10078046	上腕動脈捕捉症候群	Brachial artery entrapment syndrome
10079164	鎖骨下静脈閉塞	Subclavian vein occlusion
10080307	動脈延長拡張症	Arterial dolichoectasia
10001526	空気塞栓症	Air embolism
10002897	大動脈塞栓	Aortic embolus
10002910	大動脈血栓症	Aortic thrombosis
10003178	動脈血栓症	Arterial thrombosis
10003880	腋窩静脈血栓症	Axillary vein thrombosis
10014513	動脈塞栓症	Embolism arterial
10014522	静脈塞栓症	Embolism venous
10021338	腸骨動脈塞栓症	Iliac artery embolism
10023237	頚静脈血栓症	Jugular vein thrombosis
10034272	骨盤静脈血栓症	Pelvic venous thrombosis
10036300	分娩後静脈血栓症	Postpartum venous thrombosis
10042332	鎖骨下動脈塞栓症	Subclavian artery embolism
10042334	鎖骨下動脈血栓症	Subclavian artery thrombosis
10043570	血栓性静脈炎	Thrombophlebitis
10043581	遊走性血栓静脈炎	Thrombophlebitis migrans
10043586	新生児血栓性静脈炎	Thrombophlebitis neonatal
10043595	表在性血栓性静脈炎	Thrombophlebitis superficial
10043607	血栓症	Thrombosis
10047193	大静脈塞栓症	Vena cava embolism
10047195	大静脈血栓症	Vena cava thrombosis
10047249	静脈血栓症	Venous thrombosis
10048591	血栓後症候群	Post thrombotic syndrome
10049446	鎖骨下静脈血栓症	Subclavian vein thrombosis
10050216	パジェット・シュレッター症候群	Paget-Schroetter syndrome
10051055	深部静脈血栓症	Deep vein thrombosis
10059126	青趾症候群	Blue toe syndrome
10060905	トルソー症候群	Trousseau's syndrome
10061169	塞栓症	Embolism
10061340	末梢血管塞栓症	Peripheral embolism
10061408	四肢静脈血栓症	Venous thrombosis limb
10063363	腕頭静脈血栓症	Brachiocephalic vein thrombosis
10063518	小指球ハンマー症候群	Hypothenar hammer syndrome
10064602	新生児静脈血栓症	Venous thrombosis neonatal
10066059	奇異性塞栓症	Paradoxical embolism
10067030	妊娠中の静脈血栓症	Venous thrombosis in pregnancy
10068365	大腿動脈塞栓症	Femoral artery embolism
10068605	静脈再疎通	Venous recanalisation
10072564	末梢動脈血栓症	Peripheral artery thrombosis
10073734	微小塞栓症	Microembolism

PT コード	PT_日本語	PT_英語
10075247	異物塞栓症	Foreign body embolism
10077022	分娩後血栓症	Postpartum thrombosis
10078118	カルシウム塞栓症	Calcium embolism
10079251	腫瘍随伴性血栓症	Paraneoplastic thrombosis
10079261	アテローム塞栓症	Atheroembolism
10002329	動脈瘤	Aneurysm
10002331	動静脈瘤	Aneurysm arteriovenous
10002882	大動脈瘤	Aortic aneurysm
10002886	大動脈瘤破裂	Aortic aneurysm rupture
10002895	大動脈解離	Aortic dissection
10016427	大腿動脈瘤	Femoral artery aneurysm
10042331	鎖骨下動脈瘤	Subclavian artery aneurysm
10048380	動脈瘤破裂	Aneurysm ruptured
10052326	大腿動脈解離	Femoral artery dissection
10057520	末梢動脈解離	Peripheral artery dissection
10057521	末梢動脈瘤	Peripheral artery aneurysm
10061660	動脈解離	Artery dissection
10062174	静脈性血管瘤	Venous aneurysm
10067975	大動脈壁内血腫	Aortic intramural haematoma
10068119	大動脈解離破裂	Aortic dissection rupture
10070296	動脈腸管瘻	Arterioenteric fistula
10070693	血管解離	Vascular dissection
10072788	大動脈解離による偽腔拡張	False lumen dilatation of aortic dissection
10074337	急性大動脈症候群	Acute aortic syndrome
10074396	穿通性アテローム動脈硬化性潰瘍	Penetrating atherosclerotic ulcer
10074971	動脈壁内血腫	Arterial intramural haematoma
10077109	静脈解離	Vein dissection
10077118	穿通性大動脈潰瘍	Penetrating aortic ulcer
10079908	末梢動脈瘤破裂	Peripheral artery aneurysm rupture
10002924	大動脈十二指腸瘻	Aorto-duodenal fistula
10003173	動脈破裂	Arterial rupture
10003226	動静脈瘻	Arteriovenous fistula
10007189	毛細血管障害	Capillary disorder
10007191	毛細血管脆弱	Capillary fragility
10015284	紅痛症	Erythromelalgia
10016825	潮紅	Flushing
10020565	充血	Hyperaemia
10029113	血管新生	Neovascularisation
10033546	蒼白	Pallor
10034636	末梢血管障害	Peripheral vascular disorder
10042335	鎖骨下動脈スチール症候群	Subclavian steal syndrome
10047073	血管脆弱化	Vascular fragility

PT コード	PT_日本語	PT_英語
10047095	血管痛	Vascular pain
10047141	血管拡張	Vasodilatation
10047183	静脈退色	Vein discolouration
10047184	静脈障害	Vein disorder
10047190	静脈壁肥厚	Vein wall hypertrophy
10048554	内皮細胞機能不全	Endothelial dysfunction
10048737	静脈穿刺不良	Poor venous access
10048995	紅色チアノーゼ	Erythrocyanosis
10051474	静脈結石	Phlebolith
10051550	頚動脈圧痛	Carotidynia
10051753	血管石灰化	Vascular calcification
10052076	血行動態不安定	Haemodynamic instability
10052664	血管シャント	Vascular shunt
10053649	血管破裂	Vascular rupture
10054156	上腸間膜動脈症候群	Superior mesenteric artery syndrome
10054208	大動脈石灰化	Aortic calcification
10054793	動脈線維症	Arterial fibrosis
10054805	大血管障害	Macroangiopathy
10057453	大動脈拡張	Aortic dilatation
10058648	大動脈障害	Aortic disorder
10059245	血管障害	Angiopathy
10059865	頚静脈拡張	Jugular vein distension
10060800	ほてり	Hot flush
10060874	大動脈破裂	Aortic rupture
10060963	動脈障害	Arterial disorder
10061636	血管異形成	Angiodysplasia
10062173	静脈閉塞性疾患	Venoocclusive disease
10062198	微小血管症	Microangiopathy
10063837	再潅流障害	Reperfusion injury
10065510	大動脈延長	Aortic elongation
10066243	大動脈壁肥厚	Aortic wall hypertrophy
10066363	血行力学的リバウンド	Haemodynamic rebound
10066397	内臓うっ血	Visceral congestion
10068717	表在静脈隆起	Superficial vein prominence
10069111	下大静脈拡張	Inferior vena cava dilatation
10069729	側副血行	Collateral circulation
10071248	上大静脈拡張	Superior vena cava dilatation
10072789	腸骨動脈破裂	Iliac artery rupture
10072809	動脈壁肥厚	Arterial wall hypertrophy
10072810	血管壁肥厚	Vascular wall hypertrophy
10074621	静脈虚脱	Vein collapse
10075393	血管陽性リモデリング	Positive vessel remodelling

PT コード	PT_日本語	PT_英語
10077110	静脈破裂	Vein rupture
10077262	血管内ガス	Intravascular gas
10077466	外膜嚢腫	Adventitial cystic disease
10079468	血管壁変色	Vascular wall discolouration
10015719	失血	Exsanguination
10015867	血液溢出	Extravasation blood
10018833	血瘤	Haematocoele
10018852	血腫	Haematoma
10055798	出血	Haemorrhage
10057687	血性分泌物	Bloody discharge
10060964	動脈出血	Arterial haemorrhage
10061993	新生児出血	Haemorrhage neonatal
10065441	静脈出血	Venous haemorrhage
10069510	帽状腱膜下血腫	Subgaleal haematoma
10075192	内出血	Internal haemorrhage
10079562	アッヘンバッハ症候群	Achenbach syndrome
10068149	血管穿孔	Vessel perforation
10075729	大動脈穿孔	Aortic perforation
10075730	下肢動脈穿孔	Lower limb artery perforation
10075731	腸骨動脈穿孔	Iliac artery perforation
10075732	動脈穿孔	Arterial perforation
10075733	静脈穿孔	Venous perforation
10075739	大腿動脈穿孔	Femoral artery perforation
10075740	鎖骨下動脈穿孔	Subclavian artery perforation
10075741	上大静脈穿孔	Superior vena cava perforation
10075742	下大静脈穿孔	Inferior vena cava perforation
10075743	鎖骨下静脈穿孔	Subclavian vein perforation
10075744	腸骨静脈穿孔	Iliac vein perforation
10075745	大腿静脈穿孔	Femoral vein perforation
10005144	出血性静脈瘤	Bleeding varicose vein
10043605	血栓性静脈瘤	Thrombosed varicose vein
10046995	静脈瘤性潰瘍	Varicose ulceration
10046996	静脈瘤	Varicose vein
10046999	静脈瘤破裂	Varicose vein ruptured
10047261	静脈弁破裂	Venous valve ruptured
10056717	静脈瘤性静脈炎	Varicophlebitis
10062696	くも状静脈	Spider vein
10000358	進行性高血圧	Accelerated hypertension
10002482	血管硬化	Angiosclerosis
10012758	拡張期高血圧	Diastolic hypertension
10015488	本態性高血圧症	Essential hypertension
10020772	高血圧	Hypertension

PT コード	PT_日本語	PT_英語
10020802	高血圧クリーゼ	Hypertensive crisis
10025600	悪性高血圧	Malignant hypertension
10026924	胎児に影響する母体の高血圧症	Maternal hypertension affecting foetus
10033771	奇異的昇圧反応	Paradoxical pressor response
10038562	腎血管性高血圧	Renovascular hypertension
10039834	二次性高血圧	Secondary hypertension
10042957	収縮期高血圧	Systolic hypertension
10048007	断薬性高血圧	Withdrawal hypertension
10049079	不安定高血圧	Labile hypertension
10049781	新生児高血圧	Hypertension neonatal
10057615	内分泌性高血圧	Endocrine hypertension
10058179	高血圧緊急症	Hypertensive emergency
10059238	高血圧性血管障害	Hypertensive angiopathy
10065508	起立性高血圧	Orthostatic hypertension
10065918	高血圧前症	Prehypertension
10067598	神経性高血圧	Neurogenic hypertension
10067895	チラミン反応	Tyramine reaction
10078932	仰臥位高血圧	Supine hypertension
10079496	高血圧性終末器官損傷	Hypertensive end-organ damage
消化器症状		
10061428	食欲減退	Decreased appetite
10060961	食欲障害	Appetite disorder
10012775	拒食	Diet refusal
10020710	過食	Hyperphagia
10021654	食欲亢進	Increased appetite
10056465	食物渇望	Food craving
10061832	摂食障害症状	Eating disorder symptom
10063743	過小食	Hypophagia
10064720	満腹感欠如	Lack of satiety
10067951	食塩渇望	Salt craving
10076659	遅食	Bradyphagia
10080283	食物拒否	Food refusal
10014062	摂食障害	Eating disorder
10036476	プラダーウィリ症候群	Prader-Willi syndrome
10059186	早期満腹	Early satiety
10066431	クリューバー・ビューシー症候群	Kluver-Bucy syndrome
10067315	睡眠関連摂食障害	Sleep-related eating disorder
10068034	脂肪性器性ジストロフィー	Adiposogenital dystrophy
10000050	腹部癒着	Abdominal adhesions
10000059	腹部不快感	Abdominal discomfort
10000060	腹部膨満	Abdominal distension
10000077	腹部腫瘤	Abdominal mass

PT コード	PT_日本語	PT_英語
10000081	腹痛	Abdominal pain
10000084	下腹部痛	Abdominal pain lower
10000087	上腹部痛	Abdominal pain upper
10000090	腹部硬直	Abdominal rigidity
10000097	腹部圧痛	Abdominal tenderness
10000133	異常便	Abnormal faeces
10000451	無酸症	Achlorhydria
10000647	急性腹症	Acute abdomen
10001901	アマルガム刺青	Amalgam tattoo
10002150	肛門拡張	Anal dilatation
10002153	裂肛	Anal fissure
10002156	痔瘻	Anal fistula
10002161	肛門白板症	Anal leukoplakia
10002168	肛門ポリープ	Anal polyp
10002172	肛門皮膚垂	Anal skin tags
10002173	肛門痙攣	Anal spasm
10002176	肛門狭窄	Anal stenosis
10002180	肛門潰瘍	Anal ulcer
10002248	穿孔性吻合部潰瘍	Anastomotic ulcer perforation
10002250	閉塞性吻合部潰瘍	Anastomotic ulcer, obstructive
10002581	肛門直腸狭窄	Anorectal stenosis
10002582	肛門直腸潰瘍	Anorectal ulcer
10002644	肛門直腸障害	Anorectal disorder
10002959	アフタ性潰瘍	Aphthous ulcer
10003068	唾液欠乏	Aptyalism
10003445	腹水	Ascites
10004137	バレット食道	Barrett's oesophagus
10004542	胃石	Bezoar
10006326	呼気臭	Breath odour
10006532	頬舌症候群	Buccoglossal syndrome
10007645	噴門痙攣	Cardiospasm
10008399	便習慣変化	Change of bowel habit
10008417	口唇炎	Cheilitis
10008418	口唇症	Cheilosis
10008882	慢性胃炎	Chronic gastritis
10009838	腹腔動脈圧迫症候群	Coeliac artery compression syndrome
10009839	セリアック病	Coeliac disease
10009887	大腸炎	Colitis
10009895	虚血性大腸炎	Colitis ischaemic
10009900	潰瘍性大腸炎	Colitis ulcerative
10009995	結腸瘻	Colonic fistula
10009996	結腸血腫	Colonic haematoma

PT コード	PT_日本語	PT_英語
10010774	便秘	Constipation
10011401	クローン病	Crohn's disease
10012110	便意切迫	Defaecation urgency
10012316	歯槽異常	Dental alveolar anomaly
10012318	齲歯	Dental caries
10012327	歯組織の壊死	Dental necrosis
10012328	歯髄障害	Dental pulp disorder
10012666	糖尿病性胃障害	Diabetic gastropathy
10012713	横隔膜ヘルニア	Diaphragmatic hernia
10012723	横隔膜ヘルニア、閉塞を伴う	Diaphragmatic hernia, obstructive
10012735	下痢	Diarrhoea
10012741	血性下痢	Diarrhoea haemorrhagic
10012743	新生児下痢	Diarrhoea neonatal
10013536	憩室瘻	Diverticular fistula
10013544	食道憩室炎	Diverticulitis oesophageal
10013554	憩室	Diverticulum
10013558	胃憩室	Diverticulum gastric
10013559	腸憩室	Diverticulum intestinal
10013560	出血性腸憩室	Diverticulum intestinal haemorrhagic
10013563	食道憩室	Diverticulum oesophageal
10013781	口内乾燥	Dry mouth
10013810	ダンピング症候群	Dumping syndrome
10013830	十二指腸閉塞	Duodenal obstruction
10013832	十二指腸穿孔	Duodenal perforation
10013833	十二指腸ポリープ	Duodenal polyp
10013836	十二指腸潰瘍	Duodenal ulcer
10013839	出血性十二指腸潰瘍	Duodenal ulcer haemorrhage
10013849	穿孔性十二指腸潰瘍	Duodenal ulcer perforation
10013850	閉塞を伴う穿孔性十二指腸潰瘍	Duodenal ulcer perforation, obstructive
10013855	閉塞性十二指腸潰瘍	Duodenal ulcer, obstructive
10013864	十二指腸炎	Duodenitis
10013865	出血性十二指腸炎	Duodenitis haemorrhagic
10013924	食道ジスキネジア	Dyskinesia oesophageal
10013946	消化不良	Dyspepsia
10013950	嚥下障害	Dysphagia
10014576	エナメル質異常	Enamel anomaly
10014866	小腸炎	Enteritis
10014877	白血球減少性腸炎	Enteritis leukopenic
10014884	腸ヘルニア	Enterocele
10014893	腸炎	Enterocolitis
10014896	出血性腸炎	Enterocolitis haemorrhagic
10015137	おくび	Eructation

PT コード	PT_日本語	PT_英語
10016100	変色便	Faeces discoloured
10016101	硬便	Faeces hard
10016102	白色便	Faeces pale
10016434	大腿ヘルニア	Femoral hernia
10016448	閉塞性大腿ヘルニア	Femoral hernia, obstructive
10016766	鼓腸	Flatulence
10016819	歯牙フッ素沈着症	Fluorosis dental
10016952	食中毒	Food poisoning
10017367	排便回数増加	Frequent bowel movements
10017649	胆石性イレウス	Gallstone ileus
10017753	胃アトニー	Gastric atony
10017779	胃拡張	Gastric dilatation
10017788	胃出血	Gastric haemorrhage
10017807	胃粘膜肥厚	Gastric mucosal hypertrophy
10017815	胃穿孔	Gastric perforation
10017817	胃ポリープ	Gastric polyps
10017822	胃潰瘍	Gastric ulcer
10017826	出血性胃潰瘍	Gastric ulcer haemorrhage
10017829	閉塞性出血性胃潰瘍	Gastric ulcer haemorrhage, obstructive
10017835	穿孔性胃潰瘍	Gastric ulcer perforation
10017836	閉塞性穿孔性胃潰瘍	Gastric ulcer perforation, obstructive
10017840	閉塞性胃潰瘍	Gastric ulcer, obstructive
10017853	胃炎	Gastritis
10017856	アルコール性胃炎	Gastritis alcoholic
10017857	出血性アルコール胃炎	Gastritis alcoholic haemorrhagic
10017865	びらん性胃炎	Gastritis erosive
10017866	出血性胃炎	Gastritis haemorrhagic
10017868	肥厚性胃炎	Gastritis hypertrophic
10017877	胃腸管瘻	Gastrointestinal fistula
10017885	胃食道逆流性疾患	Gastrooesophageal reflux disease
10017886	胃十二指腸潰瘍	Gastroduodenal ulcer
10017902	好酸球性胃腸炎	Gastroenteritis eosinophilic
10017928	胃腸管血管異形成	Gastrointestinal angiodysplasia
10017929	出血性胃腸管血管異形成	Gastrointestinal angiodysplasia haemorrhagic
10017944	胃腸障害	Gastrointestinal disorder
10017955	胃腸出血	Gastrointestinal haemorrhage
10017979	消化管粘膜嚢胞	Gastrointestinal mucocoele
10017980	消化管粘膜壊死	Gastrointestinal mucosal necrosis
10017982	消化管壊死	Gastrointestinal necrosis
10017999	消化器痛	Gastrointestinal pain
10018001	消化管穿孔	Gastrointestinal perforation
10018007	胃腸管狭窄	Gastrointestinal stenosis

PT コード	PT_日本語	PT_英語
10018019	消化管粘膜変色	Gastrointestinal tract mucosal discolouration
10018045	胃下垂	Gastroptosis
10018251	巨細胞歯肉腫	Giant cell epulis
10018275	歯肉萎縮	Gingival atrophy
10018276	歯肉出血	Gingival bleeding
10018278	歯肉変色	Gingival discolouration
10018280	歯肉障害	Gingival disorder
10018282	歯肉びらん	Gingival erosion
10018284	歯肉肥厚	Gingival hypertrophy
10018285	歯肉形成不全	Gingival hypoplasia
10018286	歯肉痛	Gingival pain
10018288	歯肉ポリープ	Gingival polyp
10018290	歯肉退縮	Gingival recession
10018291	歯肉腫脹	Gingival swelling
10018296	潰瘍性歯肉炎	Gingivitis ulcerative
10018386	舌炎	Glossitis
10018388	舌痛	Glossodynia
10018830	吐血	Haematemesis
10018836	血便排泄	Haematochezia
10019022	痔核	Haemorrhoids
10019023	血栓性痔核	Haemorrhoids thrombosed
10020028	裂孔ヘルニア	Hiatus hernia
10020596	セメント質の増殖	Hypercementosis
10020601	胃酸過多	Hyperchlorhydria
10020893	舌乳頭肥大	Hypertrophy of tongue papillae
10021305	回腸穿孔	Ileal perforation
10021307	回腸狭窄	Ileal stenosis
10021309	回腸潰瘍	Ileal ulcer
10021310	回腸潰瘍穿孔	Ileal ulcer perforation
10021328	イレウス	Ileus
10021333	麻痺性イレウス	Ileus paralytic
10021335	痙性イレウス	Ileus spastic
10021518	胃排出不全	Impaired gastric emptying
10021612	嵌頓裂孔ヘルニア	Incarcerated hiatus hernia
10021613	嵌頓鼠径ヘルニア	Incarcerated inguinal hernia
10021746	乳児仙痛	Infantile colic
10021972	炎症性腸疾患	Inflammatory bowel disease
10022016	鼠径ヘルニア	Inguinal hernia
10022021	閉塞性鼠径ヘルニア	Inguinal hernia, obstructive
10022640	腸管アンギナ	Intestinal angina
10022642	腸管拡張症	Intestinal dilatation
10022647	腸管瘻	Intestinal fistula

PT コード	PT_日本語	PT_英語
10022657	腸梗塞	Intestinal infarction
10022680	腸管虚血	Intestinal ischaemia
10022687	腸閉塞	Intestinal obstruction
10022694	腸管穿孔	Intestinal perforation
10022698	偽性腸閉塞	Intestinal pseudo-obstruction
10022699	腸管狭窄	Intestinal stenosis
10022714	腸潰瘍	Intestinal ulcer
10022863	腸重積症	Intussusception
10023003	過敏性腸症候群	Irritable bowel syndrome
10023044	坐骨孔ヘルニア	Ischiatic hernia
10023047	坐骨孔直腸ヘルニア	Ischiorectal hernia
10023174	空腸穿孔	Jejunal perforation
10023176	空腸狭窄	Jejunal stenosis
10023177	空腸潰瘍	Jejunal ulcer
10023178	穿孔性空腸潰瘍	Jejunal ulcer perforation
10023799	大腸潰瘍	Large intestinal ulcer
10023804	大腸穿孔	Large intestine perforation
10024389	食道白斑症	Leukoplakia oesophageal
10024396	口腔内白斑症	Leukoplakia oral
10024549	口唇変色	Lip discolouration
10024552	口唇乾燥	Lip dry
10024558	口唇浮腫	Lip oedema
10024561	口唇痛	Lip pain
10024570	口唇腫脹	Lip swelling
10024572	口唇潰瘍	Lip ulceration
10024995	腰ヘルニア	Lumbar hernia
10025213	腸管リンパ管拡張症	Lymphangiectasia intestinal
10025476	吸収不良	Malabsorption
10026712	マロリー・ワイス症候群	Mallory-Weiss syndrome
10027058	胎便イレウス	Meconium ileus
10027110	巨大結腸	Megacolon
10027141	メレナ	Melaena
10027394	腸間膜動脈閉塞	Mesenteric arterial occlusion
10027395	腸間膜動脈塞栓	Mesenteric artery embolism
10027396	腸間膜動脈狭窄	Mesenteric artery stenosis
10027397	腸間膜動脈血栓症	Mesenteric artery thrombosis
10027398	腸間膜線維症	Mesenteric fibrosis
10027401	腸間膜血行不全	Mesenteric vascular insufficiency
10027402	腸間膜静脈血栓症	Mesenteric vein thrombosis
10027403	腸間膜静脈閉塞	Mesenteric venous occlusion
10028020	口腔嚢胞	Mouth cyst
10028024	口腔内出血	Mouth haemorrhage

PT コード	PT_日本語	PT_英語
10028034	口腔内潰瘍形成	Mouth ulceration
10028140	粘液便	Mucous stools
10028813	悪心	Nausea
10028951	新生児腸閉塞	Neonatal intestinal obstruction
10029957	胃閉塞	Obstruction gastric
10029987	閉鎖孔ヘルニア	Obturator hernia
10030094	嚥下痛	Odynophagia
10030110	口腔浮腫	Oedema mouth
10030136	食道アカラシア	Oesophageal achalasia
10030164	食道拡張	Oesophageal dilatation
10030172	食道出血	Oesophageal haemorrhage
10030178	食道閉塞症	Oesophageal obstruction
10030180	食道痛	Oesophageal pain
10030181	食道穿孔	Oesophageal perforation
10030184	食道痙攣	Oesophageal spasm
10030194	食道狭窄	Oesophageal stenosis
10030201	食道潰瘍	Oesophageal ulcer
10030202	食道潰瘍出血	Oesophageal ulcer haemorrhage
10030210	食道静脈瘤出血	Oesophageal varices haemorrhage
10030216	食道炎	Oesophagitis
10030219	出血性食道炎	Oesophagitis haemorrhagic
10030972	口腔内分泌物	Oral discharge
10030973	口腔内不快感	Oral discomfort
10030983	口腔扁平苔癬	Oral lichen planus
10030995	口腔粘膜水疱形成	Oral mucosal blistering
10030996	口腔粘膜変色	Oral mucosal discolouration
10030997	口腔粘膜疹	Oral mucosal eruption
10031009	口腔内痛	Oral pain
10031010	口内丘疹	Oral papule
10031023	口腔粘膜下線維症	Oral submucosal fibrosis
10033603	膵萎縮	Pancreatic atrophy
10033615	膵嚢胞	Pancreatic cyst
10033616	膵臓障害	Pancreatic disorder
10033619	膵酵素異常	Pancreatic enzyme abnormality
10033625	膵臓出血	Pancreatic haemorrhage
10033635	膵仮性嚢胞	Pancreatic pseudocyst
10033645	膵炎	Pancreatitis
10033647	急性膵炎	Pancreatitis acute
10033649	慢性膵炎	Pancreatitis chronic
10033650	出血性膵炎	Pancreatitis haemorrhagic
10033654	壊死性膵炎	Pancreatitis necrotising
10033657	再発性膵炎	Pancreatitis relapsing

PT コード	PT_日本語	PT_英語
10034021	耳下腺管閉塞	Parotid duct obstruction
10034023	耳下腺腫大	Parotid gland enlargement
10034341	消化性潰瘍	Peptic ulcer
10034344	出血性消化性潰瘍	Peptic ulcer haemorrhage
10034354	穿孔性消化性潰瘍	Peptic ulcer perforation
10034358	閉塞性穿孔性消化性潰瘍	Peptic ulcer perforation, obstructive
10034365	閉塞性消化性潰瘍	Peptic ulcer, obstructive
10034536	歯周病	Periodontal disease
10034647	可視性蠕動不穏	Peristalsis visible
10034650	腹膜癒着	Peritoneal adhesions
10034665	腹膜線維症	Peritoneal fibrosis
10034666	腹膜出血	Peritoneal haemorrhage
10035025	口唇色素沈着	Pigmentation lip
10035630	ひだ舌	Plicated tongue
10036463	嚢炎	Pouchitis
10036772	肛門周囲痛	Proctalgia
10036774	直腸炎	Proctitis
10036778	出血性直腸炎	Proctitis haemorrhagic
10036783	潰瘍性直腸炎	Proctitis ulcerative
10037076	舌突出	Protrusion tongue
10037117	偽憩室疾患	Pseudodiverticular disease
10037143	偽性ポリポーシス	Pseudopolyposis
10037288	外陰ヘルニア	Pudendal hernia
10037628	幽門痙攣	Pylorospasm
10037838	がま腫	Ranula
10038063	直腸出血	Rectal haemorrhage
10038073	直腸穿孔	Rectal perforation
10038074	直腸ポリープ	Rectal polyp
10038077	直腸脱	Rectal prolapse
10038079	直腸狭窄	Rectal stenosis
10038080	直腸潰瘍	Rectal ulcer
10038081	出血性直腸潰瘍	Rectal ulcer haemorrhage
10038776	レッチング	Retching
10038979	後腹膜線維症	Retroperitoneal fibrosis
10038980	後腹膜出血	Retroperitoneal haemorrhage
10038982	腹膜後ヘルニア	Retroperitoneal hernia
10038983	後腹膜浮腫	Retroperitoneal oedema
10039379	唾液変性	Saliva altered
10039386	唾液管閉塞	Salivary duct obstruction
10039388	唾液管狭窄	Salivary duct stenosis
10039390	唾液腺萎縮	Salivary gland atrophy
10039394	唾液腺結石	Salivary gland calculus

PT コード	PT_日本語	PT_英語
10039408	唾液腺腫大	Salivary gland enlargement
10039411	唾液腺瘻	Salivary gland fistula
10039421	唾液腺痛	Salivary gland pain
10039424	流涎過多	Salivary hypersecretion
10039669	坐骨ヘルニア	Sciatic hernia
10040012	歯の知覚過敏	Sensitivity of teeth
10040664	鉄欠乏性嚥下障害	Sideropenic dysphagia
10041101	小腸閉塞	Small intestinal obstruction
10041103	小腸穿孔	Small intestinal perforation
10041133	小腸潰瘍	Small intestine ulcer
10041522	スピゲリウスヘルニア	Spigelian hernia
10041645	脾臓動脈瘤	Splenic artery aneurysm
10041956	停滞症候群	Stasis syndrome
10041969	脂肪便	Steatorrhoea
10042128	口内炎	Stomatitis
10042132	出血性口内炎	Stomatitis haemorrhagic
10042135	壊死性口内炎	Stomatitis necrotising
10042220	ストレス潰瘍	Stress ulcer
10042419	顎下腺腫大	Submaxillary gland enlargement
10042572	過剰歯	Supernumerary teeth
10042727	舌腫脹	Swollen tongue
10043173	脆弱歯	Teeth brittle
10043183	生歯	Teething
10043626	腸間膜血栓症	Thrombosis mesenteric vessel
10043942	舌水疱形成	Tongue blistering
10043945	舌苔	Tongue coated
10043949	舌変色	Tongue discolouration
10043951	舌障害	Tongue disorder
10043957	地図状舌	Tongue geographic
10043959	舌血腫	Tongue haematoma
10043963	舌の運動障害	Tongue movement disturbance
10043967	舌浮腫	Tongue oedema
10043981	舌痙攣	Tongue spasm
10043991	舌潰瘍	Tongue ulceration
10044019	歯強直	Tooth ankylosis
10044028	歯牙離層	Tooth delamination
10044029	歯の沈着物	Tooth deposit
10044030	歯の発育障害	Tooth development disorder
10044032	変色歯	Tooth discolouration
10044034	歯の障害	Tooth disorder
10044038	歯の磨耗	Tooth erosion
10044042	埋伏歯	Tooth impacted

PT コード	PT_日本語	PT_英語
10044044	歯の脱落	Tooth loss
10044046	歯奇形	Tooth malformation
10044052	歯の吸収症	Tooth resorption
10044055	歯痛	Toothache
10044145	中毒性腸拡張	Toxic dilatation of intestine
10045458	臍ヘルニア	Umbilical hernia
10045467	閉塞性臍ヘルニア	Umbilical hernia, obstructive
10046274	上部消化管出血	Upper gastrointestinal haemorrhage
10047027	舌下静脈瘤	Varicose veins sublingual
10047697	腸の軸捻転	Volvulus
10047700	嘔吐	Vomiting
10047708	噴出性嘔吐	Vomiting projectile
10048299	気腹	Pneumoperitoneum
10048319	胃腸管血管炎	Vasculitis gastrointestinal
10048470	口唇障害	Lip disorder
10048479	頬粘膜のあれ	Buccal mucosal roughening
10048616	腸管ポリープ	Intestinal polyp
10048657	神経因性腸	Neurogenic bowel
10048712	出血性胃十二指腸炎	Gastroduodenitis haemorrhagic
10048714	胃十二指腸炎	Gastroduodenitis
10048869	腹膜ヘルニア	Peritoneal hernia
10048949	耳下腺脂肪腫症	Parotid lipomatosis
10049047	口唇のひび割れ	Chapped lips
10049068	唾液管拡張	Sialectasia
10049069	唾液変色	Saliva discolouration
10049082	膵腫瘤	Pancreatic mass
10049098	潰瘍性食道炎	Oesophagitis ulcerative
10049101	直腸分泌物	Rectal discharge
10049150	壊死性胃炎	Necrotising gastritis
10049192	膵瘻	Pancreatic fistula
10049243	後天性舌小帯短縮症	Ankyloglossia acquired
10049251	ハイド症候群	Heyde's syndrome
10049297	口唇出血	Lip haemorrhage
10049304	歯肉水疱	Gingival blister
10049305	歯肉浮腫	Gingival oedema
10049306	歯肉そう痒症	Gingival pruritus
10049307	口唇水疱	Lip blister
10049398	歯肉潰瘍	Gingival ulceration
10049416	短腸症候群	Short-bowel syndrome
10049443	腸絨毛萎縮	Intestinal villi atrophy
10049555	肛門出血	Anal haemorrhage
10049580	歯肉色素過剰	Gingival hyperpigmentation

PT コード	PT_日本語	PT_英語
10049713	舌乾燥	Tongue dry
10049714	腹性片頭痛	Abdominal migraine
10049777	新生児メレナ	Melaena neonatal
10049823	肛門括約筋無緊張症	Anal sphincter atony
10049870	舌出血	Tongue haemorrhage
10049939	便量増加	Faecal volume increased
10050094	十二指腸狭窄	Duodenal stenosis
10050158	胃腸異形成	Gastrointestinal dysplasia
10050159	腸クロム親和性細胞過形成	Enterochromaffin cell hyperplasia
10050161	胃異形成	Gastric dysplasia
10050171	食道異形成	Oesophageal dysplasia
10050172	口腔粘膜萎縮	Oral mucosa atrophy
10050173	幽門前部狭窄	Prepyloric stenosis
10050247	肛門の炎症	Anal inflammation
10050248	便量減少	Faecal volume decreased
10050362	肛門外陰部瘻	Anovulvar fistula
10050373	肛門括約筋不全麻痺	Paresis anal sphincter
10050396	亜イレウス	Subileus
10050399	慢性胃腸出血	Chronic gastrointestinal bleeding
10050820	口腔知覚不全	Oral dysaesthesia
10050897	門脈圧亢進性胃障害	Portal hypertensive gastropathy
10050953	下部消化管出血	Lower gastrointestinal haemorrhage
10051010	十二指腸静脈瘤	Duodenal varices
10051012	胃静脈瘤	Gastric varices
10051129	肉芽腫性口唇炎	Cheilitis granulomatosa
10051153	糖尿病性胃不全麻痺	Diabetic gastroparesis
10051166	耳下腺出血	Parotid gland haemorrhage
10051244	排便困難	Dyschezia
10051252	膵石症	Pancreatolithiasis
10051337	異所性胃粘膜	Ectopic gastric mucosa
10051399	機械的イレウス	Mechanical ileus
10051411	頬ポリープ	Buccal polyp
10051425	腸管皮膚瘻	Enterocutaneous fistula
10051457	ミクリッツ病	Mikulicz's disease
10051478	肛門括約筋麻痺	Proctoparalysis
10051495	いちご舌	Strawberry tongue
10051499	唾液嚢瘤	Sialocele
10051563	腸管粘膜肥厚	Intestinal mucosal hypertrophy
10051585	胃前庭部毛細血管拡張症	Gastric antral vascular ectasia
10051589	大腸ポリープ	Large intestine polyp
10051606	壊死性大腸炎	Necrotising colitis
10051634	腹壁嚢胞	Abdominal wall cyst

PT コード	PT_日本語	PT_英語
10051650	キライディティ症候群	Chilaiditi's syndrome
10051652	舌異形成	Tongue dysplasia
10051689	後腹膜嚢胞	Retroperitoneum cyst
10051780	歯の感覚鈍麻	Hypoaesthesia teeth
10051820	ソルデス	Sordes
10051879	舌嚢胞	Tongue cyst
10051935	食道ポリープ	Oesophageal polyp
10051942	腹膜嚢胞	Peritoneal cyst
10051962	口蓋垂炎	Uvulitis
10051989	内ヘルニア	Internal hernia
10051992	口唇びらん	Lip erosion
10051999	肛門性器異形成	Anogenital dysplasia
10052002	舌発疹	Tongue eruption
10052072	線維化性結腸疾患	Fibrosing colonopathy
10052105	消化管運動低下	Gastrointestinal hypomotility
10052211	食道破裂	Oesophageal rupture
10052248	唾液腺嚢胞	Salivary gland cyst
10052317	ミクリッツ症候群	Mikulicz's syndrome
10052400	浮腫性膵炎	Oedematous pancreatitis
10052402	消化管運動過剰	Gastrointestinal hypermotility
10052405	胃運動低下	Gastric hypomotility
10052406	胃運動過剰	Gastric hypermotility
10052453	口蓋障害	Palatal disorder
10052454	口蓋粘膜異形成	Palatal dysplasia
10052488	穿孔性食道潰瘍	Oesophageal ulcer perforation
10052489	腹壁反跳痛	Abdominal rebound tenderness
10052497	穿孔性大腸潰瘍	Large intestinal ulcer perforation
10052498	穿孔性小腸潰瘍	Small intestinal ulcer perforation
10052534	大腸出血	Large intestinal haemorrhage
10052535	小腸出血	Small intestinal haemorrhage
10052541	胃軸捻転	Gastric volvulus
10052765	膵管閉塞	Pancreatic duct obstruction
10052813	空気嚥下	Aerophagia
10052820	後天性食道ウエッブ	Acquired oesophageal web
10052894	口腔そう痒症	Oral pruritus
10053155	心窩部不快感	Epigastric discomfort
10053203	腹部絞扼性ヘルニア	Abdominal strangulated hernia
10053397	心因性結腸炎	Colitis psychogenic
10053634	食道不快感	Oesophageal discomfort
10053768	胃十二指腸出血	Gastroduodenal haemorrhage
10054217	歯不快感	Dental discomfort
10054787	痔出血	Haemorrhoidal haemorrhage

PT コード	PT_日本語	PT_英語
10054819	憩室ヘルニア	Diverticular hernia
10054827	腹膜病変	Peritoneal lesion
10054828	直腸病変	Rectal lesion
10055018	歯肉嚢胞	Gingival cyst
10055024	膵腫大	Pancreatic enlargement
10055028	舌萎縮	Tongue atrophy
10055667	新生児壊死性腸炎	Necrotising enterocolitis neonatal
10055668	壊死性食道炎	Necrotising oesophagitis
10056091	食道静脈瘤	Varices oesophageal
10056273	肛門周囲紅斑	Perianal erythema
10056325	糞塊	Faecaloma
10056361	末端腸閉塞症候群	Distal intestinal obstruction syndrome
10056457	腹腔内血腫	Intra-abdominal haematoma
10056499	肛門周囲体毛乱生	Anal trichiasis
10056512	後天性過長結腸	Dolichocolon acquired
10056681	唾液管の炎症	Salivary duct inflammation
10056741	糖尿病性腸障害	Diabetic enteropathy
10056742	糖尿病性胃腸障害	Diabetic gastroenteropathy
10056743	出血性胃腸潰瘍	Gastrointestinal ulcer haemorrhage
10056819	胃障害	Gastric disorder
10056975	膵フレグモーネ	Pancreatic phlegmon
10056977	アルコール性膵炎	Alcoholic pancreatitis
10056978	胃嚢胞	Gastric cyst
10056979	顕微鏡的大腸炎	Colitis microscopic
10056984	歯垢	Dental plaque
10056988	糞石	Faecalith
10056990	腸管脱	Intestinal prolapse
10056991	小腸結腸瘻	Enterocolonic fistula
10056994	ブルンネル腺過形成	Brunner's gland hyperplasia
10056995	胃腸粘膜障害	Gastrointestinal mucosal disorder
10056998	口蓋浮腫	Palatal oedema
10057002	唾液腺腫瘤	Salivary gland mass
10057003	食道腫瘤	Oesophageal mass
10057011	直腸攣縮	Rectal spasm
10057030	腸壁気腫症	Pneumatosis intestinalis
10057071	直腸しぶり	Rectal tenesmus
10057075	胎便栓症候群	Meconium plug syndrome
10057084	胃腸粘膜色素沈着	Gastrointestinal tract mucosal pigmentation
10057207	幽門拡張	Pylorus dilatation
10057271	好酸球性結腸炎	Eosinophilic colitis
10057365	口腔白色水腫	Oral leukoedema
10057371	口の感覚鈍麻	Hypoaesthesia oral

PT コード	PT_日本語	PT_英語
10057372	口の錯感覚	Paraesthesia oral
10057391	内臓ヘルニア	Hernial eventration
10057572	胃静脈瘤出血	Gastric varices haemorrhage
10057969	逆流性胃炎	Reflux gastritis
10057974	歯肉腫	Epulis
10057986	虫垂粘液嚢胞	Appendiceal mucocoele
10058035	胃イレウス	Gastric ileus
10058061	消化管浮腫	Gastrointestinal oedema
10058095	腹膜血腫	Peritoneal haematoma
10058096	膵壊死	Pancreatic necrosis
10058113	胎便性腹膜炎	Meconium peritonitis
10058358	びらん性大腸炎	Colitis erosive
10058360	後腹膜血腫	Retroperitoneal haematoma
10058435	胃肉芽腫	Stomach granuloma
10058442	肛門肥大乳頭	Hypertrophic anal papilla
10058667	経口毒性	Oral toxicity
10058808	腹部コンパートメント症候群	Abdominal compartment syndrome
10058835	後天性巨舌症	Acquired macroglossia
10058934	新生児腸管拡張	Neonatal intestinal dilatation
10058938	アセトン血性嘔吐症	Acetonaemic vomiting
10059017	腸管腫瘤	Intestinal mass
10059024	胃腸毒性	Gastrointestinal toxicity
10059028	胃腸虚血	Gastrointestinal ischaemia
10059138	舌根沈下	Glossoptosis
10059158	排便回数減少	Infrequent bowel movements
10059175	腸出血	Intestinal haemorrhage
10059184	歯状態不良	Poor dental condition
10059237	耳介側頭神経症候群	Auriculotemporal syndrome
10059250	消化管アミロイドーシス	Gastrointestinal amyloidosis
10059344	蛋白漏出性胃腸症	Protein-losing gastroenteropathy
10059447	アレルギー性大腸炎	Allergic colitis
10059625	腹壁障害	Abdominal wall disorder
10059766	血性腹水	Haemorrhagic ascites
10060377	高ガストリン血症	Hypergastrinaemia
10060696	老人性食道	Presbyoesophagus
10060709	消化管びらん	Gastrointestinal erosion
10060717	腸間膜出血	Mesenteric haemorrhage
10060865	十二指腸胃逆流	Duodenogastric reflux
10060870	唾液腺粘液嚢胞	Salivary gland mucocoele
10060923	閉塞を伴う腹部ヘルニア	Abdominal hernia obstructive
10060926	腹部症状	Abdominal symptom
10060954	腹部ヘルニア	Abdominal hernia

PT コード	PT_日本語	PT_英語
10060960	虫垂障害	Appendix disorder
10060983	根尖肉芽腫	Apical granuloma
10061164	胃粘膜病変	Gastric mucosal lesion
10061173	消化管運動障害	Gastrointestinal motility disorder
10061248	穿孔性腸潰瘍	Intestinal ulcer perforation
10061249	腹腔内出血	Intra-abdominal haemorrhage
10061262	出血性大腸潰瘍	Large intestinal ulcer haemorrhage
10061274	不正咬合	Malocclusion
10061318	食道障害	Oesophageal disorder
10061343	腹膜障害	Peritoneal disorder
10061459	胃腸潰瘍	Gastrointestinal ulcer
10061550	出血性小腸潰瘍	Small intestinal ulcer haemorrhage
10061820	憩室穿孔	Diverticular perforation
10061935	唾液腺障害	Salivary gland disorder
10061970	胃狭窄	Gastric stenosis
10061974	胃腸管閉塞	Gastrointestinal obstruction
10061975	穿孔性胃腸潰瘍	Gastrointestinal ulcer perforation
10062023	腸管嚢胞	Intestinal cyst
10062062	大腸閉塞	Large intestinal obstruction
10062263	小腸狭窄	Small intestinal stenosis
10062363	腹腔動脈血栓	Truncus coeliacus thrombosis
10062532	びらん性十二指腸炎	Erosive duodenitis
10062570	腸膀胱瘻	Enterovesical fistula
10062879	胃食道括約筋機能不全	Gastrooesophageal sphincter insufficiency
10062890	胃石症	Gastrolithiasis
10062898	ループス腹膜炎	Peritonitis lupus
10062907	クロンカイト・カナダ症候群	Cronkhite-Canada syndrome
10062931	胃緊張亢進	Gastric hypertonia
10062937	周期性嘔吐症候群	Cyclic vomiting syndrome
10062956	口腔粘膜肥厚	Oral mucosal hypertrophy
10062959	好中球減少性大腸炎	Neutropenic colitis
10063005	腹壁腫瘤	Abdominal wall mass
10063031	腸間膜脂肪織炎	Mesenteric panniculitis
10063063	非感染性虫垂炎	Appendicitis noninfective
10063338	乳児吐出	Infantile spitting up
10063541	便通不規則	Bowel movement irregularity
10063637	後腹膜滲出液	Retroperitoneal effusion
10063655	びらん性食道炎	Erosive oesophagitis
10063658	腸絞扼	Intestinal strangulation
10063709	尿毒症性胃障害	Uraemic gastropathy
10063840	内臓下垂	Visceroptosis
10063896	出血性肛門潰瘍	Anal ulcer haemorrhage

PT コード	PT_日本語	PT_英語
10064118	骨盤底協調不全	Pelvic floor dyssynergia
10064147	胃腸の炎症	Gastrointestinal inflammation
10064212	好酸球性食道炎	Eosinophilic oesophagitis
10064223	水疱性出血性口峡炎	Angina bullosa haemorrhagica
10064231	腹膜垂炎	Epiploic appendagitis
10064260	ダグラス窩腫瘤	Douglas' pouch mass
10064342	食道浮腫	Oesophageal oedema
10064389	細菌叢異常症	Dysbacteriosis
10064482	口唇上皮剥脱	Lip exfoliation
10064487	口腔粘膜剥脱	Oral mucosal exfoliation
10064488	舌粘膜剥脱	Tongue exfoliation
10064492	嵌頓臍ヘルニア	Incarcerated umbilical hernia
10064594	口腔粘膜びらん	Oral mucosa erosion
10064666	腹膜穿孔	Peritoneal perforation
10064670	吐糞症	Faecal vomiting
10064711	門脈ガス血症	Portal venous gas
10064749	腸管ダイアフラム病	Intestinal diaphragm disease
10064835	筋線維便	Creatorrhoea
10064858	膵管拡張	Pancreatic duct dilatation
10064946	歯槽出血	Tooth socket haemorrhage
10064993	直腸裂	Rectal fissure
10065120	口腔上顎洞瘻	Oroantral fistula
10065360	肛門脱	Anal prolapse
10065560	腸間膜動脈硬化症	Mesenteric arteriosclerosis
10065567	食道食物嵌入	Oesophageal food impaction
10065611	腸管うっ血	Intestinal congestion
10065612	弛緩歯	Loose tooth
10065666	小腸捻転	Volvulus of small bowel
10065703	膵管狭窄	Pancreatic duct stenosis
10065704	腹膜壊死	Peritoneal necrosis
10065707	直腸閉塞	Rectal obstruction
10065713	胃瘻	Gastric fistula
10065720	口腔瘻	Oral cavity fistula
10065835	食道瘻	Oesophageal fistula
10065850	小腸瘻	Fistula of small intestine
10065919	舌アミロイドーシス	Tongue amyloidosis
10066075	唾液腺化生	Sialometaplasia
10066127	虚血性膵炎	Ischaemic pancreatitis
10066141	食道粘膜過形成	Oesophageal mucosal hyperplasia
10066142	サンディファー症候群	Sandifer's syndrome
10066192	口蓋垂腫大	Enlarged uvula
10066220	咳嗽後嘔吐	Post-tussive vomiting

PT コード	PT_日本語	PT_英語
10066304	口唇血腫	Lip haematoma
10066792	胃腫瘤	Stomach mass
10066870	大動脈食道瘻	Aorto-oesophageal fistula
10066892	直腸尿道瘻	Rectourethral fistula
10066894	肛門括約筋過緊張	Anal sphincter hypertonia
10066993	臍ヘルニア穿孔	Umbilical hernia perforation
10067011	腹膜透析排液混濁	Peritoneal cloudy effluent
10067091	胃胸腔瘻	Gastropleural fistula
10067171	吐き戻し	Regurgitation
10067272	肛門びらん	Anal erosion
10067325	腹腔動脈狭窄	Coeliac artery stenosis
10067357	閉塞性裂孔ヘルニア	Hiatus hernia, obstructive
10067360	舌壊死	Tongue necrosis
10067383	腹壁血腫	Abdominal wall haematoma
10067418	口腔粘膜紅斑	Oral mucosal erythema
10067419	歯肉紅斑	Gingival erythema
10067442	血性腹膜透析排液	Bloody peritoneal effluent
10067510	接触性口内炎	Contact stomatitis
10067512	グリコーゲンアカントーシス	Glycogenic acanthosis
10067515	絞扼性鼠径ヘルニア	Inguinal hernia strangulated
10067551	胃黄色腫	Gastric xanthoma
10067576	悪性嚥下障害	Malignant dysphagia
10067621	口腔障害	Oral disorder
10067715	胃腸音異常	Gastrointestinal sounds abnormal
10067738	ループス腸炎	Lupus enteritis
10067743	デュラフォア血管奇形	Dieulafoy's vascular malformation
10067745	腸管粘膜萎縮	Intestinal mucosal atrophy
10067750	ループス膵炎	Lupus pancreatitis
10067752	食道運動低下	Oesophageal hypomotility
10067766	ファーター乳頭狭窄	Papilla of Vater stenosis
10067767	消化管マラコプラキア	Malacoplakia gastrointestinal
10067786	出血性びらん性胃炎	Haemorrhagic erosive gastritis
10067788	腹壁出血	Abdominal wall haemorrhage
10067805	胃腸粘膜剥脱	Gastrointestinal mucosal exfoliation
10067985	口腔内黒斑症	Melanoplakia oral
10068065	口腔灼熱感症候群	Burning mouth syndrome
10068172	肛門そう痒症	Anal pruritus
10068239	膵梗塞	Pancreatic infarction
10068286	肛門直腸不快感	Anorectal discomfort
10068290	肛門直腸扁平上皮化生	Anorectal squamous cell metaplasia
10068411	腸上皮化生	Intestinal metaplasia
10068546	外傷性咬合	Traumatic occlusion

PT コード	PT_日本語	PT_英語
10068676	後腹膜気腫	Pneumoretroperitoneum
10068701	肛門挙筋症候群	Levator syndrome
10068792	胃脾瘻	Gastrosplenic fistula
10068823	膵石灰化	Pancreatic calcification
10068923	門脈圧亢進性腸症	Portal hypertensive enteropathy
10068924	肛門直腸静脈瘤	Anorectal varices
10068925	肛門直腸静脈瘤出血	Anorectal varices haemorrhage
10068966	腸管脂肪症	Intestinal steatosis
10069002	自己免疫性膵炎	Autoimmune pancreatitis
10069085	萎縮性舌炎	Atrophic glossitis
10069164	舌色素沈着	Tongue pigmentation
10069369	ミオコーシス	Myochosis
10069568	限外濾過不全	Ultrafiltration failure
10069665	腸間膜炎	Mesenteritis
10069703	胆汁酸吸収不良	Bile acid malabsorption
10069829	腸血腫	Intestinal haematoma
10069886	大網梗塞	Omental infarction
10070072	舌そう痒症	Tongue pruritus
10070181	胃腸血管奇形	Gastrointestinal vascular malformation
10070190	虚血性胃炎	Ischaemic gastritis
10070307	胃ヘルニア	Gastrocoele
10070313	セメント歯骨形成不全	Cemento osseous dysplasia
10070438	内因子欠乏症	Intrinsic factor deficiency
10070573	残存乳歯	Retained deciduous tooth
10070721	口唇そう痒症	Lip pruritus
10070818	食道刺激症状	Oesophageal irritation
10070840	消化管刺激症状	Gastrointestinal tract irritation
10070897	ニコチン性口内炎	Nicotinic stomatitis
10070994	胃粘膜紅斑	Gastric mucosa erythema
10071161	結腸異形成	Colon dysplasia
10071275	機能性胃腸障害	Functional gastrointestinal disorder
10071282	肥満細胞性腸炎	Mastocytic enterocolitis
10071363	唾液腺硬結	Salivary gland induration
10071369	膵嚢胞破裂	Pancreatic cyst rupture
10071502	腸静脈瘤	Intestinal varices
10071554	食道アトニー	Oesophageal atony
10071557	腸間膜血腫	Mesenteric haematoma
10071648	非感染性腹膜炎	Noninfectious peritonitis
10071732	後腹膜腫瘤	Retroperitoneal mass
10072208	食道線維症	Oesophageal fibrosis
10072228	歯髄出血	Tooth pulp haemorrhage
10072280	食道粘膜紅斑	Oesophageal mucosa erythema

PT コード	PT_日本語	PT_英語
10072284	腹壁静脈瘤	Varicose veins of abdominal wall
10072286	麻薬性腸症候群	Narcotic bowel syndrome
10072287	十二指腸毛細血管拡張症	Duodenal vascular ectasia
10072350	食道粘膜解離	Oesophageal mucosal dissection
10072419	食道運動障害	Oesophageal motility disorder
10072574	歯周の炎症	Periodontal inflammation
10072585	十二指腸乳頭炎	Duodenal papillitis
10072665	歯の脱灰	Tooth demineralisation
10072785	咽頭食道憩室	Pharyngo-oesophageal diverticulum
10072787	膵脂肪変性	Pancreatic steatosis
10072853	腹膜中皮過形成	Peritoneal mesothelial hyperplasia
10072877	腸管線維症	Intestinal fibrosis
10072890	腸管平滑筋肥大	Intestinal smooth muscle hypertrophy
10073166	幽門括約筋機能不全	Pyloric sphincter insufficiency
10073215	膵周囲静脈瘤	Peripancreatic varices
10073395	小腸ポリープ	Small intestine polyp
10073422	肛門錯感覚	Anal paraesthesia
10073530	腸石灰化	Intestinal calcification
10074061	大腸狭窄	Large intestinal stenosis
10074063	虚血性小腸炎	Ischaemic enteritis
10074068	増殖性化膿性口内炎	Pyostomatitis vegetans
10074074	食道圧迫	Oesophageal compression
10074150	胆汁性腹水	Biliary ascites
10074159	新生児胃腸出血	Neonatal gastrointestinal haemorrhage
10074160	新生児腸管穿孔	Neonatal intestinal perforation
10074182	メコニウムシスト	Meconium cyst
10074216	腸係蹄固定	Fixed bowel loop
10074403	口蓋腫脹	Palatal swelling
10074437	胃腸ポリープ出血	Gastrointestinal polyp haemorrhage
10074442	腹部ヘルニア穿孔	Abdominal hernia perforation
10074458	虫垂結石	Appendicolith
10074525	腸間膜静脈硬化症	Mesenteric phlebosclerosis
10074526	肛門直腸腫脹	Anorectal swelling
10074540	舌梗塞	Tongue infarction
10074583	腸間膜血管閉塞	Mesenteric vascular occlusion
10074686	鋸歯状舌	Scalloped tongue
10074716	アポトーシス性結腸疾患	Apoptotic colonopathy
10074725	リヒターヘルニア	Richter's hernia
10074778	舌ポリープ	Tongue polyp
10074779	口腔粘膜血腫	Oral mucosa haematoma
10074788	胃脱出	Gastric prolapse
10074846	歯槽骨吸収	Alveolar bone resorption

PT コード	PT_日本語	PT_英語
10074857	膵線維症	Pancreatic fibrosis
10074859	軟便	Faeces soft
10074863	非感染性歯肉炎	Noninfective gingivitis
10074984	嵌頓腹部ヘルニア	Abdominal incarcerated hernia
10074985	絞扼性大腿ヘルニア	Femoral hernia strangulated
10074986	絞扼性裂孔ヘルニア	Hiatus hernia strangulated
10074987	嵌頓大腿ヘルニア	Femoral hernia incarcerated
10075004	尿性腹水	Urinary ascites
10075012	被嚢性腹膜硬化症	Encapsulating peritoneal sclerosis
10075069	瀑状胃	Cascade stomach
10075203	口腔腫脹	Mouth swelling
10075243	非感染性唾液腺炎	Noninfective sialoadenitis
10075246	偽性アカラシア	Pseudoachalasia
10075254	鼠径ヘルニア穿孔	Inguinal hernia perforation
10075256	腸瘢痕	Intestinal scarring
10075308	アレルギー性胃腸炎	Allergic gastroenteritis
10075315	乳児嘔吐	Infantile vomiting
10075366	口腔内被膜	Coating in mouth
10075425	反応性胃障害	Reactive gastropathy
10075494	酸消化性障害	Acid peptic disease
10075521	肛門感覚鈍麻	Anal hypoaesthesia
10075617	敷石状舌	Cobble stone tongue
10075627	間質好酸球増多を伴う外傷性潰瘍性肉芽腫	Traumatic ulcerative granuloma with stromal eosinophilia
10075634	急性出血性潰瘍性大腸炎	Acute haemorrhagic ulcerative colitis
10075724	消化管壁肥厚	Gastrointestinal wall thickening
10075725	消化管壁異常	Gastrointestinal wall abnormal
10075726	消化管壁菲薄化	Gastrointestinal wall thinning
10075761	自己免疫性大腸炎	Autoimmune colitis
10075918	悪性腸閉塞	Malignant bowel obstruction
10075995	歯嚢胞	Dental cyst
10076058	出血性壊死性膵炎	Haemorrhagic necrotic pancreatitis
10076205	膵毒性	Pancreatic toxicity
10076229	腸管血管浮腫	Intestinal angioedema
10076253	胃線維症	Gastric fibrosis
10076265	転位歯	Malpositioned teeth
10076369	大腸びらん	Large intestine erosion
10076384	アルコール性膵疾患	Alcoholic pancreopathy
10076388	新生児胃腸障害	Neonatal gastrointestinal disorder
10076390	口内知覚過敏	Oral hyperaesthesia
10076398	胃腸粘膜充血	Gastrointestinal mucosa hyperaemia
10076473	肛門直腸感覚消失	Anorectal sensory loss

PT コード	PT_日本語	PT_英語
10076508	口腔内過角化	Oral hyperkeratosis
10076599	潰瘍性胃炎	Ulcerative gastritis
10076607	腹膜皮膚瘻	Peritoneocutaneous fistula
10076931	絞扼性臍ヘルニア	Strangulated umbilical hernia
10076952	食道多発輪状狭窄	Feline oesophagus
10076953	閉塞性排便	Obstructive defaecation
10076972	乳頭部ポリープ	Ampullary polyp
10077019	食道粘膜水疱	Oesophageal mucosal blister
10077486	食道壁内血腫	Oesophageal intramural haematoma
10077519	口蓋潰瘍	Palatal ulcer
10077552	口腔内色素沈着	Oral pigmentation
10077605	肛門失禁	Anal incontinence
10077822	食道粘膜裂傷	Oesophageal mucosal tear
10077828	大網壊死	Omental necrosis
10077829	内臓静脈血栓症	Visceral venous thrombosis
10077854	歯肉不快感	Gingival discomfort
10077855	舌不快感	Tongue discomfort
10077873	食道胸腔瘻	Oesophagopleural fistula
10077983	腹部脂肪エプロン	Abdominal fat apron
10078058	腸静脈瘤出血	Intestinal varices haemorrhage
10078094	慢性咬頬	Chronic cheek biting
10078142	胃腸血管拡張症	Gastrointestinal angiectasia
10078170	口腔挫傷	Oral contusion
10078275	歯の異常感覚	Dental dysaesthesia
10078276	歯の錯感覚	Dental paraesthesia
10078322	脾静脈性血管瘤	Splenic vein aneurysm
10078335	消化管メラノーシス	Gastrointestinal melanosis
10078375	唾液腺症	Sialadenosis
10078413	上部消化管穿孔	Upper gastrointestinal perforation
10078414	下部消化管穿孔	Lower gastrointestinal perforation
10078438	白色乳頭様所見	White nipple sign
10078474	舟状腹	Scaphoid abdomen
10078506	リンパ球性食道炎	Lymphocytic oesophagitis
10078507	線維素性唾液管炎	Sialodochitis fibrinosa
10078659	腹腔内液貯留	Intra-abdominal fluid collection
10078785	腸リンパ組織過形成	Lymphoid hyperplasia of intestine
10078915	正中離開	Diastema
10079055	胃腸ポリープ	Gastrointestinal polyp
10079075	舌紅斑	Tongue erythema
10079120	変色吐物	Discoloured vomit
10079166	区域性憩室性大腸炎	Segmental diverticular colitis
10079196	腸間膜嚢胞	Mesenteric cyst

PT コード	PT_日本語	PT_英語
10079281	膵不全	Pancreatic failure
10079293	一過性舌乳頭炎	Transient lingual papillitis
10079446	門脈圧亢進性結腸疾患	Portal hypertensive colopathy
10079517	胃壁内気腫	Gastric pneumatosis
10079553	腹腔動脈瘤	Coeliac artery aneurysm
10079554	アレルギー性口内炎	Allergic stomatitis
10079556	腸間膜動脈瘤	Mesenteric artery aneurysm
10079622	スプルー様腸疾患	Sprue-like enteropathy
10079765	裂肛出血	Anal fissure haemorrhage
10079822	閉塞性膵炎	Obstructive pancreatitis
10079869	奇形性嚥下障害	Dysphagia lusoria
10079890	胃粘膜石灰沈着症	Gastric mucosal calcinosis
10079893	陰窩炎	Cryptitis
10079938	排便障害	Defaecation disorder
10080124	口唇紅斑	Lip erythema
10080276	毛舌症	Trichoglossia
腎機能関連事象		
10001017	急性腎前性腎不全	Acute prerenal failure
10001580	アルブミン尿	Albuminuria
10002847	無尿	Anuria
10003629	無緊張性膀胱	Atonic urinary bladder
10003885	高窒素血症	Azotaemia
10004231	ベンスジョーンズ蛋白尿	Bence Jones proteinuria
10004710	ビリルビン尿	Bilirubinuria
10005033	膀胱拡大	Bladder dilatation
10005034	膀胱不快感	Bladder discomfort
10005038	膀胱憩室	Bladder diverticulum
10005042	膀胱線維症	Bladder fibrosis
10005043	膀胱肉芽腫	Bladder granuloma
10005052	膀胱刺激症状	Bladder irritation
10005053	膀胱頚部閉塞	Bladder neck obstruction
10005060	膀胱閉塞	Bladder obstruction
10005063	膀胱痛	Bladder pain
10005073	膀胱括約筋無緊張症	Bladder sphincter atony
10005082	膀胱狭窄	Bladder stenosis
10005083	膀胱毛細血管拡張	Bladder telangiectasia
10006987	膀胱結石	Calculus bladder
10007026	尿道結石	Calculus urethral
10007027	尿路結石	Calculus urinary
10008684	黄疸尿	Choluria
10008796	着色尿	Chromaturia
10009168	乳び尿	Chyluria

PT コード	PT_日本語	PT_英語
10010814	萎縮膀胱	Contracted bladder
10011479	クリオグロブリン尿	Cryoglobulinuria
10011509	結晶尿	Crystalluria
10011730	円柱尿	Cylindruria
10011793	出血性膀胱炎	Cystitis haemorrhagic
10011796	間質性膀胱炎	Cystitis interstitial
10011801	潰瘍性膀胱炎	Cystitis ulcerative
10012550	排尿筋の括約筋失調	Detrusor sphincter dyssynergia
10012660	糖尿病性末期腎疾患	Diabetic end stage renal disease
10013990	排尿困難	Dysuria
10015869	尿浸潤	Extravasation of urine
10018352	グロブリン尿	Globulinuria
10018362	糸球体血管障害	Glomerular vascular disorder
10018364	糸球体腎炎	Glomerulonephritis
10018366	急性糸球体腎炎	Glomerulonephritis acute
10018367	慢性糸球体腎炎	Glomerulonephritis chronic
10018370	膜性増殖性糸球体腎炎	Glomerulonephritis membranoproliferative
10018372	膜性糸球体腎炎	Glomerulonephritis membranous
10018374	微少病変糸球体腎炎	Glomerulonephritis minimal lesion
10018376	増殖性糸球体腎炎	Glomerulonephritis proliferative
10018378	急速進行性糸球体腎炎	Glomerulonephritis rapidly progressive
10018473	糖尿	Glycosuria
10018475	妊娠糖尿	Glycosuria during pregnancy
10018620	グッドパスチャー症候群	Goodpasture's syndrome
10018867	血尿	Haematuria
10018906	ヘモグロビン尿	Haemoglobinuria
10020524	水腎症	Hydronephrosis
10020533	水尿管症	Hydroureter
10020586	高カルシウム血症性腎症	Hypercalcaemic nephropathy
10020590	高カルシウム尿症	Hypercalciuria
10020703	高シュウ酸尿症	Hyperoxaluria
10020770	高張尿	Hypersthenuria
10020853	緊張性膀胱	Hypertonic bladder
10021096	低張尿	Hyposthenuria
10021263	ＩｇＡ腎症	IgA nephropathy
10021639	失禁	Incontinence
10022530	毛細血管間糸球体硬化症	Intercapillary glomerulosclerosis
10023077	等張尿	Isosthenuria
10023388	ケトン尿	Ketonuria
10023421	腎線維症	Kidney fibrosis
10023423	過剰運動性腎	Kidney hypermobility
10023435	矮小腎	Kidney small

PT コード	PT_日本語	PT_英語
10024602	脂肪尿	Lipiduria
10025140	ループス腎炎	Lupus nephritis
10026674	悪性腎性高血圧	Malignant renal hypertension
10026827	行軍血色素尿症	March haemoglobinuria
10027498	メトヘモグロビン尿	Methaemoglobinuria
10027525	ミクロアルブミン尿	Microalbuminuria
10027561	排尿異常	Micturition disorder
10027566	尿意切迫	Micturition urgency
10028629	ミオグロビン尿	Myoglobinuria
10029117	腎炎	Nephritis
10029120	アレルギー性腎炎	Nephritis allergic
10029132	出血性腎炎	Nephritis haemorrhagic
10029146	腎石灰沈着症	Nephrocalcinosis
10029147	腎性尿崩症	Nephrogenic diabetes insipidus
10029148	腎結石症	Nephrolithiasis
10029151	腎症	Nephropathy
10029155	中毒性ネフロパシー	Nephropathy toxic
10029158	腎下垂症	Nephroptosis
10029159	腎硬化症	Nephrosclerosis
10029164	ネフローゼ症候群	Nephrotic syndrome
10029279	神経因性膀胱	Neurogenic bladder
10029446	夜間頻尿	Nocturia
10030302	乏尿	Oliguria
10031129	起立性蛋白尿症	Orthostatic proteinuria
10034042	発作性夜間血色素尿症	Paroxysmal nocturnal haemoglobinuria
10034232	骨盤部尿管閉塞	Pelvi-ureteric obstruction
10035642	気尿症	Pneumaturia
10036018	頻尿	Pollakiuria
10036142	多尿	Polyuria
10036303	レンサ球菌感染後糸球体腎炎	Post streptococcal glomerulonephritis
10037032	蛋白尿	Proteinuria
10038357	腎アミロイドーシス	Renal amyloidosis
10038366	腎動脈瘤	Renal aneurysm
10038372	腎の動脈硬化症	Renal arteriosclerosis
10038373	腎動脈炎	Renal arteritis
10038377	腎動脈過形成	Renal artery hyperplasia
10038378	腎動脈狭窄症	Renal artery stenosis
10038380	腎動脈血栓症	Renal artery thrombosis
10038381	腎萎縮	Renal atrophy
10038419	腎仙痛	Renal colic
10038422	腎皮質壊死	Renal cortical necrosis
10038423	腎嚢胞	Renal cyst

PT コード	PT_日本語	PT_英語
10038428	腎障害	Renal disorder
10038435	腎不全	Renal failure
10038447	新生児腎不全	Renal failure neonatal
10038457	腎性糖尿	Renal glycosuria
10038459	腎血腫	Renal haematoma
10038460	腎出血	Renal haemorrhage
10038464	腎性高血圧	Renal hypertension
10038468	腎肥大	Renal hypertrophy
10038470	腎梗塞	Renal infarct
10038481	腎臓壊死	Renal necrosis
10038490	腎臓痛	Renal pain
10038491	腎乳頭壊死	Renal papillary necrosis
10038535	腎尿細管性アシドーシス	Renal tubular acidosis
10038536	腎尿細管萎縮	Renal tubular atrophy
10038537	腎尿細管障害	Renal tubular disorder
10038540	腎尿細管壊死	Renal tubular necrosis
10038546	腎血管炎	Renal vasculitis
10038547	腎静脈塞栓症	Renal vein embolism
10038548	腎静脈血栓症	Renal vein thrombosis
10038553	腎血管障害	Renal vessel disorder
10041900	鹿角状結石	Stag horn calculus
10041997	膀胱三角部狭窄	Stenosis trigone urinary bladder
10042010	無菌性膿尿	Sterile pyuria
10042170	有痛性排尿困難	Strangury
10044668	膀胱三角部炎	Trigonitis
10046337	尿酸腎症	Urate nephropathy
10046399	尿管拡張	Ureteric dilatation
10046404	尿管瘻	Ureteric fistula
10046406	尿管閉塞	Ureteric obstruction
10046411	尿管狭窄	Ureteric stenosis
10046437	尿道カルンクル	Urethral caruncle
10046442	尿道拡張	Urethral dilatation
10046443	尿道分泌物	Urethral discharge
10046445	尿道障害	Urethral disorder
10046451	尿道瘻	Urethral fistula
10046456	内尿道括約筋不全	Urethral intrinsic sphincter deficiency
10046459	尿道閉塞	Urethral obstruction
10046461	尿道痛	Urethral pain
10046464	尿道痙攣	Urethral spasm
10046477	尿道症候群	Urethral syndrome
10046494	切迫性尿失禁	Urge incontinence
10046528	膀胱出血	Urinary bladder haemorrhage

PT コード	PT_日本語	PT_英語
10046530	膀胱破裂	Urinary bladder rupture
10046542	排尿躊躇	Urinary hesitation
10046543	尿失禁	Urinary incontinence
10046555	尿閉	Urinary retention
10046566	尿路障害	Urinary tract disorder
10046607	尿異常	Urine abnormality
10046640	尿流量減少	Urine flow decreased
10046689	ウロビリン尿	Urobilinuria
10046694	尿生殖器障害	Urogenital disorder
10046696	尿生殖器瘻	Urogenital fistula
10047363	膀胱瘻	Vesical fistula
10047370	膀胱尿管逆流	Vesicoureteric reflux
10048302	尿細管間質性腎炎	Tubulointerstitial nephritis
10048469	腎腫大	Kidney enlargement
10048475	膀胱脱	Bladder prolapse
10048837	腺性膀胱炎	Cystitis glandularis
10048988	腎動脈閉塞	Renal artery occlusion
10048994	膀胱痙縮	Bladder spasm
10049027	膀胱肉柱形成	Bladder trabeculation
10049448	尿道潰瘍	Urethral ulcer
10049502	尿道嚢胞	Urethral cyst
10049576	膀胱頚部硬化症	Bladder neck sclerosis
10049710	尿道出血	Urethral haemorrhage
10049716	後天性膀胱位置異常	Bladder malposition acquired
10049739	腎動脈筋線維性形成異常	Renal artery fibromuscular dysplasia
10049776	新生児腎障害	Renal impairment neonatal
10049778	新生児無尿	Neonatal anuria
10049794	膀胱ポリープ	Urinary bladder polyp
10049810	尿管破裂	Ureteric rupture
10049814	腎嚢胞破裂	Renal cyst ruptured
10049942	腎動脈解離	Renal artery dissection
10050058	尿生殖器出血	Urogenital haemorrhage
10050091	尿貯留腫	Urinoma
10050266	尿管壊死	Ureteral necrosis
10050335	腎尿細管機能障害	Renal tubular dysfunction
10050394	高カリウム尿症	Hyperkaliuria
10050687	膀胱炎様症状	Cystitis-like symptom
10050702	圧挫症候群	Crush syndrome
10050791	白血球尿	Leukocyturia
10050977	低カルシウム尿症	Hypocalciuria
10051232	高リン酸尿症	Hyperphosphaturia
10051257	膀胱白板症	Bladder leukoplakia

PT コード	PT_日本語	PT_英語
10051258	膀胱壊死	Bladder necrosis
10051364	高尿酸尿症	Hyperuricosuria
10051394	アレルギー性膀胱炎	Allergic cystitis
10051467	腎拡張症	Nephrectasia
10051468	亜硝酸塩尿症	Nitrituria
10051506	尿管ポリープ	Ureteral polyp
10051507	尿道ポリープ	Urethral polyp
10051640	アンモニア尿	Ammoniuria
10051693	膀胱萎縮	Urinary bladder atrophy
10051704	肋骨脊柱角圧痛	Costovertebral angle tenderness
10051920	糸球体腎症	Glomerulonephropathy
10051921	ヘマチン尿	Haematinuria
10051958	尿管攣縮	Ureteral spasm
10051985	腎盂瘻	Renal pelvis fistula
10052242	腎血管硬化症	Nephroangiosclerosis
10052607	後天性ファンコニー症候群	Fanconi syndrome acquired
10052763	尿道捻転	Torsion of the urethra
10052901	終末尿滴下	Terminal dribbling
10053122	ヒドロキシプロリン尿	Hydroxyprolinuria
10053236	混合性尿失禁	Mixed incontinence
10054832	びまん性メサンギウム硬化	Diffuse mesangial sclerosis
10055171	高血圧性腎症	Hypertensive nephropathy
10055847	尿路出血	Haemorrhage urinary tract
10056246	好酸球性膀胱炎	Eosinophilic cystitis
10056277	膵腎症候群	Pancreatorenal syndrome
10056293	腎静脈閉塞	Renal vein occlusion
10056433	尿管瘤	Ureterocele
10056505	妊娠時腎障害	Renal disorder in pregnancy
10056609	尿毒症臭	Uraemia odour
10056948	自動膀胱	Automatic bladder
10057135	尿臭異常	Urine odour abnormal
10057345	腎脂肪腫症	Renal lipomatosis
10057399	腎杯憩室	Calyceal diverticulum
10058320	膀胱腫瘤	Bladder mass
10058463	外尿道口狭窄	Urethral meatus stenosis
10058484	膀胱マラコプラキア	Malacoplakia vesicae
10058524	膀胱嚢胞	Bladder cyst
10058914	低緊張性膀胱	Hypotonic urinary bladder
10059042	排尿回数減少	Micturition frequency decreased
10059209	腎周囲液貯留	Perinephric collection
10059345	腎後性腎不全	Postrenal failure
10059410	糞尿	Faecaluria

PT コード	PT_日本語	PT_英語
10059846	腎嚢胞出血	Renal cyst haemorrhage
10061011	膀胱障害	Bladder disorder
10061139	糖尿病性膀胱症	Diabetic cystopathy
10061481	腎損傷	Renal injury
10061574	尿路閉塞	Urinary tract obstruction
10061835	糖尿病性腎症	Diabetic nephropathy
10061927	腎盂腎杯拡張症	Pyelocaliectasis
10061989	糸球体硬化症	Glomerulosclerosis
10062104	腎腫瘤	Renal mass
10062220	尿管障害	Ureteral disorder
10062225	尿路痛	Urinary tract pain
10062237	腎機能障害	Renal impairment
10062550	腎塩類喪失症候群	Renal salt-wasting syndrome
10062553	強皮症腎クリーゼ	Scleroderma renal crisis
10062622	色素沈着性腎症	Pigment nephropathy
10062656	膀胱タンポナーデ	Bladder tamponade
10062854	腎水瘤	Renal hydrocele
10062903	非感染性尿道炎	Urethritis noninfective
10063057	非感染性膀胱炎	Cystitis noninfective
10063408	膀胱壁肥厚	Bladder hypertrophy
10063530	機能的単腎	Single functional kidney
10063544	腎塞栓	Renal embolism
10063575	膀胱穿孔	Bladder perforation
10063684	精液尿	Semenuria
10063897	腎虚血	Renal ischaemia
10064170	ペントース尿症	Pentosuria
10064848	慢性腎臓病	Chronic kidney disease
10064850	びらん性膀胱炎	Cystitis erosive
10064921	尿路の炎症	Urinary tract inflammation
10065286	高クロール尿症	Hyperchloruria
10065368	尿瘻	Urinary fistula
10065427	逆流性腎症	Reflux nephropathy
10065561	腎動脈の動脈硬化症	Renal artery arteriosclerosis
10065584	尿道狭窄	Urethral stenosis
10065673	腎炎症候群	Nephritic syndrome
10065743	尿管出血	Ureteric haemorrhage
10065792	腎穿孔	Kidney perforation
10065809	尿管穿孔	Ureteric perforation
10065810	尿道穿孔	Urethral perforation
10065914	尿管嚢胞	Ureteral cyst
10066218	腹圧性尿失禁	Stress urinary incontinence
10066436	尿管憩室	Ureteral diverticulum

PT コード	PT_日本語	PT_英語
10066453	メサンギウム増殖性糸球体腎炎	Mesangioproliferative glomerulonephritis
10067757	巣状分節性糸球体硬化症	Focal segmental glomerulosclerosis
10067784	尿道脱	Urethral prolapse
10067871	イムノタクトイド糸球体腎炎	Immunotactoid glomerulonephritis
10068279	細線維性糸球体腎炎	Fibrillary glomerulonephritis
10068313	尿道萎縮	Urethral atrophy
10068513	肺腎症候群	Pulmonary renal syndrome
10069034	尿細管間質性腎炎ぶどう膜炎症候群	Tubulointerstitial nephritis and uveitis syndrome
10069339	急性腎障害	Acute kidney injury
10069384	虚血性腎症	Ischaemic nephropathy
10069395	ヘモジデリン尿症	Haemosiderinuria
10069440	ヘノッホ・シェーンライン紫斑病性腎炎	Henoch-Schonlein purpura nephritis
10069448	膀胱異形成	Bladder dysplasia
10069632	膀胱機能障害	Bladder dysfunction
10069645	膀胱容量減少	Reduced bladder capacity
10069648	腹圧性排尿	Urinary straining
10069688	急性リン酸腎症	Acute phosphate nephropathy
10070505	尿道会陰瘻	Urethroperineal fistula
10070632	膀胱感覚消失	Loss of bladder sensation
10070869	後天性嚢胞性腎疾患	Acquired cystic kidney disease
10070871	低クエン酸尿症	Hypocitraturia
10071137	腰痛血尿症候群	Loin pain haematuria syndrome
10071138	栄養障害・炎症・動脈硬化症候群	Malnutrition-inflammation-atherosclerosis syndrome
10071289	下部尿路症状	Lower urinary tract symptoms
10071353	高マグネシウム尿症	Hypermagnesuria
10071445	膀胱出口部閉塞	Bladder outlet obstruction
10071503	クリスタル腎症	Crystal nephropathy
10071566	膀胱皮膚瘻	Vesicocutaneous fistula
10071718	ファウラー症候群	Fowler's syndrome
10072058	腎周囲炎	Perinephritis
10072140	膀胱壁石灰化	Bladder wall calcification
10072226	腎血管血栓症	Renal vascular thrombosis
10072370	腎前性腎不全	Prerenal failure
10072996	膀胱毒性	Urinary bladder toxicity
10073016	慢性自己免疫性糸球体腎炎	Chronic autoimmune glomerulonephritis
10073176	膀胱静脈瘤	Urinary bladder varices
10073381	浮腫性腎	Oedematous kidney
10073515	後天性アミノ酸尿	Acquired aminoaciduria
10073599	骨髄腫円柱腎症	Myeloma cast nephropathy
10073745	水腎杯	Hydrocalyx

PT コード	PT_日本語	PT_英語
10074386	腎静脈圧迫	Renal vein compression
10074480	感染後糸球体腎炎	Post infection glomerulonephritis
10074714	ループス膀胱炎	Lupus cystitis
10075537	泌尿生殖器症状	Genitourinary symptom
10075626	腫瘍随伴性ネフローゼ症候群	Paraneoplastic nephrotic syndrome
10075737	腎動脈穿孔	Renal artery perforation
10075849	カリウム喪失性腎症	Potassium wasting nephropathy
10076427	膀胱充血	Bladder hyperaemia
10076507	高ナトリウム尿症	Hypernatriuria
10076568	尿路不快感	Urinary tract discomfort
10076704	ページ腎	Page kidney
10076715	尿管圧迫	Ureteric compression
10076749	腫瘍随伴性糸球体腎炎	Paraneoplastic glomerulonephritis
10076916	腎うっ血	Kidney congestion
10077087	自己免疫性腎炎	Autoimmune nephritis
10077209	ＩｇM腎症	IgM nephropathy
10077233	膀胱化生	Bladder metaplasia
10077278	腎静脈静脈瘤	Renal vein varices
10077512	末期腎疾患	End stage renal disease
10077515	低ナトリウム尿症	Hyponatriuria
10077827	Ｃ３糸球体症	C3 glomerulopathy
10077862	閉塞性腎症	Obstructive nephropathy
10077989	尿管結石症	Ureterolithiasis
10078119	尿路上皮びらん	Urothelium erosion
10078656	腎細胞異形成	Renal cell dysplasia
10078750	尿管アカラシア	Ureteral achalasia
10078818	腎周囲浮腫	Perinephric oedema
10078907	腎静脈狭窄	Renal vein stenosis
10078933	腎尿細管損傷	Renal tubular injury
10078987	胎児腎障害	Foetal renal impairment
10079249	無窒素尿症	Anazoturia
10079250	高窒素尿症	Azoturia
10079493	尿路ポリープ	Urinary tract polyp
10079546	排尿後の尿滴下	Post micturition dribble
10080015	悪性尿路閉塞	Malignant urinary tract obstruction
10001575	尿中アルブミン	Albumin urine
10001581	尿中アルブミン陰性	Albumin urine absent
10001582	尿中アルブミン陽性	Albumin urine present
10003203	腎動脈撮影	Arteriogram renal
10003204	腎動脈造影異常	Arteriogram renal abnormal
10003205	腎動脈造影正常	Arteriogram renal normal
10004730	膀胱生検	Biopsy bladder

PT コード	PT_日本語	PT_英語
10004731	膀胱生検異常	Biopsy bladder abnormal
10004732	膀胱生検正常	Biopsy bladder normal
10004782	腎生検	Biopsy kidney
10004783	腎生検異常	Biopsy kidney abnormal
10004784	腎生検正常	Biopsy kidney normal
10004897	尿道生検	Biopsy urethra
10004898	尿道生検異常	Biopsy urethra abnormal
10004899	尿道生検正常	Biopsy urethra normal
10005461	血中クレアチン	Blood creatine
10005462	血中クレアチン異常	Blood creatine abnormal
10005463	血中クレアチン減少	Blood creatine decreased
10005464	血中クレアチン増加	Blood creatine increased
10005466	血中クレアチン正常	Blood creatine normal
10005480	血中クレアチニン	Blood creatinine
10005481	血中クレアチニン異常	Blood creatinine abnormal
10005482	血中クレアチニン減少	Blood creatinine decreased
10005483	血中クレアチニン増加	Blood creatinine increased
10005484	血中クレアチニン正常	Blood creatinine normal
10005845	血中尿素	Blood urea
10005846	血中尿素異常	Blood urea abnormal
10005850	血中尿素減少	Blood urea decreased
10005851	血中尿素増加	Blood urea increased
10005857	血中尿素正常	Blood urea normal
10005863	尿中血	Blood urine
10007880	尿中細胞	Cells in urine
10011353	尿中クレアチン	Creatine urine
10011354	尿中クレアチン異常	Creatine urine abnormal
10011355	尿中クレアチン減少	Creatine urine decreased
10011356	尿中クレアチン増加	Creatine urine increased
10011357	尿中クレアチン正常	Creatine urine normal
10011364	腎クレアチニン・クリアランス増加	Creatinine renal clearance increased
10011371	腎クレアチニン・クリアランス	Creatinine renal clearance
10011372	腎クレアチニン・クリアランス減少	Creatinine renal clearance decreased
10011374	腎クレアチニン・クリアランス正常	Creatinine renal clearance normal
10011510	尿中結晶陰性	Crystal urine absent
10011512	尿中結晶陽性	Crystal urine present
10011804	膀胱造影	Cystogram
10011805	膀胱造影異常	Cystogram abnormal
10011806	膀胱造影正常	Cystogram normal
10011814	膀胱鏡検査	Cystoscopy
10011815	膀胱鏡検査異常	Cystoscopy abnormal
10011816	膀胱鏡検査正常	Cystoscopy normal

PT コード	PT_日本語	PT_英語
10018355	糸球体濾過率	Glomerular filtration rate
10018356	糸球体濾過率異常	Glomerular filtration rate abnormal
10018358	糸球体濾過率減少	Glomerular filtration rate decreased
10018359	糸球体濾過率増加	Glomerular filtration rate increased
10018361	糸球体濾過率正常	Glomerular filtration rate normal
10018436	尿中ブドウ糖	Glucose urine
10018474	尿中ブドウ糖陰性	Glucose urine absent
10018478	尿中ブドウ糖陽性	Glucose urine present
10018868	尿中血陰性	Blood urine absent
10018870	尿中血陽性	Blood urine present
10018907	尿中ヘモグロビン陰性	Haemoglobin urine absent
10018909	尿中ヘモグロビン陽性	Haemoglobin urine present
10022868	腎イヌリンクリアランス	Inulin renal clearance
10022869	腎イヌリンクリアランス異常	Inulin renal clearance abnormal
10022870	腎イヌリンクリアランス減少	Inulin renal clearance decreased
10022871	腎イヌリンクリアランス増加	Inulin renal clearance increased
10022873	腎イヌリンクリアランス正常	Inulin renal clearance normal
10029425	窒素負平衡	Nitrogen balance negative
10034791	尿ｐＨ	pH urine
10034792	尿ｐＨ異常	pH urine abnormal
10034793	尿ｐＨ低下	pH urine decreased
10034795	尿ｐＨ上昇	pH urine increased
10034797	尿ｐＨ正常	pH urine normal
10037018	尿蛋白	Protein urine
10037033	尿中蛋白陰性	Protein urine absent
10037593	逆行性腎盂造影	Pyelogram retrograde
10037594	逆行性腎盂造影異常	Pyelogram retrograde abnormal
10037595	逆行性腎盂造影正常	Pyelogram retrograde normal
10038182	尿中赤血球陽性	Red blood cells urine positive
10038520	腎スキャン	Renal scan
10041438	尿比重	Specific gravity urine
10041439	尿比重異常	Specific gravity urine abnormal
10041440	尿比重正常	Specific gravity urine normal
10045406	膀胱超音波検査	Ultrasound bladder
10045407	膀胱超音波検査異常	Ultrasound bladder abnormal
10045408	膀胱超音波検査正常	Ultrasound bladder normal
10045421	腎超音波検査	Ultrasound kidney
10045422	腎超音波検査異常	Ultrasound kidney abnormal
10045423	腎超音波検査正常	Ultrasound kidney normal
10046358	腎尿素クリアランス減少	Urea renal clearance decreased
10046360	腎尿素クリアランス正常	Urea renal clearance normal
10046361	尿中尿素異常	Urea urine abnormal

PT コード	PT_日本語	PT_英語
10046362	尿中尿素減少	Urea urine decreased
10046364	尿中尿素増加	Urea urine increased
10046366	尿中尿素正常	Urea urine normal
10046413	尿管鏡検査	Ureteroscopy
10046414	尿管鏡検査異常	Ureteroscopy abnormal
10046415	尿管鏡検査正常	Ureteroscopy normal
10046533	尿円柱	Urinary casts
10046547	尿中窒素増加	Urinary nitrogen increased
10046558	尿路系Ｘ線	Urinary system X-ray
10046614	尿検査	Urine analysis
10046680	尿粘稠度亢進	Urine viscosity increased
10047149	バソプレシン負荷試験	Vasopressin challenge test
10047150	バソプレシン負荷試験異常	Vasopressin challenge test abnormal
10047151	バソプレシン負荷試験正常	Vasopressin challenge test normal
10047211	腎静脈造影	Venogram renal
10047212	腎静脈造影異常	Venogram renal abnormal
10047213	腎静脈造影正常	Venogram renal normal
10047965	尿中白血球陰性	White blood cells urine negative
10047967	尿中白血球陽性	White blood cells urine positive
10048546	尿中赤血球陰性	Red blood cells urine negative
10048906	膀胱内圧測定	Cystometrogram
10049696	尿中クレアチニン	Creatinine urine
10049821	尿沈渣陽性	Urinary sediment present
10050126	尿道鏡検査	Urethroscopy
10050413	尿中白血球エステラーゼ	Urine leukocyte esterase
10050663	尿中白血球	White blood cells urine
10050676	尿中赤血球	Red blood cells urine
10050710	尿中尿素	Urea urine
10050757	尿中クレアチニン増加	Creatinine urine increased
10050760	血中尿素窒素／クレアチニン比増加	Blood urea nitrogen/creatinine ratio increased
10050772	尿比重減少	Specific gravity urine decreased
10050773	尿比重増加	Specific gravity urine increased
10050795	尿中白血球エステラーゼ陽性	Urine leukocyte esterase positive
10050832	残尿量	Residual urine volume
10050957	尿中蛋白定量法	Urine protein, quantitative
10050970	尿中窒素	Urine nitrogen
10051274	フェノールスルホンフタレイン試験	Phenolsulfonphthalein test
10051275	フェノールスルホンフタレイン試験異常	Phenolsulfonphthalein test abnormal
10051276	フェノールスルホンフタレイン試験正常	Phenolsulfonphthalein test normal
10051469	尿中亜硝酸塩陽性	Nitrite urine present
10052685	尿流動態検査	Urodynamics measurement
10053114	尿中結晶	Crystal urine

PT コード	PT_日本語	PT_英語
10053119	尿中グロブリン	Globulin urine
10053123	尿中蛋白陽性	Protein urine present
10053186	尿中グロブリン陽性	Globulin urine present
10053536	尿中蛋白／クレアチニン比減少	Urine protein/creatinine ratio decreased
10053537	尿中蛋白／クレアチニン比	Urine protein/creatinine ratio
10053538	尿中蛋白／クレアチニン比増加	Urine protein/creatinine ratio increased
10053539	尿中蛋白／クレアチニン比異常	Urine protein/creatinine ratio abnormal
10053540	尿中蛋白／クレアチニン比正常	Urine protein/creatinine ratio normal
10053541	尿中アルブミン／クレアチニン比増加	Urine albumin/creatinine ratio increased
10053542	尿中アルブミン／クレアチニン比	Urine albumin/creatinine ratio
10053543	尿中アルブミン／クレアチニン比正常	Urine albumin/creatinine ratio normal
10053544	尿中アルブミン／クレアチニン比異常	Urine albumin/creatinine ratio abnormal
10053545	尿中アルブミン／クレアチニン比減少	Urine albumin/creatinine ratio decreased
10054004	腎コンピュータ断層撮影	Computerised tomogram kidney
10055003	尿中クレアチニン減少	Creatinine urine decreased
10056615	尿中窒素減少	Urinary nitrogen decreased
10056666	尿中非治療薬陽性	Nontherapeutic agent urine positive
10056700	尿中治療薬陽性	Therapeutic agent urine positive
10056701	尿中治療薬陰性	Therapeutic agent urine negative
10056702	尿中非治療薬陰性	Nontherapeutic agent urine negative
10057120	尿中尿酸増加	Urine uric acid increased
10057121	尿中移行上皮細胞陽性	Urine transitional cells present
10057138	尿中シュウ酸塩	Urine oxalate
10057139	尿中尿酸減少	Urine uric acid decreased
10057140	尿中尿酸正常	Urine uric acid normal
10057141	尿中尿酸異常	Urine uric acid abnormal
10057142	尿中尿酸	Urine uric acid
10057143	尿中薬物結晶	Medication crystals in urine
10057397	腎盂鏡検査	Pyeloscopy
10057508	腎盂鏡検査正常	Pyeloscopy normal
10057509	腎盂鏡検査異常	Pyeloscopy abnormal
10058037	シスタチンＣ増加	Cystatin C increased
10058363	尿中好酸球陽性	Eosinophils urine present
10058391	尿中好酸球	Eosinophils urine
10058392	尿中好酸球陰性	Eosinophils urine absent
10059220	尿中亜硝酸塩	Nitrite urine
10059228	尿中ヘモグロビン	Haemoglobin urine
10059261	尿細胞診異常	Urine cytology abnormal
10059263	尿細胞診	Urine cytology
10059264	尿細胞診正常	Urine cytology normal
10059742	尿中クエン酸増加	Citric acid urine increased
10059743	尿中クエン酸減少	Citric acid urine decreased

PT コード	PT_日本語	PT_英語
10059771	尿中クエン酸	Citric acid urine
10059894	尿量	Urine output
10059895	尿量減少	Urine output decreased
10059896	尿量増加	Urine output increased
10059899	血中尿素窒素／クレアチニン比	Blood urea nitrogen/creatinine ratio
10059937	血中尿素窒素／クレアチニン比減少	Blood urea nitrogen/creatinine ratio decreased
10060194	カリウム感受性検査	Potassium chloride sensitivity test
10060224	カリウム感受性検査正常	Potassium chloride sensitivity test normal
10060225	カリウム感受性検査異常	Potassium chloride sensitivity test abnormal
10060799	尿中亜硝酸塩陰性	Nitrite urine absent
10061432	尿中レチノール結合蛋白増加	Urine retinol binding protein increased
10061440	尿中レチノール結合蛋白	Urine retinol binding protein
10061441	尿中レチノール結合蛋白減少	Urine retinol binding protein decreased
10061480	腎機能検査異常	Renal function test abnormal
10061490	腎機能検査	Renal function test
10061491	腎機能検査正常	Renal function test normal
10061578	尿検査正常	Urine analysis normal
10061940	膀胱スキャン	Bladder scan
10061953	腎スキャン異常	Renal scan abnormal
10061954	腎スキャン正常	Renal scan normal
10061980	尿沈渣異常	Urinary sediment abnormal
10062138	尿路系Ｘ線異常	Urinary system x-ray abnormal
10062139	尿路系Ｘ線正常	Urinary system x-ray normal
10062226	尿検査異常	Urine analysis abnormal
10063168	尿粘稠度低下	Urine viscosity decreased
10063169	尿粘稠度異常	Urine viscosity abnormal
10063173	尿粘稠度	Urine viscosity
10064415	尿中アラニンアミノペプチダーゼ増加	Urine alanine aminopeptidase increased
10064416	尿中アラニンアミノペプチダーゼ減少	Urine alanine aminopeptidase decreased
10064417	尿中グリコール酸増加	Urine glycolic acid increased
10064422	尿中シュウ酸塩増加	Urine oxalate increased
10064423	尿中シュウ酸塩減少	Urine oxalate decreased
10064988	シスタチンＣ	Cystatin C
10064989	シスタチンＣ異常	Cystatin C abnormal
10065096	尿路造影	Urogram
10065097	尿路造影異常	Urogram abnormal
10065098	尿路造影正常	Urogram normal
10065297	尿中脂質陽性	Urinary lipids present
10067533	尿円柱陰性	Urinary casts absent
10067534	尿円柱陽性	Urinary casts present
10067758	残尿量増加	Residual urine volume increased
10067759	残尿量減少	Residual urine volume decreased

PT コード	PT_日本語	PT_英語
10068447	腎クレアチニン・クリアランス異常	Creatinine renal clearance abnormal
10068700	腎臓鏡検査	Nephroscopy
10068860	尿路結石分析	Urinary stone analysis
10069655	尿管内圧測定	Urometry
10070191	尿素除去率	Urea reduction ratio
10070418	透析効果検査	Dialysis efficacy test
10071020	尿中クレアチニン正常	Creatinine urine normal
10071021	尿中クレアチニン異常	Creatinine urine abnormal
10071295	尿路系超音波検査	Ultrasound urinary system
10071590	尿流動態検査異常	Urodynamics measurement abnormal
10072169	腎コンピュータ断層撮影正常	Computerised tomogram kidney normal
10072171	腎コンピュータ断層撮影異常	Computerised tomogram kidney abnormal
10072303	腎核磁気共鳴画像	Nuclear magnetic resonance imaging renal
10073543	腎尿素クリアランス	Urea renal clearance
10073544	腎尿素クリアランス増加	Urea renal clearance increased
10075141	リン分画排泄率	Fractional excretion of phosphate
10075142	ナトリウム分画排泄率	Fractional excretion of sodium
10075154	導管造影	Loopogram
10077358	排尿試験	Trial of void
10078383	尿管生検	Ureter biopsy
10078795	腎瘻造影	Nephrostogram
10078872	尿中ブドウ糖／クレアチニン比	Urine glucose/creatinine ratio
10078889	尿中ブドウ糖／クレアチニン比増加	Urine glucose/creatinine ratio increased
10078890	尿中ブドウ糖／クレアチニン比減少	Urine glucose/creatinine ratio decreased
10078891	尿中ブドウ糖／クレアチニン比異常	Urine glucose/creatinine ratio abnormal
10079357	尿中有機酸検査	Urine organic acid test
肝機能関連事象		
10052752	肝副葉	Accessory liver lobe
10053870	アラジール症候群	Alagille syndrome
10053684	脳肝腎症候群	Cerebrohepatorenal syndrome
10010317	先天性胆管欠損	Congenital absence of bile ducts
10010427	先天性嚢胞性肝疾患	Congenital cystic disease of liver
10056533	先天性肝線維症	Congenital hepatic fibrosis
10061065	先天性肝胆道系異常	Congenital hepatobiliary anomaly
10051130	先天性肝腫大	Congenital hepatomegaly
10068289	嚢胞性線維症肝疾患	Cystic fibrosis hepatic disease
10013003	先天性肝内胆管拡張症	Dilatation intrahepatic duct congenital
10018464	１型糖原貯蔵障害	Glycogen storage disease type I
10053250	３型糖原貯蔵障害	Glycogen storage disease type III
10053249	４型糖原貯蔵障害	Glycogen storage disease type IV
10053240	６型糖原貯蔵障害	Glycogen storage disease type VI
10079685	肝過誤腫	Hepatic hamartoma

PT コード	PT_日本語	PT_英語
10019785	新生児肝炎	Hepatitis neonatal
10019834	新生児肝細胞障害	Hepatocellular damage neonatal
10019819	肝レンズ核変性症	Hepato-lenticular degeneration
10019848	新生児肝脾腫大	Hepatosplenomegaly neonatal
10057873	遺伝性ヘモクロマトーシス	Hereditary haemochromatosis
10056528	新生児胆汁うっ滞	Neonatal cholestasis
10049995	新生児肝腫大	Neonatal hepatomegaly
10048834	多嚢胞性肝疾患	Polycystic liver disease
10036182	急性ポルフィリン症	Porphyria acute
10076609	門脈系異常	Portal venous system anomaly
10076033	進行性家族性肝内胆汁うっ滞	Progressive familial intrahepatic cholestasis
10020580	新生児高ビリルビン血症	Hyperbilirubinaemia neonatal
10023138	新生児黄疸	Jaundice neonatal
10023376	核黄疸	Kernicterus
10036186	非急性ポルフィリン症	Porphyria non-acute
10061009	ビリルビン排泄障害	Bilirubin excretion disorder
10048611	胆血症	Cholaemia
10008635	胆汁うっ滞	Cholestasis
10067969	胆汁うっ滞性肝損傷	Cholestatic liver injury
10064190	胆汁うっ滞性そう痒症	Cholestatic pruritus
10072268	薬物性肝障害	Drug-induced liver injury
10019754	胆汁うっ滞性肝炎	Hepatitis cholestatic
10020578	高ビリルビン血症	Hyperbilirubinaemia
10021209	黄疸指数上昇	Icterus index increased
10023126	黄疸	Jaundice
10023129	胆汁うっ滞性黄疸	Jaundice cholestatic
10023136	肝細胞性黄疸	Jaundice hepatocellular
10066758	混合型肝損傷	Mixed liver injury
10058117	黄疸眼	Ocular icterus
10074151	非経口栄養関連肝障害	Parenteral nutrition associated liver disease
10071634	胆汁分泌不全	Deficiency of bile secretion
10048245	黄色皮膚	Yellow skin
10000804	急性肝不全	Acute hepatic failure
10077305	慢性肝不全の急性増悪	Acute on chronic liver failure
10070815	急性黄色肝萎縮	Acute yellow liver atrophy
10003445	腹水	Ascites
10003547	固定姿勢保持困難	Asterixis
10068547	細菌感染腹水	Bacterascites
10004659	胆汁性肝硬変	Biliary cirrhosis
10004661	原発性胆汁性肝硬変	Biliary cirrhosis primary
10004664	胆管線維症	Biliary fibrosis
10067969	胆汁うっ滞性肝損傷	Cholestatic liver injury

PT コード	PT_日本語	PT_英語
10057573	慢性肝不全	Chronic hepatic failure
10010075	肝性昏睡	Coma hepatic
10063075	特発性肝硬変	Cryptogenic cirrhosis
10071265	糖尿病性肝障害	Diabetic hepatopathy
10072268	薬物性肝障害	Drug-induced liver injury
10051010	十二指腸静脈瘤	Duodenal varices
10072319	胆嚢静脈瘤	Gallbladder varices
10076237	胃静脈瘤注入	Gastric variceal injection
10076238	胃静脈瘤結紮	Gastric variceal ligation
10051012	胃静脈瘤	Gastric varices
10057572	胃静脈瘤出血	Gastric varices haemorrhage
10061997	肝切除	Hepatectomy
10019637	肝萎縮	Hepatic atrophy
10065274	肝石灰化	Hepatic calcification
10019641	肝硬変	Hepatic cirrhosis
10019660	肝性脳症	Hepatic encephalopathy
10066599	肝性脳症予防	Hepatic encephalopathy prophylaxis
10019663	肝不全	Hepatic failure
10019668	肝線維症	Hepatic fibrosis
10067365	肝性胸水	Hepatic hydrothorax
10064668	肝好酸球浸潤	Hepatic infiltration eosinophilic
10061998	肝病変	Hepatic lesion
10019692	肝壊死	Hepatic necrosis
10077215	脂肪肝－線維症	Hepatic steato-fibrosis
10019708	脂肪肝	Hepatic steatosis
10019772	劇症肝炎	Hepatitis fulminant
10062000	肝胆道系疾患	Hepatobiliary disease
10053244	肝細胞泡沫細胞症候群	Hepatocellular foamy cell syndrome
10019837	肝細胞損傷	Hepatocellular injury
10052274	肝肺症候群	Hepatopulmonary syndrome
10019845	肝腎不全	Hepatorenal failure
10019846	肝腎症候群	Hepatorenal syndrome
10019851	肝毒性	Hepatotoxicity
10071502	腸静脈瘤	Intestinal varices
10078058	腸静脈瘤出血	Intestinal varices haemorrhage
10052280	肝小腸移植	Liver and small intestine transplant
10076640	肝透析	Liver dialysis
10024670	肝障害	Liver disorder
10067125	肝損傷	Liver injury
10062040	肝臓手術	Liver operation
10024714	肝移植	Liver transplant
10025129	ルポイド肝硬変症	Lupoid hepatic cirrhosis

PT コード	PT_日本語	PT_英語
10076204	潜在性肝性脳症	Minimal hepatic encephalopathy
10066758	混合型肝損傷	Mixed liver injury
10051081	結節性再生性過形成	Nodular regenerative hyperplasia
10029530	非アルコール性脂肪肝	Non-alcoholic fatty liver
10053219	非アルコール性脂肪性肝炎	Non-alcoholic steatohepatitis
10077259	非硬変性門脈圧亢進症	Non-cirrhotic portal hypertension
10049631	肝疾患による浮腫	Oedema due to hepatic disease
10030210	食道静脈瘤出血	Oesophageal varices haemorrhage
10073215	膵周囲静脈瘤	Peripancreatic varices
10074726	門脈線維症	Portal fibrosis
10036200	門脈圧亢進症	Portal hypertension
10079446	門脈圧亢進性結腸疾患	Portal hypertensive colopathy
10068923	門脈圧亢進性腸症	Portal hypertensive enteropathy
10050897	門脈圧亢進性胃障害	Portal hypertensive gastropathy
10073979	門脈海綿状変化	Portal vein cavernous transformation
10073209	門脈拡張	Portal vein dilatation
10067281	門脈肺高血圧症	Portopulmonary hypertension
10052279	肝腎移植	Renal and liver transplant
10067338	門脈逆流	Retrograde portal vein flow
10039012	ライ症候群	Reye's syndrome
10070953	レイノルズ症候群	Reynold's syndrome
10067823	脾静脈瘤	Splenic varices
10068662	脾静脈瘤出血	Splenic varices haemorrhage
10076331	脂肪性肝炎	Steatohepatitis
10056956	亜急性肝不全	Subacute hepatic failure
10056091	食道静脈瘤	Varices oesophageal
10072284	腹壁静脈瘤	Varicose veins of abdominal wall
10078438	白色乳頭様所見	White nipple sign
10068924	肛門直腸静脈瘤	Anorectal varices
10068925	肛門直腸静脈瘤出血	Anorectal varices haemorrhage
10072629	肝内門脈肝静脈瘻	Intrahepatic portal hepatic venous fistula
10052716	腹腔静脈シャント	Peritoneovenous shunt
10036204	門脈シャント	Portal shunt
10077479	門脈シャント術	Portal shunt procedure
10069380	肝過小グラフト症候群	Small-for-size liver syndrome
10041519	くも状母斑	Spider naevus
10041661	脾腎シャント	Splenorenal shunt
10077281	脾腎シャント術	Splenorenal shunt procedure
10076239	特発性肝内門脈体循環静脈シャント	Spontaneous intrahepatic portosystemic venous shunt
10075186	ストーマ静脈瘤	Stomal varices
10066263	急性肝移植片対宿主病	Acute graft versus host disease in liver

PT コード	PT_日本語	PT_英語
10071198	アレルギー性肝炎	Allergic hepatitis
10003827	自己免疫性肝炎	Autoimmune hepatitis
10072160	慢性肝移植片対宿主病	Chronic graft versus host disease in liver
10008909	慢性肝炎	Chronic hepatitis
10064676	肝移植片対宿主病	Graft versus host disease in liver
10019717	肝炎	Hepatitis
10019727	急性肝炎	Hepatitis acute
10019754	胆汁うっ滞性肝炎	Hepatitis cholestatic
10019755	慢性活動性肝炎	Hepatitis chronic active
10019759	慢性持続性肝炎	Hepatitis chronic persistent
10019772	劇症肝炎	Hepatitis fulminant
10019795	中毒性肝炎	Hepatitis toxic
10023025	虚血性肝炎	Ischaemic hepatitis
10067737	ループス肝炎	Lupus hepatitis
10053219	非アルコール性脂肪性肝炎	Non-alcoholic steatohepatitis
10051015	放射線肝炎	Radiation hepatitis
10076331	脂肪性肝炎	Steatohepatitis
10018704	肉芽腫性肝疾患	Granulomatous liver disease
10068664	肝サルコイドーシス	Liver sarcoidosis
10075331	門脈域の炎症	Portal tract inflammation
10004269	肝の良性新生物	Benign hepatic neoplasm
10077922	肝胆道系の良性新生物	Benign hepatobiliary neoplasm
10052285	限局性結節性過形成	Focal nodular hyperplasia
10018821	肝臓血管腫	Haemangioma of liver
10067796	出血性肝嚢胞	Haemorrhagic hepatic cyst
10019629	肝腺腫	Hepatic adenoma
10019646	肝嚢胞	Hepatic cyst
10053973	肝嚢胞破裂	Hepatic cyst ruptured
10054885	肝臓血管腫破裂	Hepatic haemangioma rupture
10079685	肝過誤腫	Hepatic hamartoma
10079889	肝胆道系嚢胞	Hepatobiliary cyst
10077861	胆管肉腫	Cholangiosarcoma
10067388	肝血管肉腫	Hepatic angiosarcoma
10073069	肝癌	Hepatic cancer
10055110	遠隔転移を伴う肝癌	Hepatic cancer metastatic
10073070	再発肝癌	Hepatic cancer recurrent
10059318	肝癌第１期	Hepatic cancer stage I
10059319	肝癌第２期	Hepatic cancer stage II
10059324	肝癌第３期	Hepatic cancer stage III
10059325	肝癌第４期	Hepatic cancer stage IV
10073073	肝胆道系癌	Hepatobiliary cancer
10073074	肝胆道系上皮内癌	Hepatobiliary cancer in situ

PT コード	PT_日本語	PT_英語
10062001	肝芽腫	Hepatoblastoma
10019823	再発肝芽腫	Hepatoblastoma recurrent
10073071	肝細胞癌	Hepatocellular carcinoma
10050842	肝癌破裂	Liver carcinoma ruptured
10027761	肝細胞癌・胆管細胞癌の混合型	Mixed hepatocellular cholangiocarcinoma
10074766	肝アブレーション	Liver ablation
10019695	肝新生物	Hepatic neoplasm
10061203	肝胆道系新生物	Hepatobiliary neoplasm
10001547	アラニンアミノトランスフェラーゼ異常	Alanine aminotransferase abnormal
10001551	アラニンアミノトランスフェラーゼ増加	Alanine aminotransferase increased
10001942	アンモニア異常	Ammonia abnormal
10001946	アンモニア増加	Ammonia increased
10003445	腹水	Ascites
10003477	アスパラギン酸アミノトランスフェラーゼ異常	Aspartate aminotransferase abnormal
10003481	アスパラギン酸アミノトランスフェラーゼ増加	Aspartate aminotransferase increased
10068547	細菌感染腹水	Bacterascites
10051344	胆汁量異常	Bile output abnormal
10051343	胆汁量減少	Bile output decreased
10074150	胆汁性腹水	Biliary ascites
10067718	抱合ビリルビン異常	Bilirubin conjugated abnormal
10004685	抱合ビリルビン増加	Bilirubin conjugated increased
10077356	尿中ビリルビン陽性	Bilirubin urine present
10004792	肝生検異常	Biopsy liver abnormal
10058477	血中ビリルビン異常	Blood bilirubin abnormal
10005364	血中ビリルビン増加	Blood bilirubin increased
10005370	血中非抱合ビリルビン増加	Blood bilirubin unconjugated increased
10006408	ブロモスルフォフタレイン検査異常	Bromosulphthalein test abnormal
10077020	チャイルド・ピュー・ターコットスコア異常	Child-Pugh-Turcotte score abnormal
10068287	チャイルド・ピュー・ターコットスコア増加	Child-Pugh-Turcotte score increased
10076215	肝コンピュータ断層撮影	Computerised tomogram liver
10078360	肝コンピュータ断層撮影異常	Computerised tomogram liver abnormal
10052554	肝性口臭	Foetor hepaticus
10059710	ガラクトース排泄能検査異常	Galactose elimination capacity test abnormal
10059712	ガラクトース排泄能検査値減少	Galactose elimination capacity test decreased
10017688	γ－グルタミルトランスフェラーゼ異常	Gamma-glutamyltransferase abnormal
10017693	γ－グルタミルトランスフェラーゼ増加	Gamma-glutamyltransferase increased
10051333	グアナーゼ増加	Guanase increased
10019621	ヘパプラスチン異常	Hepaplastin abnormal
10019622	ヘパプラスチン減少	Hepaplastin decreased

PT コード	PT_日本語	PT_英語
10068997	肝動脈血流減少	Hepatic artery flow decreased
10019645	肝臓うっ血	Hepatic congestion
10062685	肝酵素異常	Hepatic enzyme abnormal
10060794	肝酵素低下	Hepatic enzyme decreased
10060795	肝酵素上昇	Hepatic enzyme increased
10019670	肝機能異常	Hepatic function abnormal
10067365	肝性胸水	Hepatic hydrothorax
10076254	肝肥大	Hepatic hypertrophy
10057110	肝腫瘤	Hepatic mass
10019705	肝臓痛	Hepatic pain
10066244	肝分離	Hepatic sequestration
10068358	肝血管抵抗増加	Hepatic vascular resistance increased
10066195	肝胆道スキャン異常	Hepatobiliary scan abnormal
10019842	肝腫大	Hepatomegaly
10019847	肝脾腫大	Hepatosplenomegaly
10020575	高アンモニア血症	Hyperammonaemia
10020578	高ビリルビン血症	Hyperbilirubinaemia
10051924	胆汁過多	Hypercholia
10068237	高トランスアミナーゼ血症	Hypertransaminasaemia
10023321	カイザー・フライシャー輪	Kayser-Fleischer ring
10024690	肝機能検査異常	Liver function test abnormal
10077677	肝機能検査値低下	Liver function test decreased
10077692	肝機能検査値上昇	Liver function test increased
10052550	肝硬結	Liver induration
10075895	肝触知	Liver palpable
10061947	肝スキャン異常	Liver scan abnormal
10024712	肝圧痛	Liver tenderness
10064712	ｍ－ＡＳＴ増加	Mitochondrial aspartate aminotransferase increased
10066869	総分岐鎖アミノ酸／チロシンモル比	Molar ratio of total branched-chain amino acid to tyrosine
10080035	肝核磁気共鳴画像異常	Nuclear magnetic resonance imaging liver abnormal
10049631	肝疾患による浮腫	Oedema due to hepatic disease
10054125	肝周囲不快感	Perihepatic discomfort
10067338	門脈逆流	Retrograde portal vein flow
10064558	総胆汁酸増加	Total bile acids increased
10062688	トランスアミナーゼ異常	Transaminases abnormal
10054889	トランスアミナーゼ上昇	Transaminases increased
10045428	肝超音波検査異常	Ultrasound liver abnormal
10050792	尿中ビリルビン増加	Urine bilirubin increased
10078438	白色乳頭様所見	White nipple sign
10056536	肝胆道Ｘ線異常	X-ray hepatobiliary abnormal

PT コード	PT_日本語	PT_英語
10000028	５－ヌクレオチダーゼ上昇	5'nucleotidase increased
10059571	血中アルカリホスファターゼ異常	Blood alkaline phosphatase abnormal
10059570	血中アルカリホスファターゼ増加	Blood alkaline phosphatase increased
10005429	血中コリンエステラーゼ異常	Blood cholinesterase abnormal
10005430	血中コリンエステラーゼ減少	Blood cholinesterase decreased
10071634	胆汁分泌不全	Deficiency of bile secretion
10049483	グルタミン酸脱水素酵素増加	Glutamate dehydrogenase increased
10059766	血性腹水	Haemorrhagic ascites
10074084	肝線維化マーカー異常	Hepatic fibrosis marker abnormal
10074413	肝線維化マーカー上昇	Hepatic fibrosis marker increased
10079686	肝リンパ球浸潤	Hepatic lymphocytic infiltration
10020942	低アルブミン血症	Hypoalbuminaemia
10024275	ロイシンアミノペプチダーゼ上昇	Leucine aminopeptidase increased
10074352	肝内鉄濃度異常	Liver iron concentration abnormal
10074354	肝内鉄濃度増加	Liver iron concentration increased
10077291	末期肝疾患モデルスコア異常	Model for end stage liver disease score abnormal
10077292	末期肝疾患モデルスコア増加	Model for end stage liver disease score increased
10068821	門脈周囲浮腫	Periportal oedema
10069000	腹腔液蛋白異常	Peritoneal fluid protein abnormal
10068999	腹腔液蛋白減少	Peritoneal fluid protein decreased
10068998	腹腔液蛋白増加	Peritoneal fluid protein increased
10066004	胆道気腫	Pneumobilia
10067337	門脈血流減少	Portal vein flow decreased
10064936	門脈圧上昇	Portal vein pressure increased
10048473	レチノール結合蛋白減少	Retinol binding protein decreased
10070480	尿中ウロビリノーゲン減少	Urobilinogen urine decreased
10070479	尿中ウロビリノーゲン増加	Urobilinogen urine increased
10074561	後天性アンチトロンビンＩＩＩ欠乏症	Acquired antithrombin III deficiency
10068370	後天性プロテインＳ欠乏症	Acquired protein S deficiency
10077670	抗第Ｘ因子活性異常	Anti factor X activity abnormal
10077674	抗第Ｘ因子活性低下	Anti factor X activity decreased
10077671	抗第Ｘ因子活性上昇	Anti factor X activity increased
10049547	アンチトロンビンＩＩＩ減少	Antithrombin III decreased
10005518	血中フィブリノゲン異常	Blood fibrinogen abnormal
10005520	血中フィブリノゲン減少	Blood fibrinogen decreased
10005818	血中トロンビン異常	Blood thrombin abnormal
10005820	血中トロンビン減少	Blood thrombin decreased
10005824	血中トロンボプラスチン異常	Blood thromboplastin abnormal
10005826	血中トロンボプラスチン減少	Blood thromboplastin decreased
10009736	凝固因子減少	Coagulation factor decreased

PT コード	PT_日本語	PT_英語
10061770	凝固第ＩＸ因子量異常	Coagulation factor IX level abnormal
10009746	凝固第ＩＸ因子量減少	Coagulation factor IX level decreased
10061771	凝固第Ｖ因子量異常	Coagulation factor V level abnormal
10009754	凝固第Ｖ因子量減少	Coagulation factor V level decreased
10061772	凝固第ＶＩＩ因子量異常	Coagulation factor VII level abnormal
10009761	凝固第ＶＩＩ因子量減少	Coagulation factor VII level decreased
10061774	凝固第Ｘ因子量異常	Coagulation factor X level abnormal
10009775	凝固第Ｘ因子量減少	Coagulation factor X level decreased
10074737	線溶亢進	Hyperfibrinolysis
10020973	凝固低下状態	Hypocoagulable state
10051125	低フィブリノゲン血症	Hypofibrinogenaemia
10021085	低プロトロンビン血症	Hypoprothrombinaemia
10058517	低トロンビン血症	Hypothrombinaemia
10058518	低トロンボプラスチン血症	Hypothromboplastinaemia
10022592	国際標準比異常	International normalised ratio abnormal
10022595	国際標準比増加	International normalised ratio increased
10037005	プロテインＣ減少	Protein C decreased
10051736	プロテインＳ異常	Protein S abnormal
10051120	プロテインＳ減少	Protein S decreased
10037048	プロトロンビン量異常	Prothrombin level abnormal
10037050	プロトロンビン量減少	Prothrombin level decreased
10037057	プロトロンビン時間異常	Prothrombin time abnormal
10037063	プロトロンビン時間延長	Prothrombin time prolonged
10061918	プロトロンビン時間比異常	Prothrombin time ratio abnormal
10037068	プロトロンビン時間比増加	Prothrombin time ratio increased
10051319	トロンビン時間異常	Thrombin time abnormal
10051390	トロンビン時間延長	Thrombin time prolonged

Table S-008 Summary of Demographic and Baseline Characteristics in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Sex					
Male	127 (69.8%)	49 (65.3%)	138 (76.7%)	54 (72.0%)	241 (73.0%)
Female	55 (30.2%)	26 (34.7%)	42 (23.3%)	21 (28.0%)	89 (27.0%)
Age (years)					
n	182	75	180	75	330
Mean (SD)	61.2 (9.91)	58.7 (8.51)	61.3 (9.78)	57.7 (10.76)	59.9 (9.85)
Median	61.5	59.0	62.0	61.0	61.0
Min, Max	32, 83	33, 74	34, 82	33, 72	33, 82
Age category					
< 65 years	106 (58.2%)	54 (72.0%)	97 (53.9%)	47 (62.7%)	198 (60.0%)
>= 65 years	76 (41.8%)	21 (28.0%)	83 (46.1%)	28 (37.3%)	132 (40.0%)
< 75 years	169 (92.9%)	75 (100.0%)	171 (95.0%)	75 (100.0%)	321 (97.3%)
>= 75 years	13 (7.1%)	0	9 (5.0%)	0	9 (2.7%)
Height (cm)					
n	182	75	180	75	330
Mean (SD)	165.05 (8.534)	164.27 (8.881)	165.09 (8.358)	164.80 (8.506)	164.84 (8.493)
Median	166.00	166.00	165.55	166.00	166.00
Min, Max	141.0, 185.0	138.0, 179.0	143.0, 184.7	145.0, 184.0	138.0, 184.7
Weight (kg) at baseline					
n	182	75	180	75	330
Mean (SD)	69.74 (13.668)	68.51 (15.183)	69.65 (13.548)	73.13 (15.486)	70.18 (14.437)
Median	67.90	67.00	68.90	73.00	69.10
Min, Max	40.2, 113.2	35.6, 115.8	42.5, 124.0	41.5, 122.3	35.6, 124.0
BMI (kg/m2) at baseline					
n	182	75	180	75	330
Mean (SD)	25.518 (4.2878)	25.241 (4.5998)	25.465 (4.0765)	26.754 (4.3512)	25.707 (4.2884)
Median	24.725	24.430	25.010	26.320	25.290
Min, Max	18.53, 43.46	18.07, 39.14	18.36, 40.26	18.51, 41.60	18.07, 41.60
BMI category at baseline					
< 25 kg/m2	95 (52.2%)	39 (52.0%)	90 (50.0%)	28 (37.3%)	157 (47.6%)
>= 25 kg/m2	87 (47.8%)	36 (48.0%)	90 (50.0%)	47 (62.7%)	173 (52.4%)
>= 25 to < 30 kg/m2	64 (35.2%)	22 (29.3%)	66 (36.7%)	33 (44.0%)	121 (36.7%)
>= 30 kg/m2	23 (12.6%)	14 (18.7%)	24 (13.3%)	14 (18.7%)	52 (15.8%)
BMI (kg/m2) for male at baseline					
n	127	49	138	54	241
Mean (SD)	25.290 (3.6707)	25.410 (4.2742)	25.403 (3.9234)	26.569 (4.0448)	25.666 (4.0361)
Median	24.720	24.890	25.030	26.215	25.340

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Min, Max	18.53, 35.83	19.05, 39.14	18.36, 40.26	18.51, 39.04	18.36, 40.26
BMI category for male at baseline					
< 25 kg/m2	67 (36.8%)	25 (33.3%)	69 (38.3%)	19 (25.3%)	113 (34.2%)
>= 25 kg/m2	60 (33.0%)	24 (32.0%)	69 (38.3%)	35 (46.7%)	128 (38.8%)
>= 25 to < 30 kg/m2	47 (25.8%)	16 (21.3%)	51 (28.3%)	27 (36.0%)	94 (28.5%)
>= 30 kg/m2	13 (7.1%)	8 (10.7%)	18 (10.0%)	8 (10.7%)	34 (10.3%)
BMI (kg/m2) for female at baseline					
n	55	26	42	21	89
Mean (SD)	26.044 (5.4572)	24.922 (5.2336)	25.669 (4.5890)	27.231 (5.1346)	25.819 (4.9305)
Median	24.730	23.220	24.980	28.930	25.100
Min, Max	19.07, 43.46	18.07, 35.39	18.57, 37.45	18.69, 41.60	18.07, 41.60
BMI category for female at baseline					
< 25 kg/m2	28 (15.4%)	14 (18.7%)	21 (11.7%)	9 (12.0%)	44 (13.3%)
>= 25 kg/m2	27 (14.8%)	12 (16.0%)	21 (11.7%)	12 (16.0%)	45 (13.6%)
>= 25 to < 30 kg/m2	17 (9.3%)	6 (8.0%)	15 (8.3%)	6 (8.0%)	27 (8.2%)
>= 30 kg/m2	10 (5.5%)	6 (8.0%)	6 (3.3%)	6 (8.0%)	18 (5.5%)
Waist circumference (cm) at baseline					
n	182	75	180	75	330
Mean (SD)	89.87 (10.145)	89.32 (11.230)	89.76 (10.137)	92.56 (11.073)	90.30 (10.649)
Median	90.00	88.00	88.95	92.00	89.25
Min, Max	67.0, 124.0	63.0, 114.0	66.5, 119.0	69.0, 129.0	63.0, 129.0
Waist circumference category at baseline					
< 85 cm	58 (31.9%)	25 (33.3%)	57 (31.7%)	16 (21.3%)	98 (29.7%)
>= 85 cm	124 (68.1%)	50 (66.7%)	123 (68.3%)	59 (78.7%)	232 (70.3%)
< 90 cm	89 (48.9%)	40 (53.3%)	96 (53.3%)	30 (40.0%)	166 (50.3%)
>= 90 cm	93 (51.1%)	35 (46.7%)	84 (46.7%)	45 (60.0%)	164 (49.7%)
Waist circumference (cm) for male at baseline					
n	127	49	138	54	241
Mean (SD)	89.77 (9.347)	90.20 (10.422)	89.81 (9.848)	92.22 (10.607)	90.43 (10.144)
Median	89.30	88.00	89.00	91.00	89.00
Min, Max	67.0, 118.0	67.0, 114.0	70.0, 119.0	69.0, 127.0	67.0, 127.0
Waist circumference category for male at baseline					
< 85 cm	40 (22.0%)	13 (17.3%)	42 (23.3%)	10 (13.3%)	65 (19.7%)
>= 85 cm	87 (47.8%)	36 (48.0%)	96 (53.3%)	44 (58.7%)	176 (53.3%)

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Waist circumference (cm) for female at baseline					
n	55	26	42	21	89
Mean (SD)	90.11 (11.875)	87.65 (12.662)	89.61 (11.159)	93.43 (12.424)	89.94 (11.964)
Median	91.00	88.50	88.00	93.00	89.50
Min, Max	71.0, 124.0	63.0, 108.0	66.5, 116.0	72.0, 129.0	63.0, 129.0
Waist circumference category for female at baseline					
< 90 cm	25 (13.7%)	13 (17.3%)	26 (14.4%)	6 (8.0%)	45 (13.6%)
>= 90 cm	30 (16.5%)	13 (17.3%)	16 (8.9%)	15 (20.0%)	44 (13.3%)
Does the patient drink alcohol?					
Yes	98 (53.8%)	43 (57.3%)	104 (57.8%)	41 (54.7%)	188 (57.0%)
No	84 (46.2%)	32 (42.7%)	76 (42.2%)	34 (45.3%)	142 (43.0%)
HbA1c (%) at baseline					
n	182	75	180	75	330
Mean (SD)	7.91 (0.678)	7.94 (0.679)	7.94 (0.724)	7.92 (0.620)	7.94 (0.689)
Median	7.80	7.80	7.80	7.90	7.80
Min, Max	6.9, 10.2	6.9, 9.5	6.7, 9.8	6.9, 9.6	6.7, 9.8
HbA1c category at baseline					
< 8.0%	107 (58.8%)	47 (62.7%)	107 (59.4%)	42 (56.0%)	196 (59.4%)
>= 8.0%	75 (41.2%)	28 (37.3%)	73 (40.6%)	33 (44.0%)	134 (40.6%)
>= 8.0 to < 9.0%	59 (32.4%)	20 (26.7%)	50 (27.8%)	30 (40.0%)	100 (30.3%)
>= 9.0%	16 (8.8%)	8 (10.7%)	23 (12.8%)	3 (4.0%)	34 (10.3%)
Duration of diabetes (year)					
n	182	75	180	75	330
Mean (SD)	6.86 (6.222)	7.20 (6.272)	7.12 (5.557)	5.29 (5.124)	6.72 (5.671)
Median	5.04	6.00	5.87	4.21	5.51
Min, Max	0.2, 35.0	0.3, 31.0	0.3, 27.9	0.2, 24.0	0.2, 31.0
Duration of diabetes category					
< 1 year	25 (13.7%)	10 (13.3%)	20 (11.1%)	13 (17.3%)	43 (13.0%)
>= 1 to < 5 years	64 (35.2%)	22 (29.3%)	56 (31.1%)	29 (38.7%)	107 (32.4%)
>= 5 to < 10 years	49 (26.9%)	21 (28.0%)	56 (31.1%)	26 (34.7%)	103 (31.2%)
>= 10 years	44 (24.2%)	22 (29.3%)	48 (26.7%)	7 (9.3%)	77 (23.3%)
Previous treatment status					
Treatment naive	111 (61.0%)	33 (44.0%)	109 (60.6%)	29 (38.7%)	171 (51.8%)
Previously treated	71 (39.0%)	42 (56.0%)	71 (39.4%)	46 (61.3%)	159 (48.2%)

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Previous medication class					
SU	3 (1.6%)	3 (4.0%)	5 (2.8%)	2 (2.7%)	10 (3.0%)
GLIN	2 (1.1%)	0	1 (0.6%)	0	1 (0.3%)
BIG	20 (11.0%)	8 (10.7%)	11 (6.1%)	6 (8.0%)	25 (7.6%)
AGI	5 (2.7%)	1 (1.3%)	7 (3.9%)	0	8 (2.4%)
TZD	1 (0.5%)	4 (5.3%)	3 (1.7%)	2 (2.7%)	9 (2.7%)
DPP4-I	34 (18.7%)	22 (29.3%)	43 (23.9%)	29 (38.7%)	94 (28.5%)
GLP1-RA	0	0	0	0	0
SGLT2-I	11 (6.0%)	6 (8.0%)	8 (4.4%)	8 (10.7%)	22 (6.7%)
Missing	106 (58.2%)	31 (41.3%)	102 (56.7%)	28 (37.3%)	161 (48.8%)
Complication of diabetes					
Yes	31 (17.0%)	17 (22.7%)	31 (17.2%)	15 (20.0%)	63 (19.1%)
No	151 (83.0%)	58 (77.3%)	149 (82.8%)	60 (80.0%)	267 (80.9%)
Metabolic Syndrome at baseline					
Yes	85 (46.7%)	35 (46.7%)	78 (43.3%)	45 (60.0%)	158 (47.9%)
No	97 (53.3%)	40 (53.3%)	102 (56.7%)	30 (40.0%)	172 (52.1%)
Hypertension					
Yes	104 (57.1%)	33 (44.0%)	100 (55.6%)	44 (58.7%)	177 (53.6%)
No	78 (42.9%)	42 (56.0%)	80 (44.4%)	31 (41.3%)	153 (46.4%)
Dyslipidemia					
Yes	101 (55.5%)	30 (40.0%)	104 (57.8%)	24 (32.0%)	158 (47.9%)
No	81 (44.5%)	45 (60.0%)	76 (42.2%)	51 (68.0%)	172 (52.1%)
Hepatic parameter abnormality at baseline					
Yes	31 (17.0%)	14 (18.7%)	24 (13.3%)	14 (18.7%)	52 (15.8%)
No	151 (83.0%)	61 (81.3%)	156 (86.7%)	61 (81.3%)	278 (84.2%)
eGFR (mL/min/1.73m2) at baseline					
n	182	75	180	75	330
Mean (SD)	71.5014 (12.40252)	73.8000 (12.56443)	73.5632 (12.76615)	75.2400 (15.16026)	73.9981 (13.27919)
Median	69.3015	73.0000	73.4670	73.0000	73.0000
Min, Max	49.175, 109.000	50.000, 101.000	45.156, 115.412	48.000, 117.000	45.156, 117.000
CKD stage at baseline					
CKD Stage 1	16 (8.8%)	9 (12.0%)	21 (11.7%)	14 (18.7%)	44 (13.3%)
CKD Stage 2	137 (75.3%)	56 (74.7%)	131 (72.8%)	52 (69.3%)	239 (72.4%)
CKD Stage 3a	29 (15.9%)	10 (13.3%)	28 (15.6%)	9 (12.0%)	47 (14.2%)
FPG (mg/dL) at baseline					

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
n	182	75	180	75	330
Mean (SD)	159.80 (27.065)	164.51 (31.747)	163.76 (29.505)	165.21 (31.289)	164.26 (30.346)
Median	154.93	157.00	161.50	159.00	159.00
Min, Max	108.1, 283.0	120.0, 277.0	106.0, 264.0	115.0, 279.0	106.0, 279.0
FPG category at baseline					
< 160 mg/dL	106 (58.2%)	40 (53.3%)	88 (48.9%)	39 (52.0%)	167 (50.6%)
>= 160 mg/dL	76 (41.8%)	35 (46.7%)	92 (51.1%)	36 (48.0%)	163 (49.4%)
HOMA-IR at baseline					
n	181	75	180	75	330
Mean (SD)	3.2325 (2.95323)	4.1984 (3.64270)	2.8512 (2.16907)	4.6283 (3.45357)	3.5612 (2.97574)
Median	2.4600	3.0400	2.2725	4.2300	2.5970
Min, Max	0.221, 18.550	0.370, 16.700	0.140, 12.060	0.560, 20.660	0.140, 20.660
HOMA-IR category at baseline					
< 2.5	92 (50.5%)	32 (42.7%)	101 (56.1%)	23 (30.7%)	156 (47.3%)
>= 2.5 to < 4.0	47 (25.8%)	16 (21.3%)	37 (20.6%)	13 (17.3%)	66 (20.0%)
>= 4.0	42 (23.1%)	27 (36.0%)	42 (23.3%)	39 (52.0%)	108 (32.7%)
Missing	1 (0.5%)	0	0	0	0
HOMA-B (%) at baseline					
n	181	75	180	75	330
Mean (SD)	31.4877 (28.75952)	35.8813 (29.58623)	25.4485 (18.91016)	40.7600 (26.76550)	31.2995 (24.42326)
Median	24.6560	27.1000	20.0270	33.5000	24.5635
Min, Max	1.893, 227.400	3.100, 191.800	1.900, 119.100	5.100, 147.100	1.900, 191.800
HOMA-B category at baseline					
< 30.0 %	113 (62.1%)	43 (57.3%)	134 (74.4%)	34 (45.3%)	211 (63.9%)
>= 30.0 %	68 (37.4%)	32 (42.7%)	46 (25.6%)	41 (54.7%)	119 (36.1%)
Missing	1 (0.5%)	0	0	0	0
QUICKI at baseline					
n	181	75	180	75	330
Mean (SD)	0.3412 (0.04290)	0.3296 (0.04238)	0.3446 (0.04299)	0.3195 (0.03429)	0.3355 (0.04225)
Median	0.3330	0.3240	0.3375	0.3090	0.3310
Min, Max	0.258, 0.512	0.261, 0.459	0.271, 0.572	0.255, 0.424	0.255, 0.572
QUICKI category at baseline					
< 0.33	81 (44.5%)	41 (54.7%)	70 (38.9%)	48 (64.0%)	159 (48.2%)
>= 0.33	100 (54.9%)	34 (45.3%)	110 (61.1%)	27 (36.0%)	171 (51.8%)

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Missing	1 (0.5%)	0	0	0	0

- Abbreviations: bid, Twice a day; SD, standard deviation; BMI, body mass index; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- Percentages are based on Population N.
- Due to the misinput of previous treatment status, 15 subjects were randomized as "previously treated" but re-classified as "treatment naive" for the analysis during the Blind Data Review Meeting. Thus, there was a difference between the number of treatment naive patients in the previous treatment status and that of patients with missing previous medication class, because the previous medication class was analyzed according to the original data within the Electronic Data Capture system. Refer to 2.7.6.18 for details.

Control No:<<t-s-008-demog-24wdb.sas, 2020-03-06T00:06:46>>

Table S-009 Summary of Demographic and Baseline Characteristics in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Sex											
Male	106 (79.1%)	101 (79.5%)	43 (67.2%)	46 (71.9%)	48 (75.0%)	54 (83.1%)	39 (61.9%)	44 (62.9%)	45 (71.4%)	420 (72.4%)	526 (73.7%)
Female	28 (20.9%)	26 (20.5%)	21 (32.8%)	18 (28.1%)	16 (25.0%)	11 (16.9%)	24 (38.1%)	26 (37.1%)	18 (28.6%)	160 (27.6%)	188 (26.3%)
Age (years)											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	59.4 (10.78)	60.3 (10.38)	58.1 (10.81)	57.6 (10.83)	56.6 (12.01)	57.1 (10.72)	63.6 (8.95)	57.4 (10.95)	57.1 (10.04)	58.7 (10.75)	58.8 (10.75)
Median	59.0	60.0	58.0	58.5	56.0	55.0	66.0	58.0	57.0	59.0	59.0
Min, Max	23, 84	25, 83	33, 77	21, 75	30, 77	34, 78	44, 80	35, 78	30, 78	21, 83	21, 84
Age category											
< 65 years	86 (64.2%)	76 (59.8%)	42 (65.6%)	47 (73.4%)	41 (64.1%)	44 (67.7%)	28 (44.4%)	46 (65.7%)	45 (71.4%)	369 (63.6%)	455 (63.7%)
>= 65 years	48 (35.8%)	51 (40.2%)	22 (34.4%)	17 (26.6%)	23 (35.9%)	21 (32.3%)	35 (55.6%)	24 (34.3%)	18 (28.6%)	211 (36.4%)	259 (36.3%)
< 75 years	127 (94.8%)	122 (96.1%)	61 (95.3%)	61 (95.3%)	62 (96.9%)	61 (93.8%)	58 (92.1%)	67 (95.7%)	61 (96.8%)	553 (95.3%)	680 (95.2%)
>= 75 years	7 (5.2%)	5 (3.9%)	3 (4.7%)	3 (4.7%)	2 (3.1%)	4 (6.2%)	5 (7.9%)	3 (4.3%)	2 (3.2%)	27 (4.7%)	34 (4.8%)
Height (cm)											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	166.40 (8.927)	165.87 (8.334)	164.19 (8.265)	166.11 (8.747)	165.72 (9.025)	166.20 (9.363)	162.11 (8.862)	163.98 (9.559)	165.61 (9.027)	165.07 (8.895)	165.32 (8.910)
Median	168.05	167.40	165.60	167.60	166.65	166.50	162.60	166.25	167.60	166.60	166.70

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Min, Max	144.0, 183.3	145.0, 183.0	146.5, 181.4	146.3, 183.7	144.4, 183.2	127.6, 188.0	142.3, 180.4	139.8, 183.0	147.5, 188.1	127.6, 188.1	127.6, 188.1
Weight (kg) at baseline											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	71.02 (13.785)	70.64 (13.761)	68.28 (13.850)	72.25 (11.451)	72.62 (16.757)	75.57 (16.133)	64.88 (12.882)	70.85 (15.130)	72.76 (16.512)	70.96 (14.764)	70.97 (14.576)
Median	69.10	67.80	68.30	72.30	68.55	74.00	63.00	72.60	70.70	68.90	69.00
Min, Max	44.6, 129.0	44.3, 114.6	43.3, 104.7	46.9, 99.1	46.6, 132.8	44.2, 117.2	45.4, 117.4	39.0, 119.2	41.2, 129.8	39.0, 132.8	39.0, 132.8
BMI (kg/m2) at baseline											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	25.550 (3.8825)	25.607 (4.2137)	25.268 (4.5984)	26.185 (3.6807)	26.248 (4.6020)	27.247 (4.9274)	24.548 (3.4297)	26.198 (4.3576)	26.320 (4.3463)	25.922 (4.3232)	25.852 (4.2438)
Median	24.970	24.690	24.415	26.115	25.260	27.340	24.200	25.890	24.960	25.265	25.155
Min, Max	18.51, 42.03	18.20, 37.41	18.46, 38.76	18.51, 34.08	19.34, 44.28	19.48, 41.84	18.63, 40.01	18.20, 37.77	18.91, 38.63	18.20, 44.28	18.20, 44.28
BMI category at baseline											
< 25 kg/m2	67 (50.0%)	65 (51.2%)	35 (54.7%)	22 (34.4%)	31 (48.4%)	24 (36.9%)	38 (60.3%)	27 (38.6%)	32 (50.8%)	274 (47.2%)	341 (47.8%)
>= 25 kg/m2	67 (50.0%)	62 (48.8%)	29 (45.3%)	42 (65.6%)	33 (51.6%)	41 (63.1%)	25 (39.7%)	43 (61.4%)	31 (49.2%)	306 (52.8%)	373 (52.2%)
>= 25 to < 30 kg/m2	51 (38.1%)	43 (33.9%)	18 (28.1%)	29 (45.3%)	26 (40.6%)	25 (38.5%)	23 (36.5%)	31 (44.3%)	24 (38.1%)	219 (37.8%)	270 (37.8%)
>= 30 kg/m2	16 (11.9%)	19 (15.0%)	11 (17.2%)	13 (20.3%)	7 (10.9%)	16 (24.6%)	2 (3.2%)	12 (17.1%)	7 (11.1%)	87 (15.0%)	103 (14.4%)
BMI (kg/m2) for male at baseline											
n	106	101	43	46	48	54	39	44	45	420	526

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mean (SD)	25.571 (3.8889)	25.426 (3.9509)	25.084 (3.9310)	25.858 (3.3502)	26.143 (4.2683)	27.498 (4.9262)	25.149 (3.7014)	26.064 (4.0039)	26.596 (4.4741)	25.953 (4.1408)	25.876 (4.0906)
Median	24.865	24.690	24.460	26.090	25.260	28.045	24.730	25.505	26.180	25.350	25.205
Min, Max	18.51, 42.03	18.72, 35.65	18.46, 35.64	18.51, 34.08	20.49, 39.65	19.48, 41.84	19.70, 40.01	18.57, 37.24	21.51, 38.63	18.46, 41.84	18.46, 42.03
BMI category for male at baseline											
< 25 kg/m2	54 (40.3%)	52 (40.9%)	24 (37.5%)	16 (25.0%)	23 (35.9%)	19 (29.2%)	23 (36.5%)	18 (25.7%)	21 (33.3%)	196 (33.8%)	250 (35.0%)
>= 25 kg/m2	52 (38.8%)	49 (38.6%)	19 (29.7%)	30 (46.9%)	25 (39.1%)	35 (53.8%)	16 (25.4%)	26 (37.1%)	24 (38.1%)	224 (38.6%)	276 (38.7%)
>= 25 to < 30 kg/m2	37 (27.6%)	36 (28.3%)	13 (20.3%)	24 (37.5%)	19 (29.7%)	20 (30.8%)	14 (22.2%)	20 (28.6%)	18 (28.6%)	164 (28.3%)	201 (28.2%)
>= 30 kg/m2	15 (11.2%)	13 (10.2%)	6 (9.4%)	6 (9.4%)	6 (9.4%)	15 (23.1%)	2 (3.2%)	6 (8.6%)	6 (9.5%)	60 (10.3%)	75 (10.5%)
BMI (kg/m2) for female at baseline											
n	28	26	21	18	16	11	24	26	18	160	188
Mean (SD)	25.470 (3.9281)	26.310 (5.1382)	25.643 (5.8255)	27.019 (4.4123)	26.563 (5.6324)	26.014 (4.9752)	23.570 (2.7318)	26.425 (4.9748)	25.631 (4.0474)	25.839 (4.7817)	25.784 (4.6569)
Median	25.035	24.840	22.930	27.680	25.085	27.120	23.795	26.230	24.810	25.050	25.035
Min, Max	19.51, 38.65	18.20, 37.41	19.78, 38.76	19.17, 32.81	19.34, 44.28	19.70, 37.27	18.63, 27.97	18.20, 37.77	18.91, 37.69	18.20, 44.28	18.20, 44.28
BMI category for female at baseline											
< 25 kg/m2	13 (9.7%)	13 (10.2%)	11 (17.2%)	6 (9.4%)	8 (12.5%)	5 (7.7%)	15 (23.8%)	9 (12.9%)	11 (17.5%)	78 (13.4%)	91 (12.7%)
>= 25 kg/m2	15 (11.2%)	13 (10.2%)	10 (15.6%)	12 (18.8%)	8 (12.5%)	6 (9.2%)	9 (14.3%)	17 (24.3%)	7 (11.1%)	82 (14.1%)	97 (13.6%)
>= 25 to < 30 kg/m2	14 (10.4%)	7 (5.5%)	5 (7.8%)	5 (7.8%)	7 (10.9%)	5 (7.7%)	9 (14.3%)	11 (15.7%)	6 (9.5%)	55 (9.5%)	69 (9.7%)
>= 30 kg/m2	1 (0.7%)	6 (4.7%)	5 (7.8%)	7 (10.9%)	1 (1.6%)	1 (1.5%)	0	6 (8.6%)	1 (1.6%)	27 (4.7%)	28 (3.9%)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Waist circumference (cm) at baseline											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	90.37 (8.662)	90.77 (9.649)	88.94 (10.358)	91.15 (8.581)	91.52 (10.746)	93.33 (11.436)	88.92 (9.629)	92.38 (10.380)	91.62 (10.895)	91.07 (10.213)	90.94 (9.938)
Median	90.00	89.00	87.50	91.00	91.15	92.00	88.00	92.00	89.70	90.00	90.00
Min, Max	71.5, 115.0	73.5, 115.5	74.0, 117.5	71.0, 113.4	74.6, 127.0	70.0, 118.0	73.0, 129.0	63.3, 119.5	72.0, 124.0	63.3, 129.0	63.3, 129.0
Waist circumference category at baseline											
< 85 cm	37 (27.6%)	38 (29.9%)	23 (35.9%)	15 (23.4%)	21 (32.8%)	13 (20.0%)	23 (36.5%)	13 (18.6%)	15 (23.8%)	161 (27.8%)	198 (27.7%)
>= 85 cm	97 (72.4%)	89 (70.1%)	41 (64.1%)	49 (76.6%)	43 (67.2%)	52 (80.0%)	40 (63.5%)	57 (81.4%)	48 (76.2%)	419 (72.2%)	516 (72.3%)
< 90 cm	65 (48.5%)	68 (53.5%)	37 (57.8%)	26 (40.6%)	31 (48.4%)	28 (43.1%)	38 (60.3%)	26 (37.1%)	32 (50.8%)	286 (49.3%)	351 (49.2%)
>= 90 cm	69 (51.5%)	59 (46.5%)	27 (42.2%)	38 (59.4%)	33 (51.6%)	37 (56.9%)	25 (39.7%)	44 (62.9%)	31 (49.2%)	294 (50.7%)	363 (50.8%)
Waist circumference (cm) for male at baseline											
n	106	101	43	46	48	54	39	44	45	420	526
Mean (SD)	90.94 (8.716)	90.37 (9.150)	89.40 (9.355)	90.57 (9.179)	91.53 (10.286)	93.94 (11.630)	90.39 (10.174)	92.82 (9.805)	92.26 (11.609)	91.34 (10.107)	91.26 (9.836)
Median	90.60	88.50	88.50	91.00	92.25	92.25	88.50	91.50	89.50	90.00	90.00
Min, Max	71.5, 115.0	76.5, 115.5	74.2, 117.5	71.0, 113.4	74.6, 122.0	70.0, 118.0	73.0, 129.0	71.0, 119.5	75.0, 124.0	70.0, 129.0	70.0, 129.0
Waist circumference category for male at baseline											

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
< 85 cm	27 (20.1%)	33 (26.0%)	11 (17.2%)	12 (18.8%)	14 (21.9%)	9 (13.8%)	14 (22.2%)	7 (10.0%)	12 (19.0%)	112 (19.3%)	139 (19.5%)
>= 85 cm	79 (59.0%)	68 (53.5%)	32 (50.0%)	34 (53.1%)	34 (53.1%)	45 (69.2%)	25 (39.7%)	37 (52.9%)	33 (52.4%)	308 (53.1%)	387 (54.2%)
Waist circumference (cm) for female at baseline											
n	28	26	21	18	16	11	24	26	18	160	188
Mean (SD)	88.22 (8.248)	92.34 (11.452)	88.00 (12.361)	92.62 (6.831)	91.49 (12.391)	90.38 (10.417)	86.54 (8.328)	91.64 (11.451)	90.02 (8.962)	90.34 (10.485)	90.02 (10.192)
Median	88.05	90.60	83.00	93.25	88.50	88.30	86.75	92.65	90.30	90.00	89.95
Min, Max	76.0, 111.0	73.5, 114.0	74.0, 115.0	81.5, 102.0	78.0, 127.0	77.2, 108.8	73.5, 105.0	63.3, 114.2	72.0, 109.0	63.3, 127.0	63.3, 127.0
Waist circumference category for female at baseline											
< 90 cm	16 (11.9%)	10 (7.9%)	12 (18.8%)	6 (9.4%)	9 (14.1%)	6 (9.2%)	17 (27.0%)	10 (14.3%)	8 (12.7%)	78 (13.4%)	94 (13.2%)
>= 90 cm	12 (9.0%)	16 (12.6%)	9 (14.1%)	12 (18.8%)	7 (10.9%)	5 (7.7%)	7 (11.1%)	16 (22.9%)	10 (15.9%)	82 (14.1%)	94 (13.2%)
Does the patient drink alcohol?											
Yes	64 (47.8%)	61 (48.0%)	23 (35.9%)	25 (39.1%)	28 (43.8%)	26 (40.0%)	26 (41.3%)	23 (32.9%)	32 (50.8%)	244 (42.1%)	308 (43.1%)
No	70 (52.2%)	66 (52.0%)	41 (64.1%)	39 (60.9%)	36 (56.3%)	39 (60.0%)	37 (58.7%)	47 (67.1%)	31 (49.2%)	336 (57.9%)	406 (56.9%)
HbA1c (%) at baseline											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	7.83 (0.730)	8.63 (0.903)	8.48 (0.837)	8.16 (0.607)	8.37 (0.771)	8.72 (0.942)	8.23 (0.750)	8.66 (0.848)	8.50 (0.748)	8.49 (0.835)	8.37 (0.856)
Median	7.60	8.40	8.50	8.15	8.20	8.40	8.10	8.65	8.30	8.30	8.20

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Min, Max	6.3, 10.2	6.9, 11.1	7.1, 10.2	7.1, 10.0	7.3, 10.8	7.4, 11.5	7.1, 10.4	7.3, 10.4	7.5, 10.8	6.9, 11.5	6.3, 11.5
HbA1c category at baseline											
< 8.0%	89 (66.4%)	33 (26.0%)	23 (35.9%)	26 (40.6%)	20 (31.3%)	16 (24.6%)	24 (38.1%)	17 (24.3%)	16 (25.4%)	175 (30.2%)	264 (37.0%)
>= 8.0%	45 (33.6%)	94 (74.0%)	41 (64.1%)	38 (59.4%)	44 (68.8%)	49 (75.4%)	39 (61.9%)	53 (75.7%)	47 (74.6%)	405 (69.8%)	450 (63.0%)
>= 8.0 to < 9.0%	34 (25.4%)	52 (40.9%)	22 (34.4%)	32 (50.0%)	31 (48.4%)	24 (36.9%)	28 (44.4%)	26 (37.1%)	31 (49.2%)	246 (42.4%)	280 (39.2%)
>= 9.0%	11 (8.2%)	42 (33.1%)	19 (29.7%)	6 (9.4%)	13 (20.3%)	25 (38.5%)	11 (17.5%)	27 (38.6%)	16 (25.4%)	159 (27.4%)	170 (23.8%)
Duration of diabetes (year)											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	5.85 (5.954)	10.59 (6.585)	7.90 (4.893)	8.96 (6.266)	7.47 (6.826)	9.27 (6.597)	7.96 (5.600)	10.73 (5.895)	9.55 (5.651)	9.24 (6.207)	8.60 (6.297)
Median	4.17	8.92	6.94	7.17	5.63	7.71	7.11	10.63	8.50	8.19	7.41
Min, Max	0.3, 42.9	1.0, 37.2	0.5, 29.2	0.5, 27.3	0.5, 30.8	0.5, 33.7	0.6, 27.8	1.0, 28.7	0.6, 31.2	0.5, 37.2	0.3, 42.9
Duration of diabetes category											
< 1 year	23 (17.2%)	0	4 (6.3%)	2 (3.1%)	6 (9.4%)	2 (3.1%)	2 (3.2%)	1 (1.4%)	1 (1.6%)	18 (3.1%)	41 (5.7%)
>= 1 to < 5 years	49 (36.6%)	23 (18.1%)	14 (21.9%)	20 (31.3%)	20 (31.3%)	18 (27.7%)	18 (28.6%)	14 (20.0%)	11 (17.5%)	138 (23.8%)	187 (26.2%)
>= 5 to < 10 years	37 (27.6%)	50 (39.4%)	28 (43.8%)	15 (23.4%)	22 (34.4%)	19 (29.2%)	24 (38.1%)	18 (25.7%)	26 (41.3%)	202 (34.8%)	239 (33.5%)
>= 10 years	25 (18.7%)	54 (42.5%)	18 (28.1%)	27 (42.2%)	16 (25.0%)	26 (40.0%)	19 (30.2%)	37 (52.9%)	25 (39.7%)	222 (38.3%)	247 (34.6%)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Previous treatment status											
Treatment naive	134 (100.0%)	0	0	0	0	0	0	0	0	0	134 (18.8%)
Previously treated	0	127 (100.0%)	64 (100.0%)	64 (100.0%)	64 (100.0%)	65 (100.0%)	63 (100.0%)	70 (100.0%)	63 (100.0%)	580 (100.0%)	580 (81.2%)
Previous medication class											
SU	0	127 (100.0%)	0	0	0	0	0	0	0	127 (21.9%)	127 (17.8%)
GLIN	0	0	64 (100.0%)	0	0	0	0	0	0	64 (11.0%)	64 (9.0%)
BIG	0	0	0	64 (100.0%)	0	0	0	0	0	64 (11.0%)	64 (9.0%)
AGI	0	0	0	0	64 (100.0%)	0	0	0	0	64 (11.0%)	64 (9.0%)
TZD	0	0	0	0	0	65 (100.0%)	0	0	0	65 (11.2%)	65 (9.1%)
DPP4-I	0	0	0	0	0	0	63 (100.0%)	0	0	63 (10.9%)	63 (8.8%)
GLP1-RA	0	0	0	0	0	0	0	70 (100.0%)	0	70 (12.1%)	70 (9.8%)
SGLT2-I	0	0	0	0	0	0	0	0	63 (100.0%)	63 (10.9%)	63 (8.8%)
Missing	134 (100.0%)	0	0	0	0	0	0	0	0	0	134 (18.8%)
Complication of diabetes											
Yes	23 (17.2%)	46 (36.2%)	24 (37.5%)	24 (37.5%)	16 (25.0%)	10 (15.4%)	22 (34.9%)	32 (45.7%)	16 (25.4%)	190 (32.8%)	213 (29.8%)
No	111 (82.8%)	81 (63.8%)	40 (62.5%)	40 (62.5%)	48 (75.0%)	55 (84.6%)	41 (65.1%)	38 (54.3%)	47 (74.6%)	390 (67.2%)	501 (70.2%)
Metabolic Syndrome at baseline											
Yes	62 (46.3%)	64 (50.4%)	28 (43.8%)	36 (56.3%)	32 (50.0%)	32 (49.2%)	25 (39.7%)	39 (55.7%)	31 (49.2%)	287 (49.5%)	349 (48.9%)
No	72 (53.7%)	63 (49.6%)	36 (56.3%)	28 (43.8%)	32 (50.0%)	33 (50.8%)	38 (60.3%)	31 (44.3%)	32 (50.8%)	293 (50.5%)	365 (51.1%)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Hypertension											
Yes	68 (50.7%)	62 (48.8%)	38 (59.4%)	32 (50.0%)	39 (60.9%)	23 (35.4%)	30 (47.6%)	37 (52.9%)	42 (66.7%)	303 (52.2%)	371 (52.0%)
No	66 (49.3%)	65 (51.2%)	26 (40.6%)	32 (50.0%)	25 (39.1%)	42 (64.6%)	33 (52.4%)	33 (47.1%)	21 (33.3%)	277 (47.8%)	343 (48.0%)
Dyslipidemia											
Yes	99 (73.9%)	97 (76.4%)	42 (65.6%)	50 (78.1%)	52 (81.3%)	46 (70.8%)	45 (71.4%)	56 (80.0%)	49 (77.8%)	437 (75.3%)	536 (75.1%)
No	35 (26.1%)	30 (23.6%)	22 (34.4%)	14 (21.9%)	12 (18.8%)	19 (29.2%)	18 (28.6%)	14 (20.0%)	14 (22.2%)	143 (24.7%)	178 (24.9%)
Hepatic parameter abnormality at baseline											
Yes	18 (13.4%)	16 (12.6%)	11 (17.2%)	10 (15.6%)	9 (14.1%)	9 (13.8%)	12 (19.0%)	20 (28.6%)	13 (20.6%)	100 (17.2%)	118 (16.5%)
No	116 (86.6%)	111 (87.4%)	53 (82.8%)	54 (84.4%)	55 (85.9%)	56 (86.2%)	51 (81.0%)	50 (71.4%)	50 (79.4%)	480 (82.8%)	596 (83.5%)
eGFR (mL/min/1.73m2) at baseline											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	75.9410 (15.46019)	76.9823 (12.42985)	78.4059 (12.14961)	82.6959 (18.27707)	78.2605 (13.15447)	79.6182 (15.32343)	75.2570 (13.51408)	79.5616 (14.70430)	83.7246 (14.61521)	79.0625 (14.33676)	78.4767 (14.59404)
Median	74.7075	75.0670	76.3985	78.6110	75.1270	77.6040	74.0860	76.2835	81.5280	76.8400	76.2230
Min, Max	50.434, 128.497	53.846, 109.147	47.529, 106.850	53.846, 144.708	56.190, 126.681	54.517, 126.681	51.852, 123.045	54.750, 146.911	52.607, 116.376	47.529, 146.911	47.529, 146.911
CKD stage at baseline											

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
CKD Stage 1	24 (17.9%)	22 (17.3%)	12 (18.8%)	18 (28.1%)	13 (20.3%)	16 (24.6%)	9 (14.3%)	16 (22.9%)	21 (33.3%)	127 (21.9%)	151 (21.1%)
CKD Stage 2	91 (67.9%)	96 (75.6%)	50 (78.1%)	42 (65.6%)	49 (76.6%)	44 (67.7%)	47 (74.6%)	51 (72.9%)	40 (63.5%)	419 (72.2%)	510 (71.4%)
CKD Stage 3a	19 (14.2%)	9 (7.1%)	2 (3.1%)	4 (6.3%)	2 (3.1%)	5 (7.7%)	7 (11.1%)	3 (4.3%)	2 (3.2%)	34 (5.9%)	53 (7.4%)
FPG (mg/dL) at baseline											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	163.19 (25.578)	185.13 (37.679)	179.76 (33.493)	174.86 (30.714)	173.93 (31.336)	171.62 (32.202)	180.10 (32.963)	191.04 (39.655)	165.57 (27.745)	178.70 (34.607)	175.79 (33.635)
Median	162.14	176.55	179.26	173.85	171.15	167.54	176.55	181.96	158.54	174.75	171.15
Min, Max	104.5, 236.0	109.9, 282.8	113.5, 254.0	97.3, 257.6	113.5, 263.0	120.7, 291.9	122.5, 254.0	115.3, 282.8	120.7, 236.0	97.3, 291.9	97.3, 291.9
FPG category at baseline											
< 160 mg/dL	63 (47.0%)	29 (22.8%)	20 (31.3%)	18 (28.1%)	20 (31.3%)	26 (40.0%)	20 (31.7%)	14 (20.0%)	33 (52.4%)	180 (31.0%)	243 (34.0%)
>= 160 mg/dL	71 (53.0%)	98 (77.2%)	44 (68.8%)	46 (71.9%)	44 (68.8%)	39 (60.0%)	43 (68.3%)	56 (80.0%)	30 (47.6%)	400 (69.0%)	471 (66.0%)
HOMA-IR at baseline											
n	134	127	64	64	63	65	63	70	63	579	713
Mean (SD)	2.3930 (1.74208)	2.6331 (2.11409)	2.6327 (2.40824)	2.4167 (1.69594)	2.4320 (1.63392)	1.9866 (1.19588)	2.5675 (2.06929)	3.4361 (4.43326)	2.2551 (1.79802)	2.5635 (2.37967)	2.5314 (2.27341)
Median	1.9185	1.8660	1.7785	2.0195	1.9670	1.7960	2.0810	2.4785	1.8340	1.9590	1.9370
Min, Max	0.191, 9.962	0.334, 11.425	0.224, 14.174	0.341, 7.579	0.475, 8.059	0.355, 6.452	0.336, 9.184	0.614, 30.974	0.376, 9.753	0.224, 30.974	0.191, 30.974
HOMA-IR category at baseline											
< 2.5	89 (66.4%)	80 (63.0%)	42 (65.6%)	41 (64.1%)	39 (60.9%)	48 (73.8%)	38 (60.3%)	36 (51.4%)	42 (66.7%)	366 (63.1%)	455 (63.7%)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
>= 2.5 to < 4.0	25 (18.7%)	17 (13.4%)	10 (15.6%)	14 (21.9%)	17 (26.6%)	11 (16.9%)	14 (22.2%)	20 (28.6%)	12 (19.0%)	115 (19.8%)	140 (19.6%)
>= 4.0	20 (14.9%)	30 (23.6%)	12 (18.8%)	9 (14.1%)	7 (10.9%)	6 (9.2%)	11 (17.5%)	14 (20.0%)	9 (14.3%)	98 (16.9%)	118 (16.5%)
Missing	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
HOMA-B (%) at baseline											
n	134	127	64	64	63	65	63	70	63	579	713
Mean (SD)	21.9054 (15.62979)	17.9899 (15.19508)	18.4103 (16.15717)	18.9228 (14.18966)	20.5917 (21.39695)	17.0525 (12.03362)	18.1849 (13.31663)	19.5868 (15.41910)	19.6933 (15.53126)	18.7170 (15.49861)	19.3162 (15.56233)
Median	18.1615	13.1080	12.7115	15.2195	14.9040	13.1660	13.8740	15.4040	15.8670	14.1150	14.8020
Min, Max	3.686, 96.918	2.145, 83.561	1.676, 105.908	3.268, 75.276	3.457, 160.371	2.879, 66.095	3.145, 61.209	3.949, 88.687	2.956, 83.574	1.676, 160.371	1.676, 160.371
HOMA-B category at baseline											
< 30.0 %	108 (80.6%)	108 (85.0%)	53 (82.8%)	53 (82.8%)	53 (82.8%)	57 (87.7%)	52 (82.5%)	59 (84.3%)	55 (87.3%)	490 (84.5%)	598 (83.8%)
>= 30.0 %	26 (19.4%)	19 (15.0%)	11 (17.2%)	11 (17.2%)	10 (15.6%)	8 (12.3%)	11 (17.5%)	11 (15.7%)	8 (12.7%)	89 (15.3%)	115 (16.1%)
Missing	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
QUICKI at baseline											
n	134	127	64	64	63	65	63	70	63	579	713
Mean (SD)	0.3509 (0.03966)	0.3489 (0.04062)	0.3512 (0.04396)	0.3512 (0.04085)	0.3485 (0.03680)	0.3568 (0.03552)	0.3502 (0.04115)	0.3367 (0.03393)	0.3562 (0.04187)	0.3497 (0.03970)	0.3499 (0.03966)
Median	0.3460	0.3470	0.3500	0.3435	0.3450	0.3490	0.3420	0.3330	0.3480	0.3450	0.3460
Min, Max	0.277, 0.530	0.273, 0.469	0.266, 0.510	0.287, 0.467	0.285, 0.438	0.293, 0.464	0.280, 0.469	0.244, 0.418	0.278, 0.459	0.244, 0.510	0.244, 0.530

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
QUICKI category at baseline											
< 0.33	42 (31.3%)	45 (35.4%)	19 (29.7%)	22 (34.4%)	22 (34.4%)	13 (20.0%)	24 (38.1%)	28 (40.0%)	17 (27.0%)	190 (32.8%)	232 (32.5%)
>= 0.33	92 (68.7%)	82 (64.6%)	45 (70.3%)	42 (65.6%)	41 (64.1%)	52 (80.0%)	39 (61.9%)	42 (60.0%)	46 (73.0%)	389 (67.1%)	481 (67.4%)
Missing	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)

- Abbreviations: SD, standard deviation; BMI, body mass index; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- Percentages are based on Population N.

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Table S-010 Summary of Demographic and Baseline Characteristics in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Sex		
Male	69 (64.5%)	66 (61.1%)
Female	38 (35.5%)	42 (38.9%)
Age (years)		
n	107	108
Mean (SD)	57.6 (10.10)	59.3 (10.49)
Median	59.0	60.0
Min, Max	26, 77	34, 76
Age category		
< 65 years	76 (71.0%)	68 (63.0%)
>= 65 years	31 (29.0%)	40 (37.0%)
< 75 years	104 (97.2%)	101 (93.5%)
>= 75 years	3 (2.8%)	7 (6.5%)
Height (cm)		
n	107	108
Mean (SD)	164.57 (9.469)	162.77 (9.649)
Median	165.00	164.10
Min, Max	137.2, 186.8	134.8, 182.2
Weight (kg) at baseline		
n	107	108
Mean (SD)	67.54 (11.816)	67.13 (12.266)
Median	66.90	65.40
Min, Max	44.2, 106.2	41.8, 104.1
BMI (kg/m2) at baseline		
n	107	108
Mean (SD)	24.887 (3.5104)	25.244 (3.6302)
Median	24.220	24.940
Min, Max	16.82, 34.28	18.17, 38.80
BMI category at baseline		
< 25 kg/m2	60 (56.1%)	56 (51.9%)
>= 25 kg/m2	47 (43.9%)	52 (48.1%)
>= 25 to < 30 kg/m2	35 (32.7%)	44 (40.7%)
>= 30 kg/m2	12 (11.2%)	8 (7.4%)
BMI (kg/m2) for male at baseline		
n	69	66
Mean (SD)	24.505 (3.3987)	25.263 (3.4761)
Median	24.130	24.975
Min, Max	16.82, 34.28	18.17, 38.80
BMI category for male at baseline		
< 25 kg/m2	42 (39.3%)	34 (31.5%)

	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
>= 25 kg/m2	27 (25.2%)	32 (29.6%)
>= 25 to < 30 kg/m2	20 (18.7%)	28 (25.9%)
>= 30 kg/m2	7 (6.5%)	4 (3.7%)
BMI (kg/m2) for female at baseline		
n	38	42
Mean (SD)	25.580 (3.6483)	25.214 (3.9031)
Median	25.195	24.885
Min, Max	20.28, 34.22	19.05, 36.65
BMI category for female at baseline		
< 25 kg/m2	18 (16.8%)	22 (20.4%)
>= 25 kg/m2	20 (18.7%)	20 (18.5%)
>= 25 to < 30 kg/m2	15 (14.0%)	16 (14.8%)
>= 30 kg/m2	5 (4.7%)	4 (3.7%)
Waist circumference (cm) at baseline		
n	107	108
Mean (SD)	88.82 (8.858)	89.34 (9.172)
Median	88.50	89.00
Min, Max	69.8, 113.0	68.0, 120.0
Waist circumference category at baseline		
< 85 cm	32 (29.9%)	32 (29.6%)
>= 85 cm	75 (70.1%)	76 (70.4%)
< 90 cm	61 (57.0%)	59 (54.6%)
>= 90 cm	46 (43.0%)	49 (45.4%)
Waist circumference (cm) for male at baseline		
n	69	66
Mean (SD)	88.12 (8.538)	89.81 (8.303)
Median	87.50	89.50
Min, Max	70.0, 110.0	71.0, 117.2
Waist circumference category for male at baseline		
< 85 cm	22 (20.6%)	16 (14.8%)
>= 85 cm	47 (43.9%)	50 (46.3%)
Waist circumference (cm) for female at baseline		
n	38	42
Mean (SD)	90.09 (9.394)	88.62 (10.457)
Median	89.75	88.00
Min, Max	69.8, 113.0	68.0, 120.0
Waist circumference category for female at baseline		
< 90 cm	19 (17.8%)	24 (22.2%)
>= 90 cm	19 (17.8%)	18 (16.7%)

	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Does the patient drink alcohol?		
Yes	52 (48.6%)	47 (43.5%)
No	55 (51.4%)	61 (56.5%)
HbA1c (%) at baseline		
n	107	108
Mean (SD)	8.83 (0.814)	8.74 (0.721)
Median	8.80	8.70
Min, Max	7.4, 10.8	7.4, 10.4
HbA1c category at baseline		
< 8.0%	16 (15.0%)	16 (14.8%)
>= 8.0%	91 (85.0%)	92 (85.2%)
>= 8.0 to < 9.0%	44 (41.1%)	53 (49.1%)
>= 9.0%	47 (43.9%)	39 (36.1%)
Duration of diabetes (year)		
n	107	108
Mean (SD)	13.37 (7.400)	13.26 (8.151)
Median	12.37	11.74
Min, Max	0.3, 37.7	0.4, 36.4
Duration of diabetes category		
< 1 year	1 (0.9%)	2 (1.9%)
>= 1 to < 5 years	11 (10.3%)	14 (13.0%)
>= 5 to < 10 years	23 (21.5%)	29 (26.9%)
>= 10 years	72 (67.3%)	63 (58.3%)
Previous treatment status		
Insulin monotherapy	86 (80.4%)	87 (80.6%)
Insulin in combination with 1 OHA	21 (19.6%)	21 (19.4%)
Previous medication class		
SU	1 (0.9%)	0
GLIN	2 (1.9%)	2 (1.9%)
BIG	11 (10.3%)	9 (8.3%)
AGI	0	0
TZD	0	0
DPP4-I	6 (5.6%)	4 (3.7%)
GLP1-RA	0	0
SGLT2-I	1 (0.9%)	6 (5.6%)
Missing	86 (80.4%)	87 (80.6%)
Complication of diabetes		
Yes	53 (49.5%)	45 (41.7%)
No	54 (50.5%)	63 (58.3%)
Metabolic Syndrome at baseline		
Yes	50 (46.7%)	39 (36.1%)
No	57 (53.3%)	69 (63.9%)

	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Hypertension		
Yes	48 (44.9%)	57 (52.8%)
No	59 (55.1%)	51 (47.2%)
Dyslipidemia		
Yes	81 (75.7%)	77 (71.3%)
No	26 (24.3%)	31 (28.7%)
Hepatic parameter abnormality at baseline		
Yes	15 (14.0%)	17 (15.7%)
No	92 (86.0%)	91 (84.3%)
eGFR (mL/min/1.73m2) at baseline		
n	107	108
Mean (SD)	77.3683 (13.72944)	77.0865 (12.31103)
Median	75.7270	75.3615
Min, Max	60.249, 138.012	60.196, 129.390
CKD stage at baseline		
CKD Stage 1	14 (13.1%)	16 (14.8%)
CKD Stage 2	93 (86.9%)	92 (85.2%)
FPG (mg/dL) at baseline		
n	107	108
Mean (SD)	147.54 (38.578)	153.03 (37.690)
Median	147.73	154.93
Min, Max	66.7, 228.8	75.7, 243.2
FPG category at baseline		
< 160 mg/dL	68 (63.6%)	61 (56.5%)
>= 160 mg/dL	39 (36.4%)	47 (43.5%)
Insulin type		
Basal	78 (72.9%)	73 (67.6%)
Premix	29 (27.1%)	35 (32.4%)
Insulin frequency		
Daily	79 (73.8%)	74 (68.5%)
Twice daily	28 (26.2%)	34 (31.5%)
Insulin total daily dose (IU/day)		
n	107	108
Mean (SD)	22.2 (9.76)	20.5 (10.00)
Median	20.0	19.0

	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Min, Max	8, 40	8, 40

- Abbreviations: bid, Twice a day; SD, standard deviation; BMI, body mass index; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent; FPG, Fasting Plasma Glucose
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2.
- Percentages are based on Population N.

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Table S-011 Summary of Demographic and Baseline Characteristics in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Sex			
Male	64 (63.4%)	66 (61.1%)	130 (62.2%)
Female	37 (36.6%)	42 (38.9%)	79 (37.8%)
Age (years)			
n	101	108	209
Mean (SD)	58.0 (9.61)	59.3 (10.49)	58.7 (10.07)
Median	59.0	60.0	59.0
Min, Max	35, 77	34, 76	34, 77
Age category			
< 65 years	72 (71.3%)	68 (63.0%)	140 (67.0%)
>= 65 years	29 (28.7%)	40 (37.0%)	69 (33.0%)
< 75 years	98 (97.0%)	101 (93.5%)	199 (95.2%)
>= 75 years	3 (3.0%)	7 (6.5%)	10 (4.8%)
Height (cm)			
n	101	108	209
Mean (SD)	164.28 (9.404)	162.77 (9.649)	163.50 (9.538)
Median	165.00	164.10	164.50
Min, Max	137.2, 181.3	134.8, 182.2	134.8, 182.2
Weight (kg) at baseline			
n	101	108	209
Mean (SD)	66.84 (10.994)	67.13 (12.266)	66.99 (11.642)
Median	66.80	65.40	66.60
Min, Max	44.2, 98.8	41.8, 104.1	41.8, 104.1
BMI (kg/m2) at baseline			
n	101	108	209
Mean (SD)	24.742 (3.4345)	25.244 (3.6302)	25.002 (3.5374)
Median	24.130	24.940	24.610
Min, Max	16.82, 34.22	18.17, 38.80	16.82, 38.80
BMI category at baseline			
< 25 kg/m2	58 (57.4%)	56 (51.9%)	114 (54.5%)
>= 25 kg/m2	43 (42.6%)	52 (48.1%)	95 (45.5%)
>= 25 to < 30 kg/m2	33 (32.7%)	44 (40.7%)	77 (36.8%)
>= 30 kg/m2	10 (9.9%)	8 (7.4%)	18 (8.6%)
BMI (kg/m2) for male at baseline			
n	64	66	130
Mean (SD)	24.272 (3.2098)	25.263 (3.4761)	24.775 (3.3716)
Median	24.060	24.975	24.340
Min, Max	16.82, 32.78	18.17, 38.80	16.82, 38.80
BMI category for male at baseline			

	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
< 25 kg/m2	40 (39.6%)	34 (31.5%)	74 (35.4%)
>= 25 kg/m2	24 (23.8%)	32 (29.6%)	56 (26.8%)
>= 25 to < 30 kg/m2	19 (18.8%)	28 (25.9%)	47 (22.5%)
>= 30 kg/m2	5 (5.0%)	4 (3.7%)	9 (4.3%)
BMI (kg/m2) for female at baseline			
n	37	42	79
Mean (SD)	25.557 (3.6959)	25.214 (3.9031)	25.374 (3.7871)
Median	25.070	24.885	24.920
Min, Max	20.28, 34.22	19.05, 36.65	19.05, 36.65
BMI category for female at baseline			
< 25 kg/m2	18 (17.8%)	22 (20.4%)	40 (19.1%)
>= 25 kg/m2	19 (18.8%)	20 (18.5%)	39 (18.7%)
>= 25 to < 30 kg/m2	14 (13.9%)	16 (14.8%)	30 (14.4%)
>= 30 kg/m2	5 (5.0%)	4 (3.7%)	9 (4.3%)
Waist circumference (cm) at baseline			
n	101	108	209
Mean (SD)	88.38 (8.604)	89.34 (9.172)	88.88 (8.894)
Median	88.50	89.00	88.50
Min, Max	69.8, 113.0	68.0, 120.0	68.0, 120.0
Waist circumference category at baseline			
< 85 cm	32 (31.7%)	32 (29.6%)	64 (30.6%)
>= 85 cm	69 (68.3%)	76 (70.4%)	145 (69.4%)
< 90 cm	59 (58.4%)	59 (54.6%)	118 (56.5%)
>= 90 cm	42 (41.6%)	49 (45.4%)	91 (43.5%)
Waist circumference (cm) for male at baseline			
n	64	66	130
Mean (SD)	87.38 (7.933)	89.81 (8.303)	88.61 (8.182)
Median	87.25	89.50	88.50
Min, Max	70.0, 107.6	71.0, 117.2	70.0, 117.2
Waist circumference category for male at baseline			
< 85 cm	22 (21.8%)	16 (14.8%)	38 (18.2%)
>= 85 cm	42 (41.6%)	50 (46.3%)	92 (44.0%)
Waist circumference (cm) for female at baseline			
n	37	42	79
Mean (SD)	90.10 (9.524)	88.62 (10.457)	89.31 (9.995)
Median	89.50	88.00	88.80
Min, Max	69.8, 113.0	68.0, 120.0	68.0, 120.0
Waist circumference category for female at baseline			

	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
< 90 cm	19 (18.8%)	24 (22.2%)	43 (20.6%)
>= 90 cm	18 (17.8%)	18 (16.7%)	36 (17.2%)
Does the patient drink alcohol?			
Yes	50 (49.5%)	47 (43.5%)	97 (46.4%)
No	51 (50.5%)	61 (56.5%)	112 (53.6%)
HbA1c (%) at baseline			
n	101	108	209
Mean (SD)	8.82 (0.806)	8.74 (0.721)	8.78 (0.762)
Median	8.80	8.70	8.70
Min, Max	7.4, 10.8	7.4, 10.4	7.4, 10.8
HbA1c category at baseline			
< 8.0%	16 (15.8%)	16 (14.8%)	32 (15.3%)
>= 8.0%	85 (84.2%)	92 (85.2%)	177 (84.7%)
>= 8.0 to < 9.0%	41 (40.6%)	53 (49.1%)	94 (45.0%)
>= 9.0%	44 (43.6%)	39 (36.1%)	83 (39.7%)
Duration of diabetes (year)			
n	101	108	209
Mean (SD)	13.54 (7.525)	13.26 (8.151)	13.40 (7.837)
Median	12.37	11.74	12.32
Min, Max	0.3, 37.7	0.4, 36.4	0.3, 37.7
Duration of diabetes category			
< 1 year	1 (1.0%)	2 (1.9%)	3 (1.4%)
>= 1 to < 5 years	10 (9.9%)	14 (13.0%)	24 (11.5%)
>= 5 to < 10 years	22 (21.8%)	29 (26.9%)	51 (24.4%)
>= 10 years	68 (67.3%)	63 (58.3%)	131 (62.7%)
Previous treatment status			
Insulin monotherapy	83 (82.2%)	87 (80.6%)	170 (81.3%)
Insulin in combination with 1 OHA	18 (17.8%)	21 (19.4%)	39 (18.7%)
Previous medication class			
SU	1 (1.0%)	0	1 (0.5%)
GLIN	2 (2.0%)	2 (1.9%)	4 (1.9%)
BIG	8 (7.9%)	9 (8.3%)	17 (8.1%)
AGI	0	0	0
TZD	0	0	0
DPP4-I	6 (5.9%)	4 (3.7%)	10 (4.8%)
GLP1-RA	0	0	0
SGLT2-I	1 (1.0%)	6 (5.6%)	7 (3.3%)
Missing	83 (82.2%)	87 (80.6%)	170 (81.3%)
Complication of diabetes			
Yes	48 (47.5%)	45 (41.7%)	93 (44.5%)
No	53 (52.5%)	63 (58.3%)	116 (55.5%)

	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Metabolic Syndrome at baseline			
Yes	46 (45.5%)	39 (36.1%)	85 (40.7%)
No	55 (54.5%)	69 (63.9%)	124 (59.3%)
Hypertension			
Yes	45 (44.6%)	57 (52.8%)	102 (48.8%)
No	56 (55.4%)	51 (47.2%)	107 (51.2%)
Dyslipidemia			
Yes	77 (76.2%)	77 (71.3%)	154 (73.7%)
No	24 (23.8%)	31 (28.7%)	55 (26.3%)
Hepatic parameter abnormality at baseline			
Yes	14 (13.9%)	17 (15.7%)	31 (14.8%)
No	87 (86.1%)	91 (84.3%)	178 (85.2%)
eGFR (mL/min/1.73m2) at baseline			
n	101	108	209
Mean (SD)	77.4240 (13.26638)	77.0865 (12.31103)	77.2496 (12.75183)
Median	75.7540	75.3615	75.7270
Min, Max	60.249, 138.012	60.196, 129.390	60.196, 138.012
CKD stage at baseline			
CKD Stage 1	13 (12.9%)	16 (14.8%)	29 (13.9%)
CKD Stage 2	88 (87.1%)	92 (85.2%)	180 (86.1%)
FPG (mg/dL) at baseline			
n	101	108	209
Mean (SD)	146.43 (38.296)	153.03 (37.690)	149.84 (38.037)
Median	144.12	154.93	149.53
Min, Max	66.7, 225.2	75.7, 243.2	66.7, 243.2
FPG category at baseline			
< 160 mg/dL	65 (64.4%)	61 (56.5%)	126 (60.3%)
>= 160 mg/dL	36 (35.6%)	47 (43.5%)	83 (39.7%)
Insulin type			
Basal	74 (73.3%)	73 (67.6%)	147 (70.3%)
Premix	27 (26.7%)	35 (32.4%)	62 (29.7%)
Insulin frequency			
Daily	75 (74.3%)	74 (68.5%)	149 (71.3%)
Twice daily	26 (25.7%)	34 (31.5%)	60 (28.7%)
Insulin total daily dose (IU/day)			
n	101	108	209
Mean (SD)	22.1 (9.87)	20.5 (10.00)	21.3 (9.95)
Median	20.0	19.0	20.0

	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Min, Max	8, 40	8, 40	8, 40

- Abbreviations: SD, standard deviation; BMI, body mass index; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent; FPG, Fasting Plasma Glucose
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Baseline values in the double-blind period were used for the summary "at baseline" for Placebo/Imeglimin + Insulin group.
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2
- Percentages are based on Population N.

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Table S-024 Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any TEAE	99 (54.4%)	51 (68.0%)	93 (51.7%)	55 (73.3%)	199 (60.3%)
Infections and infestations (感染症および寄生虫症)	32 (17.6%)	27 (36.0%)	50 (27.8%)	26 (34.7%)	103 (31.2%)
Nasopharyngitis (上咽頭炎)	20 (11.0%)	20 (26.7%)	33 (18.3%)	18 (24.0%)	71 (21.5%)
Bronchitis (気管支炎)	1 (0.5%)	3 (4.0%)	2 (1.1%)	1 (1.3%)	6 (1.8%)
Gastroenteritis (胃腸炎)	2 (1.1%)	2 (2.7%)	2 (1.1%)	0	4 (1.2%)
Pharyngitis (咽頭炎)	2 (1.1%)	1 (1.3%)	3 (1.7%)	0	4 (1.2%)
Periodontitis (歯周炎)	2 (1.1%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Influenza (インフルエンザ)	0	0	3 (1.7%)	1 (1.3%)	4 (1.2%)
Upper respiratory tract infection (上気道感染)	2 (1.1%)	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Conjunctivitis (結膜炎)	0	0	3 (1.7%)	0	3 (0.9%)
Cystitis (膀胱炎)	1 (0.5%)	2 (2.7%)	0	0	2 (0.6%)
Otitis externa (外耳炎)	1 (0.5%)	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Gastroenteritis viral (ウイルス性胃腸炎)	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Herpes zoster (帯状疱疹)	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Infected dermal cyst (感染性皮膚嚢腫)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Oral herpes (口腔ヘルペス)	2 (1.1%)	0	0	0	0
Asymptomatic bacteriuria (無症候性細菌尿)	0	0	1 (0.6%)	0	1 (0.3%)
Bronchitis bacterial (細菌性気管支炎)	0	0	1 (0.6%)	0	1 (0.3%)
Conjunctivitis bacterial (細菌性結膜炎)	0	0	0	1 (1.3%)	1 (0.3%)
Gingivitis (歯肉炎)	1 (0.5%)	0	0	0	0
Helicobacter infection (ヘリコバクター感染)	1 (0.5%)	0	0	0	0
Hordeolum (麦粒腫)	0	0	1 (0.6%)	0	1 (0.3%)
Parotitis (耳下腺炎)	0	0	0	1 (1.3%)	1 (0.3%)
Pericoronitis (歯冠周囲炎)	0	0	0	1 (1.3%)	1 (0.3%)
Pharyngitis streptococcal (レンサ球菌性咽頭炎)	1 (0.5%)	0	0	0	0
Pulpitis dental (歯髄炎)	0	1 (1.3%)	0	0	1 (0.3%)
Tooth abscess (歯膿瘍)	1 (0.5%)	0	0	0	0
Gastrointestinal disorders (胃腸障害)	20 (11.0%)	11 (14.7%)	26 (14.4%)	24 (32.0%)	61 (18.5%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Diarrhoea (下痢)	1 (0.5%)	3 (4.0%)	5 (2.8%)	6 (8.0%)	14 (4.2%)
Abdominal discomfort (腹部不快感)	0	1 (1.3%)	3 (1.7%)	7 (9.3%)	11 (3.3%)
Vomiting (嘔吐)	4 (2.2%)	0	1 (0.6%)	4 (5.3%)	5 (1.5%)
Nausea (悪心)	1 (0.5%)	1 (1.3%)	1 (0.6%)	5 (6.7%)	7 (2.1%)
Dental caries (齲歯)	4 (2.2%)	0	2 (1.1%)	1 (1.3%)	3 (0.9%)
Constipation (便秘)	2 (1.1%)	1 (1.3%)	2 (1.1%)	1 (1.3%)	4 (1.2%)
Abdominal pain upper (上腹部痛)	1 (0.5%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)	1 (0.5%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Dyspepsia (消化不良)	0	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Gastritis (胃炎)	0	1 (1.3%)	2 (1.1%)	0	3 (0.9%)
Periodontal disease (歯周病)	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Abdominal distension (腹部膨満)	0	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Abdominal pain (腹痛)	0	0	2 (1.1%)	0	2 (0.6%)
Chronic gastritis (慢性胃炎)	0	0	2 (1.1%)	0	2 (0.6%)
Duodenal ulcer (十二指腸潰瘍)	2 (1.1%)	0	0	0	0
Faeces soft (軟便)	2 (1.1%)	0	0	0	0
Stomatitis (口内炎)	0	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Abdominal pain lower (下腹部痛)	1 (0.5%)	0	0	0	0
Abnormal faeces (異常便)	0	0	1 (0.6%)	0	1 (0.3%)
Duodenal polyp (十二指腸ポリープ)	0	1 (1.3%)	0	0	1 (0.3%)
Duodenitis (十二指腸炎)	0	1 (1.3%)	0	0	1 (0.3%)
Enteritis (小腸炎)	0	0	0	1 (1.3%)	1 (0.3%)
Enterocolitis (腸炎)	1 (0.5%)	0	0	0	0
Epigastric discomfort (心窩部不快感)	0	0	1 (0.6%)	0	1 (0.3%)
Gastric polyps (胃ポリープ)	1 (0.5%)	0	0	0	0
Ileus (イレウス)	0	0	1 (0.6%)	0	1 (0.3%)
Large intestine polyp (大腸ポリープ)	0	0	1 (0.6%)	0	1 (0.3%)
Loose tooth (弛緩歯)	0	0	1 (0.6%)	0	1 (0.3%)
Melaena (メレナ)	1 (0.5%)	0	0	0	0
Tooth loss (歯の脱落)	1 (0.5%)	0	0	0	0
Metabolism and nutrition disorders (代謝および栄養障害)	21 (11.5%)	8 (10.7%)	9 (5.0%)	5 (6.7%)	22 (6.7%)
Hyperglycaemia (高血糖)	16 (8.8%)	3 (4.0%)	1 (0.6%)	1 (1.3%)	5 (1.5%)
Hypoglycaemia (低血糖)	2 (1.1%)	5 (6.7%)	5 (2.8%)	4 (5.3%)	14 (4.2%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Dyslipidaemia (脂質異常症)	3 (1.6%)	0	2 (1.1%)	0	2 (0.6%)
Hyperuricaemia (高尿酸血症)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	17 (9.3%)	9 (12.0%)	11 (6.1%)	5 (6.7%)	25 (7.6%)
Arthralgia (関節痛)	4 (2.2%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Back pain (背部痛)	0	4 (5.3%)	1 (0.6%)	1 (1.3%)	6 (1.8%)
Muscle spasms (筋痙縮)	3 (1.6%)	0	3 (1.7%)	0	3 (0.9%)
Periarthritis (関節周囲炎)	2 (1.1%)	0	1 (0.6%)	0	1 (0.3%)
Musculoskeletal pain (筋骨格痛)	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Musculoskeletal stiffness (筋骨格硬直)	1 (0.5%)	1 (1.3%)	0	0	1 (0.3%)
Osteoarthritis (変形性関節症)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Plantar fasciitis (足底筋膜炎)	2 (1.1%)	0	0	0	0
Arthritis (関節炎)	0	1 (1.3%)	0	0	1 (0.3%)
Fasciitis (筋膜炎)	1 (0.5%)	0	0	0	0
Intervertebral disc degeneration (椎間板変性症)	0	0	1 (0.6%)	0	1 (0.3%)
Intervertebral disc protrusion (椎間板突出)	0	1 (1.3%)	0	0	1 (0.3%)
Joint swelling (関節腫脹)	1 (0.5%)	0	0	0	0
Mastication disorder (咀嚼障害)	0	0	0	1 (1.3%)	1 (0.3%)
Muscular weakness (筋力低下)	0	0	1 (0.6%)	0	1 (0.3%)
Musculoskeletal chest pain (筋骨格系胸痛)	0	1 (1.3%)	0	0	1 (0.3%)
Myalgia (筋肉痛)	0	0	1 (0.6%)	0	1 (0.3%)
Neck pain (頚部痛)	0	0	0	1 (1.3%)	1 (0.3%)
Osteoporosis (骨粗鬆症)	1 (0.5%)	0	0	0	0
Pain in extremity (四肢痛)	0	1 (1.3%)	0	0	1 (0.3%)
Spinal osteoarthritis (変形性脊椎症)	0	0	1 (0.6%)	0	1 (0.3%)
Spondylolisthesis (脊椎すべり症)	1 (0.5%)	0	0	0	0
Temporomandibular joint syndrome (顎関節症候群)	0	0	0	1 (1.3%)	1 (0.3%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	6 (3.3%)	5 (6.7%)	8 (4.4%)	6 (8.0%)	19 (5.8%)
Contusion (挫傷)	1 (0.5%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Arthropod sting (節足動物刺傷)	0	2 (2.7%)	0	2 (2.7%)	4 (1.2%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Hand fracture (手骨折)	0	1 (1.3%)	0	1 (1.3%)	2 (0.6%)
Ligament sprain (靱帯捻挫)	0	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Radius fracture (橈骨骨折)	0	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Skin abrasion (皮膚擦過傷)	0	0	2 (1.1%)	0	2 (0.6%)
Arthropod bite (節足動物咬傷)	1 (0.5%)	0	0	0	0
Bone contusion (骨挫傷)	0	0	0	1 (1.3%)	1 (0.3%)
Clavicle fracture (鎖骨骨折)	0	0	1 (0.6%)	0	1 (0.3%)
Fall (転倒)	0	0	0	1 (1.3%)	1 (0.3%)
Femur fracture (大腿骨骨折)	0	0	1 (0.6%)	0	1 (0.3%)
Limb injury (四肢損傷)	1 (0.5%)	0	0	0	0
Lower limb fracture (下肢骨折)	1 (0.5%)	0	0	0	0
Meniscus injury (半月板損傷)	1 (0.5%)	0	0	0	0
Muscle rupture (筋断裂)	1 (0.5%)	0	0	0	0
Post procedural haemorrhage (処置後出血)	0	0	1 (0.6%)	0	1 (0.3%)
Rib fracture (肋骨骨折)	0	1 (1.3%)	0	0	1 (0.3%)
Thermal burn (熱傷)	0	0	1 (0.6%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	12 (6.6%)	3 (4.0%)	5 (2.8%)	5 (6.7%)	13 (3.9%)
Eczema (湿疹)	2 (1.1%)	2 (2.7%)	2 (1.1%)	3 (4.0%)	7 (2.1%)
Dermatitis contact (接触皮膚炎)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Dyshidrotic eczema (異汗性湿疹)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Ingrowing nail (嵌入爪)	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Miliaria (汗疹)	1 (0.5%)	1 (1.3%)	0	0	1 (0.3%)
Alopecia areata (円形脱毛症)	1 (0.5%)	0	0	0	0
Drug eruption (薬疹)	1 (0.5%)	0	0	0	0
Dry skin (皮膚乾燥)	0	0	1 (0.6%)	0	1 (0.3%)
Eczema asteatotic (皮脂欠乏性湿疹)	1 (0.5%)	0	0	0	0
Pruritus (そう痒症)	1 (0.5%)	0	0	0	0
Pustular psoriasis (膿疱性乾癬)	1 (0.5%)	0	0	0	0
Rash (発疹)	1 (0.5%)	0	0	0	0
Toxic skin eruption (中毒性皮疹)	1 (0.5%)	0	0	0	0
Urticaria (蕁麻疹)	1 (0.5%)	0	0	0	0
Xanthoma (黄色腫)	0	0	0	1 (1.3%)	1 (0.3%)
Nervous system disorders (神経系障害)	10 (5.5%)	6 (8.0%)	7 (3.9%)	1 (1.3%)	14 (4.2%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Dizziness (浮動性めまい)	4 (2.2%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Headache (頭痛)	2 (1.1%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Cervical radiculopathy (頚髄神経根障害)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Dizziness postural (体位性めまい)	1 (0.5%)	1 (1.3%)	0	0	1 (0.3%)
Presyncope (失神寸前の状態)	0	0	2 (1.1%)	0	2 (0.6%)
Carpal tunnel syndrome (手根管症候群)	0	0	1 (0.6%)	0	1 (0.3%)
Dysgeusia (味覚異常)	0	0	0	1 (1.3%)	1 (0.3%)
Hypoaesthesia (感覚鈍麻)	1 (0.5%)	0	0	0	0
IVth nerve disorder (第 4 脳神経障害)	0	1 (1.3%)	0	0	1 (0.3%)
Intercostal neuralgia (肋間神経痛)	1 (0.5%)	0	0	0	0
Loss of consciousness (意識消失)	0	0	1 (0.6%)	0	1 (0.3%)
Orthostatic intolerance (起立不耐性)	0	1 (1.3%)	0	0	1 (0.3%)
Spondylitic myelopathy (脊椎炎性脊髄症)	0	0	1 (0.6%)	0	1 (0.3%)
Thoracic outlet syndrome (胸郭出口症候群)	0	1 (1.3%)	0	0	1 (0.3%)
Investigations (臨床検査)	7 (3.8%)	5 (6.7%)	4 (2.2%)	6 (8.0%)	15 (4.5%)
Culture urine positive (尿培養陽性)	1 (0.5%)	1 (1.3%)	0	4 (5.3%)	5 (1.5%)
Blood bilirubin increased (血中ビリルビン増加)	2 (1.1%)	0	0	0	0
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)	2 (1.1%)	0	0	0	0
Gamma-glutamyltransferase increased (γ－グルタミルトランスフェラーゼ増加)	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Urine albumin/creatinine ratio increased (尿中アルブミン／クレアチニン比増加)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Activated partial thromboplastin time prolonged (活性化部分トロンボプラスチン時間延長)	0	1 (1.3%)	0	0	1 (0.3%)
Alanine aminotransferase increased (アラニンアミノトランスフェラーゼ増加)	1 (0.5%)	0	0	0	0
Aspartate aminotransferase increased (アスパラギン酸アミノトランスフェラーゼ増加)	1 (0.5%)	0	0	0	0
Blood glucagon increased (血中グルカゴン増加)	0	0	0	1 (1.3%)	1 (0.3%)
Blood pressure increased (血圧上昇)	1 (0.5%)	0	0	0	0

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C-reactive protein increased (Ｃ－反応性蛋白増加)	0	0	1 (0.6%)	0	1 (0.3%)
Electrocardiogram T wave inversion (心電図Ｔ波逆転)	0	0	0	1 (1.3%)	1 (0.3%)
Eosinophil count increased (好酸球数増加)	0	1 (1.3%)	0	0	1 (0.3%)
International normalised ratio increased (国際標準比増加)	0	1 (1.3%)	0	0	1 (0.3%)
Lipase increased (リパーゼ増加)	0	1 (1.3%)	0	0	1 (0.3%)
Liver function test increased (肝機能検査値上昇)	0	0	1 (0.6%)	0	1 (0.3%)
Neutrophil count decreased (好中球数減少)	0	0	1 (0.6%)	0	1 (0.3%)
Occult blood (便潜血)	0	1 (1.3%)	0	0	1 (0.3%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	5 (2.7%)	1 (1.3%)	4 (2.2%)	5 (6.7%)	10 (3.0%)
Fatigue (疲労)	1 (0.5%)	0	2 (1.1%)	2 (2.7%)	4 (1.2%)
Malaise (倦怠感)	1 (0.5%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Pyrexia (発熱)	2 (1.1%)	0	0	0	0
Chest discomfort (胸部不快感)	0	0	1 (0.6%)	0	1 (0.3%)
Feeling abnormal (異常感)	0	0	0	1 (1.3%)	1 (0.3%)
Oedema peripheral (末梢性浮腫)	0	0	0	1 (1.3%)	1 (0.3%)
Thirst (口渇)	1 (0.5%)	0	0	0	0
Eye disorders (眼障害)	4 (2.2%)	2 (2.7%)	4 (2.2%)	3 (4.0%)	9 (2.7%)
Cataract (白内障)	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Chalazion (霰粒腫)	0	1 (1.3%)	0	1 (1.3%)	2 (0.6%)
Diabetic retinopathy (糖尿病網膜症)	0	0	2 (1.1%)	0	2 (0.6%)
Glaucoma (緑内障)	0	0	2 (1.1%)	0	2 (0.6%)
Vitreous floaters (硝子体浮遊物)	2 (1.1%)	0	0	0	0
Dry eye (眼乾燥)	1 (0.5%)	0	0	0	0
Eye inflammation (眼の炎症)	0	0	0	1 (1.3%)	1 (0.3%)
Eye swelling (眼部腫脹)	0	1 (1.3%)	0	0	1 (0.3%)
Macular fibrosis (黄斑線維症)	0	0	1 (0.6%)	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	4 (2.2%)	3 (4.0%)	0	2 (2.7%)	5 (1.5%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Oropharyngeal pain (口腔咽頭痛)	1 (0.5%)	0	0	2 (2.7%)	2 (0.6%)
Upper respiratory tract inflammation (上気道の炎症)	2 (1.1%)	1 (1.3%)	0	0	1 (0.3%)
Rhinitis allergic (アレルギー性鼻炎)	0	2 (2.7%)	0	0	2 (0.6%)
Allergic cough (アレルギー性咳嗽)	1 (0.5%)	0	0	0	0
Asthma (喘息)	1 (0.5%)	0	0	0	0
Cardiac disorders (心臓障害)	2 (1.1%)	0	2 (1.1%)	3 (4.0%)	5 (1.5%)
Palpitations (動悸)	2 (1.1%)	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Atrial fibrillation (心房細動)	0	0	0	1 (1.3%)	1 (0.3%)
Bradycardia (徐脈)	0	0	1 (0.6%)	0	1 (0.3%)
Ventricular extrasystoles (心室性期外収縮)	0	0	0	1 (1.3%)	1 (0.3%)
Vascular disorders (血管障害)	3 (1.6%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Hypertension (高血圧)	2 (1.1%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Arteriosclerosis (動脈硬化症)	1 (0.5%)	0	0	0	0
Ear and labyrinth disorders (耳および迷路障害)	1 (0.5%)	0	2 (1.1%)	3 (4.0%)	5 (1.5%)
Vertigo (回転性めまい)	0	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Ear congestion (耳閉)	0	0	0	1 (1.3%)	1 (0.3%)
Eustachian tube stenosis (耳管狭窄)	1 (0.5%)	0	0	0	0
Vertigo positional (頭位性回転性めまい)	0	0	1 (0.6%)	0	1 (0.3%)
Hepatobiliary disorders (肝胆道系障害)	3 (1.6%)	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Hepatic steatosis (脂肪肝)	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Gallbladder polyp (胆嚢ポリープ)	1 (0.5%)	0	0	0	0
Hepatic function abnormal (肝機能異常)	0	0	1 (0.6%)	0	1 (0.3%)
Hepatomegaly (肝腫大)	0	0	0	1 (1.3%)	1 (0.3%)
Liver injury (肝損傷)	1 (0.5%)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	0	0	4 (2.2%)	1 (1.3%)	5 (1.5%)
Bladder cancer (膀胱癌)	0	0	1 (0.6%)	0	1 (0.3%)

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Pancreatic carcinoma metastatic (遠隔転移を伴う膵癌)	0	0	0	1 (1.3%)	1 (0.3%)
Prostate cancer (前立腺癌)	0	0	1 (0.6%)	0	1 (0.3%)
Seborrhoeic keratosis (脂漏性角化症)	0	0	1 (0.6%)	0	1 (0.3%)
Solid pseudopapillary tumour of the pancreas (膵の充実性偽乳頭状腫瘍)	0	0	1 (0.6%)	0	1 (0.3%)
Psychiatric disorders (精神障害)	1 (0.5%)	1 (1.3%)	0	1 (1.3%)	2 (0.6%)
Insomnia (不眠症)	0	1 (1.3%)	0	1 (1.3%)	2 (0.6%)
Anxiety (不安)	1 (0.5%)	0	0	0	0
Renal and urinary disorders (腎および尿路障害)	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Calculus urinary (尿路結石)	1 (0.5%)	0	0	0	0
Diabetic nephropathy (糖尿病性腎症)	0	1 (1.3%)	0	0	1 (0.3%)
Ureterolithiasis (尿管結石症)	0	0	1 (0.6%)	0	1 (0.3%)
Reproductive system and breast disorders (生殖系および乳房障害)	2 (1.1%)	1 (1.3%)	0	0	1 (0.3%)
Benign prostatic hyperplasia (良性前立腺肥大症)	1 (0.5%)	0	0	0	0
Dysmenorrhoea (月経困難症)	1 (0.5%)	0	0	0	0
Metrorrhagia (不正子宮出血)	0	1 (1.3%)	0	0	1 (0.3%)
Prostatitis (前立腺炎)	1 (0.5%)	0	0	0	0
Blood and lymphatic system disorders (血液およびリンパ系障害)	0	0	1 (0.6%)	0	1 (0.3%)
Anaemia (貧血)	0	0	1 (0.6%)	0	1 (0.3%)
Endocrine disorders (内分泌障害)	0	0	0	1 (1.3%)	1 (0.3%)
Thyroid cyst (甲状腺嚢腫)	0	0	0	1 (1.3%)	1 (0.3%)
Thyroid mass (甲状腺腫瘤)	0	0	0	1 (1.3%)	1 (0.3%)
Social circumstances (社会環境)	1 (0.5%)	0	0	0	0
Menopause (閉経)	1 (0.5%)	0	0	0	0
Surgical and medical procedures (外科および内科処置)	0	0	1 (0.6%)	0	1 (0.3%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Blepharoplasty (眼瞼形成)	0	0	1 (0.6%)	0	1 (0.3%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

Control No:<<t-s-024-aesoc-24wdb.sas, 2020-03-06T00:07:29>>

Table S-025 Summary of Treatment Emergent Adverse Events Related to Treatment by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any TEAE related to treatment	13 (7.1%)	4 (5.3%)	9 (5.0%)	18 (24.0%)	31 (9.4%)
Gastrointestinal disorders (胃腸障害)	3 (1.6%)	1 (1.3%)	4 (2.2%)	12 (16.0%)	17 (5.2%)
Diarrhoea (下痢)	1 (0.5%)	0	2 (1.1%)	3 (4.0%)	5 (1.5%)
Nausea (悪心)	1 (0.5%)	0	1 (0.6%)	4 (5.3%)	5 (1.5%)
Abdominal discomfort (腹部不快感)	0	0	1 (0.6%)	4 (5.3%)	5 (1.5%)
Vomiting (嘔吐)	0	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Dyspepsia (消化不良)	0	1 (1.3%)	0	0	1 (0.3%)
Faeces soft (軟便)	1 (0.5%)	0	0	0	0
Stomatitis (口内炎)	0	0	0	1 (1.3%)	1 (0.3%)
Metabolism and nutrition disorders (代謝および栄養障害)	6 (3.3%)	2 (2.7%)	3 (1.7%)	4 (5.3%)	9 (2.7%)
Hypoglycaemia (低血糖)	2 (1.1%)	1 (1.3%)	3 (1.7%)	4 (5.3%)	8 (2.4%)
Hyperglycaemia (高血糖)	3 (1.6%)	1 (1.3%)	0	0	1 (0.3%)
Hyperuricaemia (高尿酸血症)	1 (0.5%)	0	0	0	0
Investigations (臨床検査)	1 (0.5%)	1 (1.3%)	2 (1.1%)	1 (1.3%)	4 (1.2%)
Activated partial thromboplastin time prolonged (活性化部分トロンボプラスチン時間延長)	0	1 (1.3%)	0	0	1 (0.3%)
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)	1 (0.5%)	0	0	0	0
Blood glucagon increased (血中グルカゴン増加)	0	0	0	1 (1.3%)	1 (0.3%)
Culture urine positive (尿培養陽性)	0	0	0	1 (1.3%)	1 (0.3%)
International normalised ratio increased (国際標準比増加)	0	1 (1.3%)	0	0	1 (0.3%)
Liver function test increased (肝機能検査値上昇)	0	0	1 (0.6%)	0	1 (0.3%)
Urine albumin/creatinine ratio increased (尿中アルブミン／クレアチニン比増加)	0	0	1 (0.6%)	0	1 (0.3%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	1 (0.5%)	0	0	2 (2.7%)	2 (0.6%)
Feeling abnormal (異常感)	0	0	0	1 (1.3%)	1 (0.3%)
Malaise (倦怠感)	0	0	0	1 (1.3%)	1 (0.3%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Thirst (口渇)	1 (0.5%)	0	0	0	0
Eye disorders (眼障害)	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Glaucoma (緑内障)	0	0	1 (0.6%)	0	1 (0.3%)
Vitreous floaters (硝子体浮遊物)	1 (0.5%)	0	0	0	0
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	2 (1.1%)	0	0	0	0
Eczema (湿疹)	1 (0.5%)	0	0	0	0
Pruritus (そう痒症)	1 (0.5%)	0	0	0	0
Blood and lymphatic system disorders (血液およびリンパ系障害)	0	0	1 (0.6%)	0	1 (0.3%)
Anaemia (貧血)	0	0	1 (0.6%)	0	1 (0.3%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	0	0	0	1 (1.3%)	1 (0.3%)
Temporomandibular joint syndrome (顎関節症候群)	0	0	0	1 (1.3%)	1 (0.3%)
Nervous system disorders (神経系障害)	1 (0.5%)	0	0	0	0
Intercostal neuralgia (肋間神経痛)	1 (0.5%)	0	0	0	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

Control No:<<t-s-025-aesoc-24wdb.sas, 2020-03-06T00:07:33>>

Table S-031 Summary of Treatment Emergent Lactic Acidosis-related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any Lactic Acidosis-related TEAEs	0	2 (1.6%)	0	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Investigations (臨床検査)	0	2 (1.6%)	0	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Blood lactic acid increased (血中乳酸増加)	0	2 (1.6%)	0	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

Control No:<<t-s-031-aeint-019lt.sas, 2020-03-06T00:06:28>>

Table S-032 Summary of Cardiovascular Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any Cardiovascular TEAE	0	1 (0.8%)	0	1 (1.6%)	0	0	0	1 (1.4%)	1 (1.6%)	4 (0.7%)	4 (0.6%)
Cardiac disorders (心臓障害)	0	1 (0.8%)	0	1 (1.6%)	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Acute myocardial infarction (急性心筋梗塞)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Myocardial infarction (心筋梗塞)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Nervous system disorders (神経系障害)	0	0	0	0	0	0	0	1 (1.4%)	1 (1.6%)	2 (0.3%)	2 (0.3%)
Cerebral infarction (脳梗塞)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Lacunar infarction (ラクナ梗塞)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

Control No:<<t-s-032-aeint-019lt.sas, 2020-03-06T00:06:32>>

Table S-053 Summary of Treatment Emergent Lactic Acidosis-related Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any Lactic Acidosis-related TEAEs	0	1 (0.9%)	1 (0.5%)
Investigations (臨床検査)	0	1 (0.9%)	1 (0.5%)
Blood lactic acid increased (血中乳酸増加)	0	1 (0.9%)	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

Control No:<<t-s-053-aeint-020lt.sas, 2020-03-06T00:07:22>>

Table S-057 Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any TEAE	77 (76.2%)	92 (85.2%)	169 (80.9%)
Infections and infestations (感染症および寄生虫症)	30 (29.7%)	52 (48.1%)	82 (39.2%)
Nasopharyngitis (上咽頭炎)	16 (15.8%)	36 (33.3%)	52 (24.9%)
Bronchitis (気管支炎)	5 (5.0%)	4 (3.7%)	9 (4.3%)
Influenza (インフルエンザ)	4 (4.0%)	5 (4.6%)	9 (4.3%)
Gastroenteritis (胃腸炎)	4 (4.0%)	1 (0.9%)	5 (2.4%)
Cystitis (膀胱炎)	1 (1.0%)	3 (2.8%)	4 (1.9%)
Herpes zoster (帯状疱疹)	1 (1.0%)	2 (1.9%)	3 (1.4%)
Periodontitis (歯周炎)	1 (1.0%)	2 (1.9%)	3 (1.4%)
Conjunctivitis (結膜炎)	2 (2.0%)	0	2 (1.0%)
Folliculitis (毛包炎)	0	2 (1.9%)	2 (1.0%)
Hordeolum (麦粒腫)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Pharyngitis (咽頭炎)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Urinary tract infection (尿路感染)	0	2 (1.9%)	2 (1.0%)
Asymptomatic bacteriuria (無症候性細菌尿)	0	1 (0.9%)	1 (0.5%)
Erysipelas (丹毒)	0	1 (0.9%)	1 (0.5%)
Furuncle (せつ)	0	1 (0.9%)	1 (0.5%)
Gastroenteritis viral (ウイルス性胃腸炎)	1 (1.0%)	0	1 (0.5%)
Gingivitis (歯肉炎)	0	1 (0.9%)	1 (0.5%)
Helicobacter infection (ヘリコバクター感染)	1 (1.0%)	0	1 (0.5%)
Herpes simplex (単純ヘルペス)	1 (1.0%)	0	1 (0.5%)
Oral herpes (口腔ヘルペス)	1 (1.0%)	0	1 (0.5%)
Otitis media acute (急性中耳炎)	1 (1.0%)	0	1 (0.5%)
Pneumonia mycoplasmal (マイコプラズマ性肺炎)	1 (1.0%)	0	1 (0.5%)
Rhinitis (鼻炎)	0	1 (0.9%)	1 (0.5%)
Sinusitis (副鼻腔炎)	0	1 (0.9%)	1 (0.5%)
Soft tissue infection (軟部組織感染)	0	1 (0.9%)	1 (0.5%)
Tinea pedis (足部白癬)	0	1 (0.9%)	1 (0.5%)
Tonsillitis (扁桃炎)	0	1 (0.9%)	1 (0.5%)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Upper respiratory tract infection (上気道感染)	1 (1.0%)	0	1 (0.5%)
Metabolism and nutrition disorders (代謝および栄養障害)	37 (36.6%)	42 (38.9%)	79 (37.8%)
Hypoglycaemia (低血糖)	36 (35.6%)	39 (36.1%)	75 (35.9%)
Dyslipidaemia (脂質異常症)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Hyperglycaemia (高血糖)	0	2 (1.9%)	2 (1.0%)
Hyponatraemia (低ナトリウム血症)	1 (1.0%)	0	1 (0.5%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	9 (8.9%)	24 (22.2%)	33 (15.8%)
Back pain (背部痛)	1 (1.0%)	6 (5.6%)	7 (3.3%)
Muscle spasms (筋痙縮)	1 (1.0%)	4 (3.7%)	5 (2.4%)
Arthralgia (関節痛)	1 (1.0%)	3 (2.8%)	4 (1.9%)
Spinal osteoarthritis (変形性脊椎症)	0	4 (3.7%)	4 (1.9%)
Musculoskeletal stiffness (筋骨格硬直)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Osteoarthritis (変形性関節症)	0	2 (1.9%)	2 (1.0%)
Synovial cyst (滑液嚢腫)	0	2 (1.9%)	2 (1.0%)
Tenosynovitis (腱鞘炎)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Trigger finger (弾発指)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Chondrocalcinosis pyrophosphate (ピロリン酸カルシウム結晶性軟骨石灰化症)	1 (1.0%)	0	1 (0.5%)
Intervertebral disc protrusion (椎間板突出)	0	1 (0.9%)	1 (0.5%)
Lumbar spinal stenosis (腰部脊柱管狭窄症)	0	1 (0.9%)	1 (0.5%)
Musculoskeletal pain (筋骨格痛)	1 (1.0%)	0	1 (0.5%)
Myofascitis (筋筋膜炎)	0	1 (0.9%)	1 (0.5%)
Neck pain (頚部痛)	0	1 (0.9%)	1 (0.5%)
Nodal osteoarthritis (結節性変形性関節症)	0	1 (0.9%)	1 (0.5%)
Pain in extremity (四肢痛)	0	1 (0.9%)	1 (0.5%)
Synovitis (滑膜炎)	0	1 (0.9%)	1 (0.5%)
Temporomandibular joint syndrome (顎関節症候群)	0	1 (0.9%)	1 (0.5%)
Tendonitis (腱炎)	1 (1.0%)	0	1 (0.5%)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Gastrointestinal disorders (胃腸障害)	10 (9.9%)	20 (18.5%)	30 (14.4%)
Constipation (便秘)	0	6 (5.6%)	6 (2.9%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)	2 (2.0%)	3 (2.8%)	5 (2.4%)
Nausea (悪心)	2 (2.0%)	3 (2.8%)	5 (2.4%)
Abdominal discomfort (腹部不快感)	1 (1.0%)	3 (2.8%)	4 (1.9%)
Diarrhoea (下痢)	2 (2.0%)	2 (1.9%)	4 (1.9%)
Toothache (歯痛)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Abdominal pain upper (上腹部痛)	0	2 (1.9%)	2 (1.0%)
Chronic gastritis (慢性胃炎)	2 (2.0%)	0	2 (1.0%)
Dental caries (齲歯)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Gastritis (胃炎)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Periodontal disease (歯周病)	0	2 (1.9%)	2 (1.0%)
Vomiting (嘔吐)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Abdominal distension (腹部膨満)	0	1 (0.9%)	1 (0.5%)
Colitis ulcerative (潰瘍性大腸炎)	0	1 (0.9%)	1 (0.5%)
Large intestine polyp (大腸ポリープ)	1 (1.0%)	0	1 (0.5%)
Eye disorders (眼障害)	6 (5.9%)	10 (9.3%)	16 (7.7%)
Cataract (白内障)	1 (1.0%)	2 (1.9%)	3 (1.4%)
Diabetic retinopathy (糖尿病網膜症)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Ocular hypertension (高眼圧症)	0	2 (1.9%)	2 (1.0%)
Vitreous haemorrhage (硝子体出血)	0	2 (1.9%)	2 (1.0%)
Accommodation disorder (調節障害)	1 (1.0%)	0	1 (0.5%)
Angle closure glaucoma (閉塞隅角緑内障)	0	1 (0.9%)	1 (0.5%)
Conjunctival hyperaemia (結膜充血)	1 (1.0%)	0	1 (0.5%)
Conjunctivitis allergic (アレルギー性結膜炎)	0	1 (0.9%)	1 (0.5%)
Diabetic retinal oedema (糖尿病性網膜浮腫)	0	1 (0.9%)	1 (0.5%)
Dry eye (眼乾燥)	0	1 (0.9%)	1 (0.5%)
Glaucoma (緑内障)	1 (1.0%)	0	1 (0.5%)
Macular oedema (黄斑浮腫)	1 (1.0%)	0	1 (0.5%)
Pingueculitis (瞼裂斑炎)	1 (1.0%)	0	1 (0.5%)
Retinal detachment (網膜剥離)	0	1 (0.9%)	1 (0.5%)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Retinal haemorrhage (網膜出血)	0	1 (0.9%)	1 (0.5%)
Trichiasis (睫毛乱生)	0	1 (0.9%)	1 (0.5%)
Nervous system disorders (神経系障害)	6 (5.9%)	8 (7.4%)	14 (6.7%)
Headache (頭痛)	3 (3.0%)	3 (2.8%)	6 (2.9%)
Dizziness (浮動性めまい)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Autonomic nervous system imbalance (自律神経失調)	1 (1.0%)	0	1 (0.5%)
Carpal tunnel syndrome (手根管症候群)	1 (1.0%)	0	1 (0.5%)
Epilepsy (てんかん)	0	1 (0.9%)	1 (0.5%)
Facial paralysis (顔面麻痺)	0	1 (0.9%)	1 (0.5%)
Sciatica (坐骨神経痛)	0	1 (0.9%)	1 (0.5%)
Somnolence (傾眠)	0	1 (0.9%)	1 (0.5%)
Syncope (失神)	1 (1.0%)	0	1 (0.5%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)	2 (2.0%)	11 (10.2%)	13 (6.2%)
Dermatitis (皮膚炎)	1 (1.0%)	2 (1.9%)	3 (1.4%)
Eczema (湿疹)	0	2 (1.9%)	2 (1.0%)
Urticaria (蕁麻疹)	0	2 (1.9%)	2 (1.0%)
Acne (ざ瘡)	0	1 (0.9%)	1 (0.5%)
Cold sweat (冷汗)	0	1 (0.9%)	1 (0.5%)
Drug eruption (薬疹)	0	1 (0.9%)	1 (0.5%)
Hand dermatitis (手皮膚炎)	1 (1.0%)	0	1 (0.5%)
Hyperkeratosis (過角化)	0	1 (0.9%)	1 (0.5%)
Miliaria (汗疹)	0	1 (0.9%)	1 (0.5%)
Pruritus (そう痒症)	0	1 (0.9%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)	7 (6.9%)	4 (3.7%)	11 (5.3%)
Upper respiratory tract inflammation (上気道の炎症)	3 (3.0%)	1 (0.9%)	4 (1.9%)
Asthma (喘息)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Cough (咳嗽)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Sputum increased (喀痰増加)	2 (2.0%)	0	2 (1.0%)
Pulmonary embolism (肺塞栓症)	0	1 (0.9%)	1 (0.5%)
Rhinitis allergic (アレルギー性鼻炎)	1 (1.0%)	0	1 (0.5%)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	2 (2.0%)	8 (7.4%)	10 (4.8%)
Contusion (挫傷)	0	3 (2.8%)	3 (1.4%)
Stress fracture (ストレス骨折)	0	2 (1.9%)	2 (1.0%)
Clavicle fracture (鎖骨骨折)	1 (1.0%)	0	1 (0.5%)
Hand fracture (手骨折)	0	1 (0.9%)	1 (0.5%)
Heat illness (熱中症)	0	1 (0.9%)	1 (0.5%)
Ligament sprain (靱帯捻挫)	0	1 (0.9%)	1 (0.5%)
Muscle strain (肉離れ)	0	1 (0.9%)	1 (0.5%)
Scratch (引っかき傷)	1 (1.0%)	0	1 (0.5%)
Vascular disorders (血管障害)	2 (2.0%)	7 (6.5%)	9 (4.3%)
Hypertension (高血圧)	2 (2.0%)	5 (4.6%)	7 (3.3%)
Peripheral arterial occlusive disease (末梢動脈閉塞性疾患)	0	1 (0.9%)	1 (0.5%)
Venous thrombosis limb (四肢静脈血栓症)	0	1 (0.9%)	1 (0.5%)
Investigations (臨床検査)	1 (1.0%)	6 (5.6%)	7 (3.3%)
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)	1 (1.0%)	2 (1.9%)	3 (1.4%)
Aspartate aminotransferase increased (アスパラギン酸アミノトランスフェラーゼ増加)	0	1 (0.9%)	1 (0.5%)
Blood alkaline phosphatase increased (血中アルカリホスファターゼ増加)	0	1 (0.9%)	1 (0.5%)
Blood glucose abnormal (血中ブドウ糖異常)	0	1 (0.9%)	1 (0.5%)
Blood lactic acid increased (血中乳酸増加)	0	1 (0.9%)	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	4 (4.0%)	3 (2.8%)	7 (3.3%)
Papillary thyroid cancer (乳頭様甲状腺癌)	2 (2.0%)	0	2 (1.0%)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Benign neoplasm of thyroid gland (甲状腺の良性新生物)	0	1 (0.9%)	1 (0.5%)
Intraductal papillary mucinous neoplasm (膵管内乳頭粘液性腫瘍)	1 (1.0%)	0	1 (0.5%)
Lipoma (脂肪腫)	0	1 (0.9%)	1 (0.5%)
Pancreatic carcinoma (膵癌)	1 (1.0%)	0	1 (0.5%)
Uterine leiomyoma (子宮平滑筋腫)	0	1 (0.9%)	1 (0.5%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	3 (3.0%)	3 (2.8%)	6 (2.9%)
Pyrexia (発熱)	2 (2.0%)	2 (1.9%)	4 (1.9%)
Oedema peripheral (末梢性浮腫)	0	1 (0.9%)	1 (0.5%)
Sudden death (突然死)	1 (1.0%)	0	1 (0.5%)
Hepatobiliary disorders (肝胆道系障害)	3 (3.0%)	2 (1.9%)	5 (2.4%)
Hepatic steatosis (脂肪肝)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Gallbladder polyp (胆嚢ポリープ)	0	1 (0.9%)	1 (0.5%)
Hepatic function abnormal (肝機能異常)	1 (1.0%)	0	1 (0.5%)
Hyperplastic cholecystopathy (過形成性胆嚢症)	1 (1.0%)	0	1 (0.5%)
Immune system disorders (免疫系障害)	1 (1.0%)	4 (3.7%)	5 (2.4%)
Seasonal allergy (季節性アレルギー)	1 (1.0%)	4 (3.7%)	5 (2.4%)
Ear and labyrinth disorders (耳および迷路障害)	1 (1.0%)	3 (2.8%)	4 (1.9%)
Meniere's disease (メニエール病)	1 (1.0%)	0	1 (0.5%)
Tinnitus (耳鳴)	0	1 (0.9%)	1 (0.5%)
Vertigo (回転性めまい)	0	1 (0.9%)	1 (0.5%)
Vertigo positional (頭位性回転性めまい)	0	1 (0.9%)	1 (0.5%)
Cardiac disorders (心臓障害)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Atrial fibrillation (心房細動)	1 (1.0%)	0	1 (0.5%)
Cardiac failure congestive (うっ血性心不全)	1 (1.0%)	0	1 (0.5%)
Coronary artery stenosis (冠動脈狭窄)	0	1 (0.9%)	1 (0.5%)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Extrasystoles (期外収縮)	1 (1.0%)	0	1 (0.5%)
Reproductive system and breast disorders (生殖系および乳房障害)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Benign prostatic hyperplasia (良性前立腺肥大症)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Prostatomegaly (前立腺腫大)	1 (1.0%)	0	1 (0.5%)
Psychiatric disorders (精神障害)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Depressive symptom (抑うつ症状)	1 (1.0%)	0	1 (0.5%)
Insomnia (不眠症)	0	1 (0.9%)	1 (0.5%)
Renal and urinary disorders (腎および尿路障害)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Haematuria (血尿)	0	1 (0.9%)	1 (0.5%)
Renal cyst (腎嚢胞)	1 (1.0%)	0	1 (0.5%)
Blood and lymphatic system disorders (血液およびリンパ系障害)	1 (1.0%)	0	1 (0.5%)
Iron deficiency anaemia (鉄欠乏性貧血)	1 (1.0%)	0	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

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Table S-058 Summary of Treatment Emergent Adverse Events Related to Treatment by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any TEAE related to treatment	16 (15.8%)	28 (25.9%)	44 (21.1%)
Metabolism and nutrition disorders (代謝および栄養障害)	16 (15.8%)	23 (21.3%)	39 (18.7%)
Hypoglycaemia (低血糖)	16 (15.8%)	23 (21.3%)	39 (18.7%)
Gastrointestinal disorders (胃腸障害)	1 (1.0%)	4 (3.7%)	5 (2.4%)
Constipation (便秘)	0	3 (2.8%)	3 (1.4%)
Diarrhoea (下痢)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Abdominal distension (腹部膨満)	0	1 (0.9%)	1 (0.5%)
Nausea (悪心)	0	1 (0.9%)	1 (0.5%)
Vomiting (嘔吐)	0	1 (0.9%)	1 (0.5%)
Hepatobiliary disorders (肝胆道系障害)	1 (1.0%)	0	1 (0.5%)
Hyperplastic cholecystopathy (過形成性胆嚢症)	1 (1.0%)	0	1 (0.5%)
Infections and infestations (感染症および寄生虫症)	0	1 (0.9%)	1 (0.5%)
Cystitis (膀胱炎)	0	1 (0.9%)	1 (0.5%)
Investigations (臨床検査)	0	1 (0.9%)	1 (0.5%)
Blood lactic acid increased (血中乳酸増加)	0	1 (0.9%)	1 (0.5%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

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Table S-061 Summary of Treatment Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any TEAE					
Mild	88 (48.4%)	48 (64.0%)	80 (44.4%)	45 (60.0%)	173 (52.4%)
Moderate	10 (5.5%)	3 (4.0%)	7 (3.9%)	9 (12.0%)	19 (5.8%)
Severe	1 (0.5%)	0	6 (3.3%)	1 (1.3%)	7 (2.1%)
Infections and infestations (感染症および寄生虫症)					
Mild	31 (17.0%)	27 (36.0%)	50 (27.8%)	26 (34.7%)	103 (31.2%)
Moderate	1 (0.5%)	0	0	0	0
Nasopharyngitis (上咽頭炎)					
Mild	20 (11.0%)	20 (26.7%)	33 (18.3%)	18 (24.0%)	71 (21.5%)
Bronchitis (気管支炎)					
Mild	1 (0.5%)	3 (4.0%)	2 (1.1%)	1 (1.3%)	6 (1.8%)
Gastroenteritis (胃腸炎)					
Mild	1 (0.5%)	2 (2.7%)	2 (1.1%)	0	4 (1.2%)
Moderate	1 (0.5%)	0	0	0	0
Pharyngitis (咽頭炎)					
Mild	2 (1.1%)	1 (1.3%)	3 (1.7%)	0	4 (1.2%)
Periodontitis (歯周炎)					
Mild	2 (1.1%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Influenza (インフルエンザ)					
Mild	0	0	3 (1.7%)	1 (1.3%)	4 (1.2%)
Upper respiratory tract infection (上気道感染)					
Mild	2 (1.1%)	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Conjunctivitis (結膜炎)					
Mild	0	0	3 (1.7%)	0	3 (0.9%)
Cystitis (膀胱炎)					
Mild	1 (0.5%)	2 (2.7%)	0	0	2 (0.6%)
Otitis externa (外耳炎)					
Mild	1 (0.5%)	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Gastroenteritis viral (ウイルス性胃腸炎)					
Mild	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Herpes zoster (帯状疱疹)					
Mild	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Infected dermal cyst (感染性皮膚嚢腫)					
Mild	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Oral herpes (口腔ヘルペス)					
Mild	2 (1.1%)	0	0	0	0

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Asymptomatic bacteriuria (無症候性細菌尿)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Bronchitis bacterial (細菌性気管支炎)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Conjunctivitis bacterial (細菌性結膜炎)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Gingivitis (歯肉炎)					
Mild	1 (0.5%)	0	0	0	0
Helicobacter infection (ヘリコバクター感染)					
Mild	1 (0.5%)	0	0	0	0
Hordeolum (麦粒腫)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Parotitis (耳下腺炎)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Pericoronitis (歯冠周囲炎)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Pharyngitis streptococcal (レンサ球菌性咽頭炎)					
Mild	1 (0.5%)	0	0	0	0
Pulpitis dental (歯髄炎)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Tooth abscess (歯膿瘍)					
Mild	1 (0.5%)	0	0	0	0
Gastrointestinal disorders (胃腸障害)					
Mild	17 (9.3%)	11 (14.7%)	23 (12.8%)	19 (25.3%)	53 (16.1%)
Moderate	3 (1.6%)	0	3 (1.7%)	5 (6.7%)	8 (2.4%)
Diarrhoea (下痢)					
Mild	1 (0.5%)	3 (4.0%)	5 (2.8%)	6 (8.0%)	14 (4.2%)
Abdominal discomfort (腹部不快感)					
Mild	0	1 (1.3%)	3 (1.7%)	7 (9.3%)	11 (3.3%)
Vomiting (嘔吐)					
Mild	3 (1.6%)	0	1 (0.6%)	3 (4.0%)	4 (1.2%)
Moderate	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Nausea (悪心)					
Mild	1 (0.5%)	1 (1.3%)	1 (0.6%)	3 (4.0%)	5 (1.5%)
Moderate	0	0	0	2 (2.7%)	2 (0.6%)
Dental caries (齲歯)					
Mild	3 (1.6%)	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Moderate	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Constipation (便秘)					
Mild	2 (1.1%)	1 (1.3%)	2 (1.1%)	1 (1.3%)	4 (1.2%)
Abdominal pain upper (上腹部痛)					
Mild	1 (0.5%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)					
Mild	1 (0.5%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Dyspepsia (消化不良)					
Mild	0	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Gastritis (胃炎)					
Mild	0	1 (1.3%)	2 (1.1%)	0	3 (0.9%)
Periodontal disease (歯周病)					
Mild	0	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Moderate	1 (0.5%)	0	0	0	0
Abdominal distension (腹部膨満)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Moderate	0	0	1 (0.6%)	0	1 (0.3%)
Abdominal pain (腹痛)					
Mild	0	0	2 (1.1%)	0	2 (0.6%)
Chronic gastritis (慢性胃炎)					
Mild	0	0	2 (1.1%)	0	2 (0.6%)
Duodenal ulcer (十二指腸潰瘍)					
Mild	2 (1.1%)	0	0	0	0
Faeces soft (軟便)					
Mild	2 (1.1%)	0	0	0	0
Stomatitis (口内炎)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Moderate	0	0	0	1 (1.3%)	1 (0.3%)
Abdominal pain lower (下腹部痛)					
Mild	1 (0.5%)	0	0	0	0
Abnormal faeces (異常便)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Duodenal polyp (十二指腸ポリープ)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Duodenitis (十二指腸炎)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Enteritis (小腸炎)					
Moderate	0	0	0	1 (1.3%)	1 (0.3%)
Enterocolitis (腸炎)					
Mild	1 (0.5%)	0	0	0	0
Epigastric discomfort (心窩部不快感)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Gastric polyps (胃ポリープ)					
Mild	1 (0.5%)	0	0	0	0
Ileus (イレウス)					
Moderate	0	0	1 (0.6%)	0	1 (0.3%)
Large intestine polyp (大腸ポリープ)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Loose tooth (弛緩歯)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Melaena (メレナ)					
Mild	1 (0.5%)	0	0	0	0
Tooth loss (歯の脱落)					
Mild	1 (0.5%)	0	0	0	0
Metabolism and nutrition disorders (代謝および栄養障害)					
Mild	20 (11.0%)	7 (9.3%)	8 (4.4%)	5 (6.7%)	20 (6.1%)
Moderate	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Hyperglycaemia (高血糖)					
Mild	15 (8.2%)	2 (2.7%)	0	1 (1.3%)	3 (0.9%)
Moderate	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Hypoglycaemia (低血糖)					
Mild	2 (1.1%)	5 (6.7%)	5 (2.8%)	4 (5.3%)	14 (4.2%)
Dyslipidaemia (脂質異常症)					
Mild	3 (1.6%)	0	2 (1.1%)	0	2 (0.6%)
Hyperuricaemia (高尿酸血症)					
Mild	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)					
Mild	15 (8.2%)	8 (10.7%)	10 (5.6%)	3 (4.0%)	21 (6.4%)
Moderate	2 (1.1%)	1 (1.3%)	1 (0.6%)	2 (2.7%)	4 (1.2%)
Arthralgia (関節痛)					
Mild	4 (2.2%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Back pain (背部痛)					
Mild	0	3 (4.0%)	1 (0.6%)	1 (1.3%)	5 (1.5%)
Moderate	0	1 (1.3%)	0	0	1 (0.3%)
Muscle spasms (筋痙縮)					
Mild	2 (1.1%)	0	3 (1.7%)	0	3 (0.9%)
Moderate	1 (0.5%)	0	0	0	0
Periarthritis (関節周囲炎)					
Mild	2 (1.1%)	0	1 (0.6%)	0	1 (0.3%)
Musculoskeletal pain (筋骨格痛)					
Moderate	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Musculoskeletal stiffness (筋骨格硬直)					
Mild	1 (0.5%)	1 (1.3%)	0	0	1 (0.3%)
Osteoarthritis (変形性関節症)					
Mild	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Plantar fasciitis (足底筋膜炎)					
Mild	2 (1.1%)	0	0	0	0
Arthritis (関節炎)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Fasciitis (筋膜炎)					
Mild	1 (0.5%)	0	0	0	0
Intervertebral disc degeneration (椎間板変性症)					
Moderate	0	0	1 (0.6%)	0	1 (0.3%)
Intervertebral disc protrusion (椎間板突出)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Joint swelling (関節腫脹)					
Mild	1 (0.5%)	0	0	0	0
Mastication disorder (咀嚼障害)					
Moderate	0	0	0	1 (1.3%)	1 (0.3%)
Muscular weakness (筋力低下)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Musculoskeletal chest pain (筋骨格系胸痛)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Myalgia (筋肉痛)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Neck pain (頚部痛)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Osteoporosis (骨粗鬆症)					
Mild	1 (0.5%)	0	0	0	0
Pain in extremity (四肢痛)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Spinal osteoarthritis (変形性脊椎症)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Spondylolisthesis (脊椎すべり症)					
Mild	1 (0.5%)	0	0	0	0
Temporomandibular joint syndrome (顎関節症候群)					
Moderate	0	0	0	1 (1.3%)	1 (0.3%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)					
Mild	4 (2.2%)	5 (6.7%)	5 (2.8%)	4 (5.3%)	14 (4.2%)
Moderate	1 (0.5%)	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Severe	1 (0.5%)	0	2 (1.1%)	0	2 (0.6%)
Contusion (挫傷)					
Mild	1 (0.5%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Arthropod sting (節足動物刺傷)					
Mild	0	2 (2.7%)	0	2 (2.7%)	4 (1.2%)
Hand fracture (手骨折)					
Mild	0	1 (1.3%)	0	1 (1.3%)	2 (0.6%)
Ligament sprain (靱帯捻挫)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Moderate	0	0	0	1 (1.3%)	1 (0.3%)
Radius fracture (橈骨骨折)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Severe	0	0	1 (0.6%)	0	1 (0.3%)
Skin abrasion (皮膚擦過傷)					
Mild	0	0	2 (1.1%)	0	2 (0.6%)
Arthropod bite (節足動物咬傷)					
Mild	1 (0.5%)	0	0	0	0
Bone contusion (骨挫傷)					
Moderate	0	0	0	1 (1.3%)	1 (0.3%)
Clavicle fracture (鎖骨骨折)					
Moderate	0	0	1 (0.6%)	0	1 (0.3%)
Fall (転倒)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Femur fracture (大腿骨骨折)					
Severe	0	0	1 (0.6%)	0	1 (0.3%)
Limb injury (四肢損傷)					
Mild	1 (0.5%)	0	0	0	0
Lower limb fracture (下肢骨折)					
Severe	1 (0.5%)	0	0	0	0
Meniscus injury (半月板損傷)					
Moderate	1 (0.5%)	0	0	0	0
Muscle rupture (筋断裂)					
Mild	1 (0.5%)	0	0	0	0
Post procedural haemorrhage (処置後出血)					
Severe	0	0	1 (0.6%)	0	1 (0.3%)
Rib fracture (肋骨骨折)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Thermal burn (熱傷)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)					
Mild	11 (6.0%)	3 (4.0%)	5 (2.8%)	5 (6.7%)	13 (3.9%)
Moderate	1 (0.5%)	0	0	0	0
Eczema (湿疹)					
Mild	2 (1.1%)	2 (2.7%)	2 (1.1%)	3 (4.0%)	7 (2.1%)
Dermatitis contact (接触皮膚炎)					
Mild	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Dyshidrotic eczema (異汗性湿疹)					
Mild	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Ingrowing nail (嵌入爪)					
Mild	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Miliaria (汗疹)					
Mild	1 (0.5%)	1 (1.3%)	0	0	1 (0.3%)
Alopecia areata (円形脱毛症)					
Mild	1 (0.5%)	0	0	0	0
Drug eruption (薬疹)					
Mild	1 (0.5%)	0	0	0	0
Dry skin (皮膚乾燥)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Eczema asteatotic (皮脂欠乏性湿疹)					
Mild	1 (0.5%)	0	0	0	0
Pruritus (そう痒症)					
Mild	1 (0.5%)	0	0	0	0
Pustular psoriasis (膿疱性乾癬)					
Mild	1 (0.5%)	0	0	0	0
Rash (発疹)					
Mild	1 (0.5%)	0	0	0	0
Toxic skin eruption (中毒性皮疹)					
Moderate	1 (0.5%)	0	0	0	0
Urticaria (蕁麻疹)					
Mild	1 (0.5%)	0	0	0	0
Xanthoma (黄色腫)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Nervous system disorders (神経系障害)					
Mild	9 (4.9%)	5 (6.7%)	4 (2.2%)	1 (1.3%)	10 (3.0%)
Moderate	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Severe	0	0	2 (1.1%)	0	2 (0.6%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Dizziness (浮動性めまい)					
Mild	3 (1.6%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Moderate	1 (0.5%)	0	0	0	0
Headache (頭痛)					
Mild	2 (1.1%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Cervical radiculopathy (頚髄神経根障害)					
Mild	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Dizziness postural (体位性めまい)					
Mild	1 (0.5%)	1 (1.3%)	0	0	1 (0.3%)
Presyncope (失神寸前の状態)					
Moderate	0	0	1 (0.6%)	0	1 (0.3%)
Severe	0	0	1 (0.6%)	0	1 (0.3%)
Carpal tunnel syndrome (手根管症候群)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Dysgeusia (味覚異常)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Hypoaesthesia (感覚鈍麻)					
Mild	1 (0.5%)	0	0	0	0
IVth nerve disorder (第 4 脳神経障害)					
Moderate	0	1 (1.3%)	0	0	1 (0.3%)
Intercostal neuralgia (肋間神経痛)					
Mild	1 (0.5%)	0	0	0	0
Loss of consciousness (意識消失)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Orthostatic intolerance (起立不耐性)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Spondylitic myelopathy (脊椎炎性脊髄症)					
Severe	0	0	1 (0.6%)	0	1 (0.3%)
Thoracic outlet syndrome (胸郭出口症候群)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Investigations (臨床検査)					
Mild	6 (3.3%)	5 (6.7%)	4 (2.2%)	5 (6.7%)	14 (4.2%)
Moderate	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Culture urine positive (尿培養陽性)					
Mild	1 (0.5%)	1 (1.3%)	0	4 (5.3%)	5 (1.5%)
Blood bilirubin increased (血中ビリルビン増加)					
Mild	2 (1.1%)	0	0	0	0

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)					
Mild	2 (1.1%)	0	0	0	0
Gamma-glutamyltransferase increased (γ－グルタミルトランスフェラーゼ増加)					
Mild	1 (0.5%)	0	0	0	0
Moderate	0	0	0	1 (1.3%)	1 (0.3%)
Urine albumin/creatinine ratio increased (尿中アルブミン／クレアチニン比増加)					
Mild	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Activated partial thromboplastin time prolonged (活性化部分トロンボプラスチン時間延長)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Alanine aminotransferase increased (アラニンアミノトランスフェラーゼ増加)					
Mild	1 (0.5%)	0	0	0	0
Aspartate aminotransferase increased (アスパラギン酸アミノトランスフェラーゼ増加)					
Mild	1 (0.5%)	0	0	0	0
Blood glucagon increased (血中グルカゴン増加)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Blood pressure increased (血圧上昇)					
Moderate	1 (0.5%)	0	0	0	0
C-reactive protein increased (Ｃ－反応性蛋白増加)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Electrocardiogram T wave inversion (心電図Ｔ波逆転)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Eosinophil count increased (好酸球数増加)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
International normalised ratio increased (国際標準比増加)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Lipase increased (リパーゼ増加)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Liver function test increased (肝機能検査値上昇)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Neutrophil count decreased (好中球数減少)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Occult blood (便潜血)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)					
Mild	5 (2.7%)	1 (1.3%)	4 (2.2%)	5 (6.7%)	10 (3.0%)
Fatigue (疲労)					
Mild	1 (0.5%)	0	2 (1.1%)	2 (2.7%)	4 (1.2%)
Malaise (倦怠感)					
Mild	1 (0.5%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Pyrexia (発熱)					
Mild	2 (1.1%)	0	0	0	0
Chest discomfort (胸部不快感)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Feeling abnormal (異常感)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Oedema peripheral (末梢性浮腫)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Thirst (口渇)					
Mild	1 (0.5%)	0	0	0	0
Eye disorders (眼障害)					
Mild	4 (2.2%)	2 (2.7%)	4 (2.2%)	3 (4.0%)	9 (2.7%)
Cataract (白内障)					
Mild	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Chalazion (霰粒腫)					
Mild	0	1 (1.3%)	0	1 (1.3%)	2 (0.6%)
Diabetic retinopathy (糖尿病網膜症)					
Mild	0	0	2 (1.1%)	0	2 (0.6%)
Glaucoma (緑内障)					
Mild	0	0	2 (1.1%)	0	2 (0.6%)
Vitreous floaters (硝子体浮遊物)					
Mild	2 (1.1%)	0	0	0	0
Dry eye (眼乾燥)					
Mild	1 (0.5%)	0	0	0	0
Eye inflammation (眼の炎症)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Eye swelling (眼部腫脹)					

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Macular fibrosis (黄斑線維症)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)					
Mild	3 (1.6%)	3 (4.0%)	0	2 (2.7%)	5 (1.5%)
Moderate	1 (0.5%)	0	0	0	0
Oropharyngeal pain (口腔咽頭痛)					
Mild	1 (0.5%)	0	0	2 (2.7%)	2 (0.6%)
Upper respiratory tract inflammation (上気道の炎症)					
Mild	2 (1.1%)	1 (1.3%)	0	0	1 (0.3%)
Rhinitis allergic (アレルギー性鼻炎)					
Mild	0	2 (2.7%)	0	0	2 (0.6%)
Allergic cough (アレルギー性咳嗽)					
Moderate	1 (0.5%)	0	0	0	0
Asthma (喘息)					
Mild	1 (0.5%)	0	0	0	0
Cardiac disorders (心臓障害)					
Mild	2 (1.1%)	0	1 (0.6%)	3 (4.0%)	4 (1.2%)
Severe	0	0	1 (0.6%)	0	1 (0.3%)
Palpitations (動悸)					
Mild	2 (1.1%)	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Atrial fibrillation (心房細動)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Bradycardia (徐脈)					
Severe	0	0	1 (0.6%)	0	1 (0.3%)
Ventricular extrasystoles (心室性期外収縮)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Vascular disorders (血管障害)					
Mild	3 (1.6%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Hypertension (高血圧)					
Mild	2 (1.1%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Arteriosclerosis (動脈硬化症)					
Mild	1 (0.5%)	0	0	0	0
Ear and labyrinth disorders (耳および迷路障害)					
Mild	0	0	2 (1.1%)	3 (4.0%)	5 (1.5%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Moderate	1 (0.5%)	0	0	0	0
Vertigo (回転性めまい)					
Mild	0	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Ear congestion (耳閉)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Eustachian tube stenosis (耳管狭窄)					
Moderate	1 (0.5%)	0	0	0	0
Vertigo positional (頭位性回転性めまい)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Hepatobiliary disorders (肝胆道系障害)					
Mild	3 (1.6%)	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Hepatic steatosis (脂肪肝)					
Mild	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Gallbladder polyp (胆嚢ポリープ)					
Mild	1 (0.5%)	0	0	0	0
Hepatic function abnormal (肝機能異常)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Hepatomegaly (肝腫大)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Liver injury (肝損傷)					
Mild	1 (0.5%)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Moderate	0	0	1 (0.6%)	0	1 (0.3%)
Severe	0	0	2 (1.1%)	1 (1.3%)	3 (0.9%)
Bladder cancer (膀胱癌)					
Moderate	0	0	1 (0.6%)	0	1 (0.3%)
Pancreatic carcinoma metastatic (遠隔転移を伴う膵癌)					
Severe	0	0	0	1 (1.3%)	1 (0.3%)
Prostate cancer (前立腺癌)					
Severe	0	0	1 (0.6%)	0	1 (0.3%)
Seborrhoeic keratosis (脂漏性角化症)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Solid pseudopapillary tumour of the pancreas (膵の充実性偽乳頭状腫瘍)					
Severe	0	0	1 (0.6%)	0	1 (0.3%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Psychiatric disorders (精神障害)					
Mild	1 (0.5%)	1 (1.3%)	0	1 (1.3%)	2 (0.6%)
Insomnia (不眠症)					
Mild	0	1 (1.3%)	0	1 (1.3%)	2 (0.6%)
Anxiety (不安)					
Mild	1 (0.5%)	0	0	0	0
Renal and urinary disorders (腎および尿路障害)					
Mild	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Calculus urinary (尿路結石)					
Mild	1 (0.5%)	0	0	0	0
Diabetic nephropathy (糖尿病性腎症)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Ureterolithiasis (尿管結石症)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Reproductive system and breast disorders (生殖系および乳房障害)					
Mild	2 (1.1%)	1 (1.3%)	0	0	1 (0.3%)
Benign prostatic hyperplasia (良性前立腺肥大症)					
Mild	1 (0.5%)	0	0	0	0
Dysmenorrhoea (月経困難症)					
Mild	1 (0.5%)	0	0	0	0
Metrorrhagia (不正子宮出血)					
Mild	0	1 (1.3%)	0	0	1 (0.3%)
Prostatitis (前立腺炎)					
Mild	1 (0.5%)	0	0	0	0
Blood and lymphatic system disorders (血液およびリンパ系障害)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Anaemia (貧血)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Endocrine disorders (内分泌障害)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Thyroid cyst (甲状腺嚢腫)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)
Thyroid mass (甲状腺腫瘤)					
Mild	0	0	0	1 (1.3%)	1 (0.3%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Social circumstances (社会環境)					
Mild	1 (0.5%)	0	0	0	0
Menopause (閉経)					
Mild	1 (0.5%)	0	0	0	0
Surgical and medical procedures (外科および内科処置)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)
Blepharoplasty (眼瞼形成)					
Mild	0	0	1 (0.6%)	0	1 (0.3%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once by the maximum severity.
- Percentages are based on Population N.

Control No:<<t-s-061-aesev-24wdb.sas, 2020-03-06T00:08:39>>

Table S-063 Summary of Treatment Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any TEAE											
Mild	87 (64.9%)	83 (65.4%)	49 (76.6%)	41 (64.1%)	29 (45.3%)	38 (58.5%)	41 (65.1%)	50 (71.4%)	44 (69.8%)	375 (64.7%)	462 (64.7%)
Moderate	9 (6.7%)	14 (11.0%)	5 (7.8%)	3 (4.7%)	3 (4.7%)	11 (16.9%)	8 (12.7%)	4 (5.7%)	3 (4.8%)	51 (8.8%)	60 (8.4%)
Severe	2 (1.5%)	5 (3.9%)	0	4 (6.3%)	1 (1.6%)	1 (1.5%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	15 (2.6%)	17 (2.4%)
Infections and infestations (感染症および寄生虫症)											
Mild	53 (39.6%)	53 (41.7%)	35 (54.7%)	26 (40.6%)	13 (20.3%)	27 (41.5%)	26 (41.3%)	29 (41.4%)	27 (42.9%)	236 (40.7%)	289 (40.5%)
Moderate	3 (2.2%)	4 (3.1%)	2 (3.1%)	1 (1.6%)	0	5 (7.7%)	2 (3.2%)	1 (1.4%)	1 (1.6%)	16 (2.8%)	19 (2.7%)
Severe	1 (0.7%)	0	0	1 (1.6%)	0	0	0	0	1 (1.6%)	2 (0.3%)	3 (0.4%)
Nasopharyngitis (上咽頭炎)											
Mild	40 (29.9%)	39 (30.7%)	27 (42.2%)	16 (25.0%)	5 (7.8%)	17 (26.2%)	18 (28.6%)	20 (28.6%)	19 (30.2%)	161 (27.8%)	201 (28.2%)
Moderate	0	0	0	0	0	1 (1.5%)	1 (1.6%)	0	1 (1.6%)	3 (0.5%)	3 (0.4%)
Pharyngitis (咽頭炎)											
Mild	8 (6.0%)	5 (3.9%)	4 (6.3%)	0	2 (3.1%)	3 (4.6%)	3 (4.8%)	1 (1.4%)	5 (7.9%)	23 (4.0%)	31 (4.3%)
Influenza (インフルエンザ)											
Mild	2 (1.5%)	6 (4.7%)	2 (3.1%)	4 (6.3%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	1 (1.4%)	2 (3.2%)	19 (3.3%)	21 (2.9%)
Moderate	2 (1.5%)	3 (2.4%)	0	1 (1.6%)	0	1 (1.5%)	0	0	0	5 (0.9%)	7 (1.0%)
Bronchitis (気管支炎)											
Mild	1 (0.7%)	1 (0.8%)	4 (6.3%)	2 (3.1%)	0	4 (6.2%)	0	0	2 (3.2%)	13 (2.2%)	14 (2.0%)
Gastroenteritis (胃腸炎)											
Mild	2 (1.5%)	0	2 (3.1%)	3 (4.7%)	1 (1.6%)	1 (1.5%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	11 (1.9%)	13 (1.8%)
Moderate	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Periodontitis (歯周炎)											

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Mild	0	3 (2.4%)	1 (1.6%)	2 (3.1%)	0	3 (4.6%)	2 (3.2%)	1 (1.4%)	0	12 (2.1%)	12 (1.7%)
Cystitis (膀胱炎)											
Mild	1 (0.7%)	2 (1.6%)	2 (3.1%)	0	0	1 (1.5%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	10 (1.7%)	11 (1.5%)
Herpes zoster (帯状疱疹)											
Mild	1 (0.7%)	1 (0.8%)	1 (1.6%)	0	0	0	1 (1.6%)	0	2 (3.2%)	5 (0.9%)	6 (0.8%)
Moderate	1 (0.7%)	0	0	0	0	1 (1.5%)	0	1 (1.4%)	0	2 (0.3%)	3 (0.4%)
Upper respiratory tract infection (上気道感染)											
Mild	2 (1.5%)	1 (0.8%)	0	0	0	0	2 (3.2%)	0	1 (1.6%)	4 (0.7%)	6 (0.8%)
Pneumonia (肺炎)											
Mild	0	1 (0.8%)	0	1 (1.6%)	0	1 (1.5%)	0	0	0	3 (0.5%)	3 (0.4%)
Moderate	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Severe	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Tinea pedis (足部白癬)											
Mild	0	1 (0.8%)	0	0	1 (1.6%)	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	5 (0.9%)	5 (0.7%)
Urinary tract infection (尿路感染)											
Mild	0	0	0	0	3 (4.7%)	2 (3.1%)	0	0	0	5 (0.9%)	5 (0.7%)
Conjunctivitis (結膜炎)											
Mild	1 (0.7%)	2 (1.6%)	0	0	0	1 (1.5%)	0	0	0	3 (0.5%)	4 (0.6%)
Gingivitis (歯肉炎)											
Mild	0	1 (0.8%)	0	0	0	1 (1.5%)	0	2 (2.9%)	0	4 (0.7%)	4 (0.6%)
Otitis externa (外耳炎)											
Mild	2 (1.5%)	1 (0.8%)	0	0	0	1 (1.5%)	0	0	0	2 (0.3%)	4 (0.6%)
Pericoronitis (歯冠周囲炎)											
Mild	0	0	0	0	1 (1.6%)	0	0	2 (2.9%)	1 (1.6%)	4 (0.7%)	4 (0.6%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Dermatophytosis of nail (爪の皮膚糸状菌症)											
Mild	0	1 (0.8%)	0	0	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Oral herpes (口腔ヘルペス)											
Mild	0	1 (0.8%)	1 (1.6%)	0	0	0	1 (1.6%)	0	0	3 (0.5%)	3 (0.4%)
Sinusitis (副鼻腔炎)											
Mild	0	1 (0.8%)	0	1 (1.6%)	1 (1.6%)	0	0	0	0	3 (0.5%)	3 (0.4%)
Appendicitis (虫垂炎)											
Severe	1 (0.7%)	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	2 (0.3%)
Asymptomatic bacteriuria (無症候性細菌尿)											
Mild	0	1 (0.8%)	0	0	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Chronic sinusitis (慢性副鼻腔炎)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	1 (1.6%)	2 (0.3%)	2 (0.3%)
Diverticulitis (憩室炎)											
Mild	0	0	0	1 (1.6%)	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Enteritis infectious (感染性腸炎)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Folliculitis (毛包炎)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	2 (0.3%)

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Gastroenteritis viral (ウイルス性胃腸炎)											
Mild	0	0	0	1 (1.6%)	1 (1.6%)	0	0	0	0	2 (0.3%)	2 (0.3%)
Helicobacter infection (ヘリコバクター感染)											
Mild	0	0	0	1 (1.6%)	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Impetigo (膿痂疹)											
Mild	0	1 (0.8%)	0	0	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Otitis media (中耳炎)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	1 (1.6%)	2 (0.3%)	2 (0.3%)
Otitis media acute (急性中耳炎)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Moderate	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Paronychia (爪囲炎)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Moderate	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Pneumonia bacterial (細菌性肺炎)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Moderate	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Pulpitis dental (歯髄炎)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	1 (1.6%)	2 (0.3%)	2 (0.3%)
Rhinitis (鼻炎)											
Mild	0	1 (0.8%)	0	0	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)

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Acute sinusitis (急性副鼻腔炎)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Bacterial vulvovaginitis (細菌性外陰腟炎)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Cellulitis (蜂巣炎)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Eczema impetiginous (膿痂疹性湿疹)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Endometritis (子宮内膜炎)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Enterocolitis viral (ウイルス性腸炎)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Furuncle (せつ)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Nasal vestibulitis (鼻前庭炎)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Skin bacterial infection (皮膚細菌感染)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Skin infection (皮膚感染)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

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Streptococcal infection (レンサ球菌感染)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Subcutaneous abscess (皮下組織膿瘍)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Tinea infection (白癬感染)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Vaginal infection (腟感染)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorders (胃腸障害)											
Mild	27 (20.1%)	26 (20.5%)	11 (17.2%)	23 (35.9%)	3 (4.7%)	6 (9.2%)	19 (30.2%)	14 (20.0%)	15 (23.8%)	117 (20.2%)	144 (20.2%)
Moderate	2 (1.5%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	2 (3.1%)	3 (4.6%)	2 (3.2%)	0	0	11 (1.9%)	13 (1.8%)
Severe	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Nausea (悪心)											
Mild	7 (5.2%)	1 (0.8%)	0	6 (9.4%)	1 (1.6%)	0	4 (6.3%)	3 (4.3%)	4 (6.3%)	19 (3.3%)	26 (3.6%)
Moderate	2 (1.5%)	0	0	1 (1.6%)	0	1 (1.5%)	1 (1.6%)	0	0	3 (0.5%)	5 (0.7%)
Severe	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Diarrhoea (下痢)											
Mild	4 (3.0%)	3 (2.4%)	3 (4.7%)	11 (17.2%)	0	1 (1.5%)	2 (3.2%)	3 (4.3%)	2 (3.2%)	25 (4.3%)	29 (4.1%)
Moderate	0	0	1 (1.6%)	0	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Constipation (便秘)											
Mild	5 (3.7%)	8 (6.3%)	2 (3.1%)	1 (1.6%)	1 (1.6%)	1 (1.5%)	5 (7.9%)	1 (1.4%)	2 (3.2%)	21 (3.6%)	26 (3.6%)
Moderate	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)

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Gastrooesophageal reflux disease (胃食道逆流性疾患)											
Mild	3 (2.2%)	8 (6.3%)	1 (1.6%)	2 (3.1%)	0	0	0	1 (1.4%)	0	12 (2.1%)	15 (2.1%)
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Abdominal pain upper (上腹部痛)											
Mild	4 (3.0%)	1 (0.8%)	1 (1.6%)	3 (4.7%)	0	0	2 (3.2%)	1 (1.4%)	0	8 (1.4%)	12 (1.7%)
Dental caries (齲歯)											
Mild	5 (3.7%)	0	1 (1.6%)	1 (1.6%)	0	3 (4.6%)	2 (3.2%)	0	0	7 (1.2%)	12 (1.7%)
Vomiting (嘔吐)											
Mild	1 (0.7%)	0	0	3 (4.7%)	0	1 (1.5%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	9 (1.6%)	10 (1.4%)
Moderate	0	0	0	1 (1.6%)	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Abdominal discomfort (腹部不快感)											
Mild	0	2 (1.6%)	1 (1.6%)	3 (4.7%)	1 (1.6%)	0	2 (3.2%)	0	0	9 (1.6%)	9 (1.3%)
Chronic gastritis (慢性胃炎)											
Mild	0	2 (1.6%)	0	1 (1.6%)	0	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	6 (1.0%)	6 (0.8%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Dyspepsia (消化不良)											
Mild	0	2 (1.6%)	1 (1.6%)	0	0	0	2 (3.2%)	2 (2.9%)	0	7 (1.2%)	7 (1.0%)
Faeces soft (軟便)											
Mild	1 (0.7%)	1 (0.8%)	1 (1.6%)	2 (3.1%)	0	0	0	0	1 (1.6%)	5 (0.9%)	6 (0.8%)
Large intestine polyp (大腸ポリープ)											
Mild	1 (0.7%)	0	0	2 (3.1%)	0	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	5 (0.9%)	6 (0.8%)

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Abdominal pain (腹痛)											
Mild	0	1 (0.8%)	1 (1.6%)	0	0	0	1 (1.6%)	0	1 (1.6%)	4 (0.7%)	4 (0.6%)
Gastritis (胃炎)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	2 (3.2%)	3 (0.5%)	3 (0.4%)
Moderate	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Abdominal distension (腹部膨満)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	2 (3.2%)	3 (0.5%)	3 (0.4%)
Aphthous ulcer (アフタ性潰瘍)											
Mild	1 (0.7%)	0	0	1 (1.6%)	0	0	1 (1.6%)	0	0	2 (0.3%)	3 (0.4%)
Food poisoning (食中毒)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	2 (0.3%)
Abdominal pain lower (下腹部痛)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Change of bowel habit (便習慣変化)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Colitis (大腸炎)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Colitis ulcerative (潰瘍性大腸炎)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)

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Diverticulum intestinal (腸憩室)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Enteritis (小腸炎)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Enterocolitis (腸炎)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Enterovesical fistula (腸膀胱瘻)											
Moderate	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Epigastric discomfort (心窩部不快感)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Flatulence (鼓腸)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Gastric polyps (胃ポリープ)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Gastritis erosive (びらん性胃炎)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorder (胃腸障害)											
Mild	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Glossitis (舌炎)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)

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Haematochezia (血便排泄)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Inguinal hernia (鼠径ヘルニア)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Irritable bowel syndrome (過敏性腸症候群)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Lower gastrointestinal haemorrhage (下部消化管出血)											
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Mouth ulceration (口腔内潰瘍形成)											
Mild	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Pancreatic steatosis (膵脂肪変性)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Periodontal disease (歯周病)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Stomatitis (口内炎)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Tooth loss (歯の脱落)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Toothache (歯痛)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)											
Mild	14 (10.4%)	20 (15.7%)	10 (15.6%)	7 (10.9%)	5 (7.8%)	5 (7.7%)	16 (25.4%)	10 (14.3%)	4 (6.3%)	77 (13.3%)	91 (12.7%)
Moderate	1 (0.7%)	2 (1.6%)	0	0	1 (1.6%)	1 (1.5%)	0	1 (1.4%)	0	5 (0.9%)	6 (0.8%)
Back pain (背部痛)											
Mild	5 (3.7%)	9 (7.1%)	3 (4.7%)	1 (1.6%)	1 (1.6%)	3 (4.6%)	1 (1.6%)	0	0	18 (3.1%)	23 (3.2%)
Moderate	0	1 (0.8%)	0	0	1 (1.6%)	1 (1.5%)	0	0	0	3 (0.5%)	3 (0.4%)
Arthralgia (関節痛)											
Mild	1 (0.7%)	3 (2.4%)	0	2 (3.1%)	0	2 (3.1%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	12 (2.1%)	13 (1.8%)
Pain in extremity (四肢痛)											
Mild	1 (0.7%)	3 (2.4%)	2 (3.1%)	0	0	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	8 (1.4%)	9 (1.3%)
Myalgia (筋肉痛)											
Mild	2 (1.5%)	1 (0.8%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	0	0	0	2 (3.2%)	6 (1.0%)	8 (1.1%)
Spinal osteoarthritis (変形性脊椎症)											
Mild	0	0	0	0	1 (1.6%)	0	4 (6.3%)	1 (1.4%)	1 (1.6%)	7 (1.2%)	7 (1.0%)
Moderate	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Intervertebral disc protrusion (椎間板突出)											
Mild	0	0	1 (1.6%)	0	1 (1.6%)	0	4 (6.3%)	1 (1.4%)	0	7 (1.2%)	7 (1.0%)
Osteoarthritis (変形性関節症)											
Mild	2 (1.5%)	0	1 (1.6%)	1 (1.6%)	0	0	2 (3.2%)	0	0	4 (0.7%)	6 (0.8%)
Periarthritis (関節周囲炎)											
Mild	1 (0.7%)	1 (0.8%)	1 (1.6%)	0	0	0	1 (1.6%)	1 (1.4%)	0	4 (0.7%)	5 (0.7%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Lumbar spinal stenosis (腰部脊柱管狭窄症)											
Mild	0	0	0	0	0	0	1 (1.6%)	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Moderate	1 (0.7%)	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	2 (0.3%)
Muscle spasms (筋痙縮)											
Mild	0	1 (0.8%)	2 (3.1%)	0	0	0	1 (1.6%)	0	0	4 (0.7%)	4 (0.6%)
Musculoskeletal stiffness (筋骨格硬直)											
Mild	0	2 (1.6%)	2 (3.1%)	0	0	0	0	0	0	4 (0.7%)	4 (0.6%)
Trigger finger (弾発指)											
Mild	0	0	0	0	0	0	2 (3.2%)	2 (2.9%)	0	4 (0.7%)	4 (0.6%)
Musculoskeletal pain (筋骨格痛)											
Mild	2 (1.5%)	0	0	0	0	0	0	0	0	0	2 (0.3%)
Neck pain (頚部痛)											
Mild	0	0	0	0	1 (1.6%)	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Arthritis (関節炎)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Flank pain (側腹部痛)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Joint contracture (関節拘縮)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Plantar fasciitis (足底筋膜炎)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Spondylolisthesis (脊椎すべり症)											
Moderate	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Synovitis (滑膜炎)											
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Temporomandibular joint syndrome (顎関節症候群)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Tendon pain (腱痛)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Metabolism and nutrition disorders (代謝および栄養障害)											
Mild	13 (9.7%)	28 (22.0%)	10 (15.6%)	7 (10.9%)	4 (6.3%)	4 (6.2%)	8 (12.7%)	13 (18.6%)	6 (9.5%)	80 (13.8%)	93 (13.0%)
Moderate	0	0	0	1 (1.6%)	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Hypoglycaemia (低血糖)											
Mild	5 (3.7%)	21 (16.5%)	9 (14.1%)	6 (9.4%)	2 (3.1%)	2 (3.1%)	5 (7.9%)	2 (2.9%)	4 (6.3%)	51 (8.8%)	56 (7.8%)
Hyperglycaemia (高血糖)											
Mild	5 (3.7%)	7 (5.5%)	0	0	1 (1.6%)	1 (1.5%)	2 (3.2%)	8 (11.4%)	1 (1.6%)	20 (3.4%)	25 (3.5%)
Decreased appetite (食欲減退)											
Mild	3 (2.2%)	0	0	1 (1.6%)	0	1 (1.5%)	2 (3.2%)	3 (4.3%)	1 (1.6%)	8 (1.4%)	11 (1.5%)
Moderate	0	0	0	1 (1.6%)	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Hyperuricaemia (高尿酸血症)											
Mild	0	2 (1.6%)	0	0	0	0	0	0	1 (1.6%)	3 (0.5%)	3 (0.4%)
Dehydration (脱水)											
Mild	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Dyslipidaemia (脂質異常症)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Gout (痛風)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)											
Mild	8 (6.0%)	6 (4.7%)	7 (10.9%)	5 (7.8%)	3 (4.7%)	5 (7.7%)	10 (15.9%)	6 (8.6%)	3 (4.8%)	45 (7.8%)	53 (7.4%)
Moderate	2 (1.5%)	4 (3.1%)	1 (1.6%)	0	1 (1.6%)	0	3 (4.8%)	1 (1.4%)	1 (1.6%)	11 (1.9%)	13 (1.8%)
Severe	1 (0.7%)	3 (2.4%)	0	0	0	1 (1.5%)	1 (1.6%)	0	0	5 (0.9%)	6 (0.8%)
Contusion (挫傷)											
Mild	3 (2.2%)	2 (1.6%)	0	2 (3.1%)	0	0	3 (4.8%)	0	0	7 (1.2%)	10 (1.4%)
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Ligament sprain (靱帯捻挫)											
Mild	1 (0.7%)	1 (0.8%)	2 (3.1%)	0	0	1 (1.5%)	0	1 (1.4%)	0	5 (0.9%)	6 (0.8%)
Thermal burn (熱傷)											
Mild	1 (0.7%)	0	0	2 (3.1%)	0	0	0	1 (1.4%)	0	3 (0.5%)	4 (0.6%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Heat illness (熱中症)											
Mild	0	0	1 (1.6%)	0	0	0	1 (1.6%)	1 (1.4%)	0	3 (0.5%)	3 (0.4%)
Moderate	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Rib fracture (肋骨骨折)											
Mild	0	2 (1.6%)	0	0	0	0	1 (1.6%)	0	1 (1.6%)	4 (0.7%)	4 (0.6%)
Wound (創傷)											
Mild	2 (1.5%)	0	0	0	0	1 (1.5%)	0	1 (1.4%)	0	2 (0.3%)	4 (0.6%)

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Arthropod bite (節足動物咬傷)											
Mild	0	0	1 (1.6%)	0	0	0	1 (1.6%)	1 (1.4%)	0	3 (0.5%)	3 (0.4%)
Arthropod sting (節足動物刺傷)											
Mild	0	0	0	1 (1.6%)	1 (1.6%)	0	1 (1.6%)	0	0	3 (0.5%)	3 (0.4%)
Foot fracture (足骨折)											
Mild	0	0	1 (1.6%)	0	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Radius fracture (橈骨骨折)											
Mild	1 (0.7%)	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	2 (0.3%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Avulsion fracture (剥離骨折)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	1 (1.6%)	2 (0.3%)	2 (0.3%)
Hand fracture (手骨折)											
Moderate	0	0	1 (1.6%)	0	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Ligament injury (靱帯損傷)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Moderate	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Muscle strain (肉離れ)											
Mild	1 (0.7%)	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	2 (0.3%)
Tendon rupture (腱断裂)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Moderate	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Animal bite (動物咬傷)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)

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Clavicle fracture (鎖骨骨折)											
Severe	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Closed globe injury (閉鎖性眼球損傷)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Concussion (脳振盪)											
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Craniocerebral injury (頭蓋脳損傷)											
Severe	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Epicondylitis (上顆炎)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Fractured coccyx (尾骨骨折)											
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Fractured ischium (坐骨骨折)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Heat stroke (熱射病)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Laceration (裂傷)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Lower limb fracture (下肢骨折)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Meniscus injury (半月板損傷)											
Mild	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)

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Multiple fractures (多発骨折)											
Severe	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Nasal injury (鼻部損傷)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Pneumothorax traumatic (外傷性気胸)											
Severe	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Post procedural haemorrhage (処置後出血)											
Moderate	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Post-traumatic neck syndrome (外傷後頚部症候群)											
Mild	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Procedural pain (処置による疼痛)											
Mild	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Pubis fracture (恥骨骨折)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Skin abrasion (皮膚擦過傷)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Spinal compression fracture (脊椎圧迫骨折)											
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Spinal fracture (脊椎骨折)											
Moderate	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)

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Subarachnoid haemorrhage (くも膜下出血)											
Severe	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Subdural haematoma (硬膜下血腫)											
Severe	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Tooth fracture (歯牙破折)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Traumatic intracranial haemorrhage (外傷性頭蓋内出血)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)											
Mild	4 (3.0%)	10 (7.9%)	6 (9.4%)	3 (4.7%)	0	4 (6.2%)	12 (19.0%)	7 (10.0%)	5 (7.9%)	47 (8.1%)	51 (7.1%)
Eczema (湿疹)											
Mild	2 (1.5%)	4 (3.1%)	3 (4.7%)	0	0	1 (1.5%)	5 (7.9%)	4 (5.7%)	2 (3.2%)	19 (3.3%)	21 (2.9%)
Acne (ざ瘡)											
Mild	0	1 (0.8%)	2 (3.1%)	1 (1.6%)	0	0	0	0	0	4 (0.7%)	4 (0.6%)
Dermal cyst (皮膚嚢腫)											
Mild	0	1 (0.8%)	1 (1.6%)	0	0	0	1 (1.6%)	0	0	3 (0.5%)	3 (0.4%)
Hyperkeratosis (過角化)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	2 (3.2%)	3 (0.5%)	3 (0.4%)

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Dermatitis (皮膚炎)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	2 (0.3%)
Drug eruption (薬疹)											
Mild	0	0	0	1 (1.6%)	0	0	1 (1.6%)	0	0	2 (0.3%)	2 (0.3%)
Dry skin (皮膚乾燥)											
Mild	0	0	0	1 (1.6%)	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Eczema asteatotic (皮脂欠乏性湿疹)											
Mild	0	2 (1.6%)	0	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Rash (発疹)											
Mild	1 (0.7%)	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	2 (0.3%)
Asteatosis (皮脂欠乏症)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Dermatitis allergic (アレルギー性皮膚炎)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Dyshidrotic eczema (異汗性湿疹)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Erythema (紅斑)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Haemorrhage subcutaneous (皮下出血)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Leukoderma (白斑)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Miliaria (汗疹)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Nail disorder (爪の障害)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Pruritus (そう痒症)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Seborrhoeic dermatitis (脂漏性皮膚炎)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Skin mass (皮膚腫瘤)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Urticaria (蕁麻疹)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)											
Mild	7 (5.2%)	13 (10.2%)	4 (6.3%)	1 (1.6%)	5 (7.8%)	5 (7.7%)	2 (3.2%)	2 (2.9%)	5 (7.9%)	37 (6.4%)	44 (6.2%)
Upper respiratory tract inflammation (上気道の炎症)											
Mild	1 (0.7%)	1 (0.8%)	2 (3.1%)	0	1 (1.6%)	2 (3.1%)	2 (3.2%)	0	3 (4.8%)	11 (1.9%)	12 (1.7%)
Cough (咳嗽)											
Mild	3 (2.2%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	0	1 (1.5%)	0	1 (1.4%)	0	6 (1.0%)	9 (1.3%)
Oropharyngeal pain (口腔咽頭痛)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mild	1 (0.7%)	1 (0.8%)	0	0	0	1 (1.5%)	0	1 (1.4%)	1 (1.6%)	4 (0.7%)	5 (0.7%)
Rhinitis allergic (アレルギー性鼻炎)											
Mild	0	1 (0.8%)	1 (1.6%)	0	1 (1.6%)	1 (1.5%)	1 (1.6%)	0	0	5 (0.9%)	5 (0.7%)
Asthma (喘息)											
Mild	0	1 (0.8%)	0	0	1 (1.6%)	1 (1.5%)	0	0	1 (1.6%)	4 (0.7%)	4 (0.6%)
Bronchitis chronic (慢性気管支炎)											
Mild	0	2 (1.6%)	0	0	1 (1.6%)	0	0	0	0	3 (0.5%)	3 (0.4%)
Epistaxis (鼻出血)											
Mild	1 (0.7%)	2 (1.6%)	0	0	0	0	0	0	0	2 (0.3%)	3 (0.4%)
Allergic cough (アレルギー性咳嗽)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Hiccups (しゃっくり)											
Mild	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Nasal congestion (鼻閉)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Pleural thickening (胸膜肥厚)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Productive cough (湿性咳嗽)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Rhinorrhoea (鼻漏)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Eye disorders (眼障害)											
Mild	5 (3.7%)	7 (5.5%)	8 (12.5%)	2 (3.1%)	0	6 (9.2%)	5 (7.9%)	5 (7.1%)	4 (6.3%)	37 (6.4%)	42 (5.9%)
Diabetic retinopathy (糖尿病網膜症)											
Mild	2 (1.5%)	1 (0.8%)	1 (1.6%)	0	0	2 (3.1%)	3 (4.8%)	1 (1.4%)	0	8 (1.4%)	10 (1.4%)
Blepharitis (眼瞼炎)											
Mild	1 (0.7%)	2 (1.6%)	1 (1.6%)	0	0	0	0	0	1 (1.6%)	4 (0.7%)	5 (0.7%)
Dry eye (眼乾燥)											
Mild	1 (0.7%)	1 (0.8%)	1 (1.6%)	0	0	1 (1.5%)	1 (1.6%)	0	0	4 (0.7%)	5 (0.7%)
Asthenopia (眼精疲労)											
Mild	0	1 (0.8%)	2 (3.1%)	0	0	0	0	1 (1.4%)	0	4 (0.7%)	4 (0.6%)
Conjunctivitis allergic (アレルギー性結膜炎)											
Mild	0	0	1 (1.6%)	1 (1.6%)	0	0	0	1 (1.4%)	1 (1.6%)	4 (0.7%)	4 (0.6%)
Cataract (白内障)											
Mild	1 (0.7%)	0	1 (1.6%)	0	0	1 (1.5%)	0	0	0	2 (0.3%)	3 (0.4%)
Glaucoma (緑内障)											
Mild	0	0	1 (1.6%)	0	0	1 (1.5%)	1 (1.6%)	0	0	3 (0.5%)	3 (0.4%)
Ocular hyperaemia (眼充血)											
Mild	0	2 (1.6%)	0	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Posterior capsule opacification (後嚢部混濁)											
Mild	0	1 (0.8%)	0	0	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Arteriosclerotic retinopathy (動脈硬化性網膜症)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Conjunctival haemorrhage (結膜出血)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Diabetic retinal oedema (糖尿病性網膜浮腫)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Eye pain (眼痛)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Macular oedema (黄斑浮腫)											
Mild	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Pingueculitis (瞼裂斑炎)											
Mild	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Retinal haemorrhage (網膜出血)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Retinal vein occlusion (網膜静脈閉塞)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Scintillating scotoma (閃輝暗点)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Nervous system disorders (神経系障害)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mild	7 (5.2%)	3 (2.4%)	5 (7.8%)	2 (3.1%)	4 (6.3%)	6 (9.2%)	4 (6.3%)	3 (4.3%)	3 (4.8%)	30 (5.2%)	37 (5.2%)
Moderate	1 (0.7%)	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	2 (0.3%)
Severe	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Headache (頭痛)											
Mild	2 (1.5%)	1 (0.8%)	1 (1.6%)	0	1 (1.6%)	2 (3.1%)	0	0	1 (1.6%)	6 (1.0%)	8 (1.1%)
Diabetic neuropathy (糖尿病性ニューロパチー)											
Mild	1 (0.7%)	0	0	0	0	0	2 (3.2%)	2 (2.9%)	1 (1.6%)	5 (0.9%)	6 (0.8%)
Carotid arteriosclerosis (頚動脈硬化症)											
Mild	0	0	1 (1.6%)	1 (1.6%)	0	2 (3.1%)	0	0	0	4 (0.7%)	4 (0.6%)
Cervicobrachial syndrome (頚腕症候群)											
Mild	1 (0.7%)	0	0	0	2 (3.1%)	0	0	0	0	2 (0.3%)	3 (0.4%)
Dizziness (浮動性めまい)											
Mild	2 (1.5%)	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	3 (0.4%)
Intercostal neuralgia (肋間神経痛)											
Mild	0	0	3 (4.7%)	0	0	0	0	0	0	3 (0.5%)	3 (0.4%)
Loss of consciousness (意識消失)											
Mild	0	0	0	0	1 (1.6%)	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Sciatica (坐骨神経痛)											
Mild	1 (0.7%)	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	2 (0.3%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Carotid artery stenosis (頚動脈狭窄)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Carpal tunnel syndrome (手根管症候群)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Cerebral infarction (脳梗塞)											
Severe	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Dysaesthesia (異常感覚)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Hypoaesthesia (感覚鈍麻)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Lacunar infarction (ラクナ梗塞)											
Moderate	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Paraesthesia (錯感覚)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Post herpetic neuralgia (ヘルペス後神経痛)											
Moderate	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Presyncope (失神寸前の状態)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Syncope (失神)											
Mild	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Investigations (臨床検査)											
Mild	6 (4.5%)	8 (6.3%)	2 (3.1%)	2 (3.1%)	3 (4.7%)	2 (3.1%)	6 (9.5%)	1 (1.4%)	2 (3.2%)	26 (4.5%)	32 (4.5%)
Lipase increased (リパーゼ増加)											
Mild	1 (0.7%)	2 (1.6%)	0	0	1 (1.6%)	1 (1.5%)	3 (4.8%)	0	0	7 (1.2%)	8 (1.1%)
Weight decreased (体重減少)											
Mild	2 (1.5%)	0	0	1 (1.6%)	1 (1.6%)	0	1 (1.6%)	1 (1.4%)	0	4 (0.7%)	6 (0.8%)
Amylase increased (アミラーゼ増加)											
Mild	0	1 (0.8%)	1 (1.6%)	0	0	1 (1.5%)	1 (1.6%)	0	0	4 (0.7%)	4 (0.6%)
Blood creatine phosphokinase increased (血中クレアチンホスホキナーゼ増加)											
Mild	1 (0.7%)	0	0	0	0	1 (1.5%)	1 (1.6%)	0	0	2 (0.3%)	3 (0.4%)
Hepatic enzyme increased (肝酵素上昇)											
Mild	0	2 (1.6%)	0	0	0	0	0	0	1 (1.6%)	3 (0.5%)	3 (0.4%)
Blood lactic acid increased (血中乳酸増加)											
Mild	0	2 (1.6%)	0	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Gamma-glutamyltransferase increased (γ－グルタミルトランスフェラーゼ増加)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	1 (1.6%)	2 (0.3%)	2 (0.3%)

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Platelet count decreased (血小板数減少)											
Mild	1 (0.7%)	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	2 (0.3%)
Blood creatinine increased (血中クレアチニン増加)											
Mild	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
C-reactive protein increased (C－反応性蛋白増加)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Electrocardiogram repolarisation abnormality (心電図再分極異常)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Intraocular pressure increased (眼圧上昇)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Occult blood (便潜血)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Occult blood positive (便潜血陽性)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
White blood cell count increased (白血球数増加)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Vascular disorders (血管障害)											

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Mild	2 (1.5%)	7 (5.5%)	2 (3.1%)	1 (1.6%)	4 (6.3%)	3 (4.6%)	0	2 (2.9%)	1 (1.6%)	20 (3.4%)	22 (3.1%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Hypertension (高血圧)											
Mild	0	7 (5.5%)	2 (3.1%)	1 (1.6%)	3 (4.7%)	3 (4.6%)	0	2 (2.9%)	1 (1.6%)	19 (3.3%)	19 (2.7%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Orthostatic hypotension (起立性低血圧)											
Mild	1 (0.7%)	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	2 (0.3%)
Arteriosclerosis (動脈硬化症)											
Mild	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Hypotension (低血圧)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Renal and urinary disorders (腎および尿路障害)											
Mild	1 (0.7%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	3 (4.7%)	3 (4.6%)	3 (4.8%)	4 (5.7%)	3 (4.8%)	20 (3.4%)	21 (2.9%)
Diabetic nephropathy (糖尿病性腎症)											
Mild	0	1 (0.8%)	0	1 (1.6%)	2 (3.1%)	1 (1.5%)	1 (1.6%)	0	1 (1.6%)	7 (1.2%)	7 (1.0%)
Nephrolithiasis (腎結石症)											
Mild	1 (0.7%)	0	0	0	2 (3.1%)	2 (3.1%)	1 (1.6%)	1 (1.4%)	0	6 (1.0%)	7 (1.0%)
Pollakiuria (頻尿)											
Mild	0	0	0	0	0	0	0	2 (2.9%)	1 (1.6%)	3 (0.5%)	3 (0.4%)
Calculus urinary (尿路結石)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

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Haematuria (血尿)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Hypertonic bladder (緊張性膀胱)											
Mild	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Polyuria (多尿)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Renal cyst (腎嚢胞)											
Mild	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Urinary tract disorder (尿路障害)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Cardiac disorders (心臓障害)											
Mild	2 (1.5%)	1 (0.8%)	0	3 (4.7%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	2 (2.9%)	0	10 (1.7%)	12 (1.7%)
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Severe	0	1 (0.8%)	0	1 (1.6%)	0	0	0	2 (2.9%)	1 (1.6%)	5 (0.9%)	5 (0.7%)
Atrial fibrillation (心房細動)											
Mild	1 (0.7%)	0	0	0	0	1 (1.5%)	1 (1.6%)	1 (1.4%)	0	3 (0.5%)	4 (0.6%)
Angina unstable (不安定狭心症)											
Mild	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Coronary artery stenosis (冠動脈狭窄)											

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Severe	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)
Palpitations (動悸)											
Mild	0	0	0	2 (3.1%)	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Sinus bradycardia (洞性徐脈)											
Mild	0	0	0	0	0	2 (3.1%)	0	0	0	2 (0.3%)	2 (0.3%)
Ventricular extrasystoles (心室性期外収縮)											
Mild	1 (0.7%)	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	2 (0.3%)
Acute myocardial infarction (急性心筋梗塞)											
Severe	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Aortic valve incompetence (大動脈弁閉鎖不全症)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Cardiac aneurysm (心臓瘤)											
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Cardiac failure (心不全)											
Severe	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Extrasystoles (期外収縮)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Myocardial infarction (心筋梗塞)											
Severe	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Myocardial ischaemia (心筋虚血)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Sinus tachycardia (洞性頻脈)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Supraventricular extrasystoles (上室性期外収縮)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)											
Mild	4 (3.0%)	1 (0.8%)	1 (1.6%)	2 (3.1%)	0	1 (1.5%)	4 (6.3%)	1 (1.4%)	2 (3.2%)	12 (2.1%)	16 (2.2%)
Moderate	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Fatigue (疲労)											
Mild	1 (0.7%)	0	1 (1.6%)	0	0	0	2 (3.2%)	0	1 (1.6%)	4 (0.7%)	5 (0.7%)
Chest pain (胸痛)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	1 (1.6%)	2 (0.3%)	2 (0.3%)
Non-cardiac chest pain (非心臓性胸痛)											
Mild	0	0	0	0	0	1 (1.5%)	1 (1.6%)	0	0	2 (0.3%)	2 (0.3%)
Pyrexia (発熱)											
Mild	1 (0.7%)	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	2 (0.3%)
Chest discomfort (胸部不快感)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Early satiety (早期満腹)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Inflammation (炎症)											
Moderate	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Malaise (倦怠感)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Oedema peripheral (末梢性浮腫)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Thirst (口渇)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Psychiatric disorders (精神障害)											
Mild	3 (2.2%)	1 (0.8%)	1 (1.6%)	2 (3.1%)	0	1 (1.5%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	10 (1.7%)	13 (1.8%)
Moderate	0	1 (0.8%)	0	0	0	0	1 (1.6%)	0	0	2 (0.3%)	2 (0.3%)
Insomnia (不眠症)											
Mild	2 (1.5%)	1 (0.8%)	0	2 (3.1%)	0	1 (1.5%)	2 (3.2%)	1 (1.4%)	1 (1.6%)	8 (1.4%)	10 (1.4%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Apathy (無感情)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Depressed mood (抑うつ気分)											
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Depression (うつ病)											
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Mental fatigue (精神疲労)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Stress (ストレス)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Hepatobiliary disorders (肝胆道系障害)											
Mild	0	2 (1.6%)	1 (1.6%)	0	1 (1.6%)	3 (4.6%)	0	5 (7.1%)	1 (1.6%)	13 (2.2%)	13 (1.8%)
Severe	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Hepatic steatosis (脂肪肝)											
Mild	0	1 (0.8%)	1 (1.6%)	0	0	1 (1.5%)	0	2 (2.9%)	0	5 (0.9%)	5 (0.7%)
Alcoholic liver disease (アルコール性肝疾患)											
Mild	0	1 (0.8%)	0	0	0	0	0	2 (2.9%)	0	3 (0.5%)	3 (0.4%)
Cholelithiasis (胆石症)											
Mild	0	0	0	0	1 (1.6%)	0	0	2 (2.9%)	0	3 (0.5%)	3 (0.4%)
Drug-induced liver injury (薬物性肝障害)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	1 (1.6%)	2 (0.3%)	2 (0.3%)
Moderate	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Gallbladder polyp (胆嚢ポリープ)											
Mild	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)
Cholecystitis (胆嚢炎)											
Severe	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Non-alcoholic steatohepatitis (非アルコール性脂肪性肝炎)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Surgical and medical procedures (外科および内科処置)											
Mild	3 (2.2%)	3 (2.4%)	1 (1.6%)	3 (4.7%)	1 (1.6%)	0	0	1 (1.4%)	0	9 (1.6%)	12 (1.7%)
Cataract operation (白内障手術)											
Mild	1 (0.7%)	3 (2.4%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	0	0	0	0	7 (1.2%)	8 (1.1%)
Large intestinal polypectomy (大腸ポリープ切除)											
Mild	0	0	0	1 (1.6%)	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Endodontic procedure (歯内療法)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Ptosis repair (眼瞼下垂修復)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)											
Mild	0	3 (2.4%)	0	0	0	0	0	1 (1.4%)	1 (1.6%)	5 (0.9%)	5 (0.7%)
Moderate	0	0	1 (1.6%)	0	0	1 (1.5%)	1 (1.6%)	1 (1.4%)	0	4 (0.7%)	4 (0.6%)
Severe	0	1 (0.8%)	0	1 (1.6%)	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Benign neoplasm of spinal cord (脊髄の良性新生物)											
Moderate	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Cholangiocarcinoma (胆管細胞癌)											
Severe	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Colon adenoma (大腸腺腫)											
Mild	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Colon cancer stage I (結腸癌第 1 期)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Endometrial cancer stage III (子宮内膜癌第 3 期)											
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Haemangioma of liver (肝臓血管腫)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Invasive ductal breast carcinoma (浸潤性乳管癌)											
Moderate	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Rectal cancer (直腸癌)											
Severe	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Skin papilloma (皮膚乳頭腫)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Testis cancer (精巣癌)											
Moderate	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Thyroid neoplasm (甲状腺新生物)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Uterine leiomyoma (子宮平滑筋腫)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Reproductive system and breast disorders (生殖系および乳房障害)											
Mild	3 (2.2%)	1 (0.8%)	2 (3.1%)	0	1 (1.6%)	0	2 (3.2%)	1 (1.4%)	0	7 (1.2%)	10 (1.4%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Benign prostatic hyperplasia (良性前立腺肥大症)											
Mild	1 (0.7%)	0	2 (3.1%)	0	0	0	0	0	0	2 (0.3%)	3 (0.4%)
Dysmenorrhoea (月経困難症)											
Mild	1 (0.7%)	1 (0.8%)	0	0	0	0	0	1 (1.4%)	0	2 (0.3%)	3 (0.4%)
Erectile dysfunction (勃起不全)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Genital haemorrhage (性器出血)											
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Metrorrhagia (不正子宮出血)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Ovarian cyst (卵巣嚢胞)											
Mild	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Prostatitis (前立腺炎)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Uterine polyp (子宮ポリープ)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Ear and labyrinth disorders (耳および迷路障害)											
Mild	2 (1.5%)	1 (0.8%)	1 (1.6%)	3 (4.7%)	0	1 (1.5%)	0	2 (2.9%)	0	8 (1.4%)	10 (1.4%)
Vertigo (回転性めまい)											
Mild	1 (0.7%)	0	0	2 (3.1%)	0	0	0	1 (1.4%)	0	3 (0.5%)	4 (0.6%)
Tinnitus (耳鳴)											
Mild	0	0	1 (1.6%)	0	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Deafness transitory (一過性難聴)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
External ear inflammation (外耳の炎症)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Middle ear inflammation (中耳の炎症)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Sudden hearing loss (突発性難聴)											
Mild	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Vertigo positional (頭位性回転性めまい)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Immune system disorders (免疫系障害)											
Mild	1 (0.7%)	0	1 (1.6%)	1 (1.6%)	0	1 (1.5%)	0	3 (4.3%)	1 (1.6%)	7 (1.2%)	8 (1.1%)
Moderate	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Seasonal allergy (季節性アレルギー)											
Mild	1 (0.7%)	0	1 (1.6%)	1 (1.6%)	0	1 (1.5%)	0	1 (1.4%)	1 (1.6%)	5 (0.9%)	6 (0.8%)
Allergy to arthropod sting (節足動物刺傷アレルギー)											
Mild	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)
Food allergy (食物アレルギー)											
Moderate	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Blood and lymphatic system disorders (血液およびリンパ系障害)											
Mild	2 (1.5%)	1 (0.8%)	0	1 (1.6%)	0	1 (1.5%)	0	1 (1.4%)	2 (3.2%)	6 (1.0%)	8 (1.1%)
Anaemia (貧血)											
Mild	2 (1.5%)	0	0	0	0	0	0	0	0	0	2 (0.3%)
Lymphadenitis (リンパ節炎)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	1 (1.6%)	2 (0.3%)	2 (0.3%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Anaemia macrocytic (大球性貧血)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Anaemia megaloblastic (巨赤芽球性貧血)											
Mild	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Lymphadenopathy (リンパ節症)											
Mild	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Normocytic anaemia (正球性貧血)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Endocrine disorders (内分泌障害)											
Mild	0	1 (0.8%)	0	0	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Moderate	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Autoimmune thyroiditis (自己免疫性甲状腺炎)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Hypothyroidism (甲状腺機能低下症)											
Mild	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Inappropriate antidiuretic hormone secretion (抗利尿ホルモン不適合分泌)											
Moderate	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Congenital, familial and genetic disorders (先天性、家族性および遺伝性障害)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Dermoid cyst (皮様嚢腫)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Product issues (製品の問題)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Device dislocation (医療機器位置異常)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once by the maximum severity.
- Percentages are based on Population N.

Control No:<<t-s-063-aesev-019lt.sas, 2020-03-06T00:07:59>>