IIH EVOLVE

A PHASE III CLINICAL TRIAL FOR
IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

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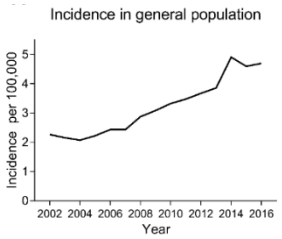
ABOUT IIH

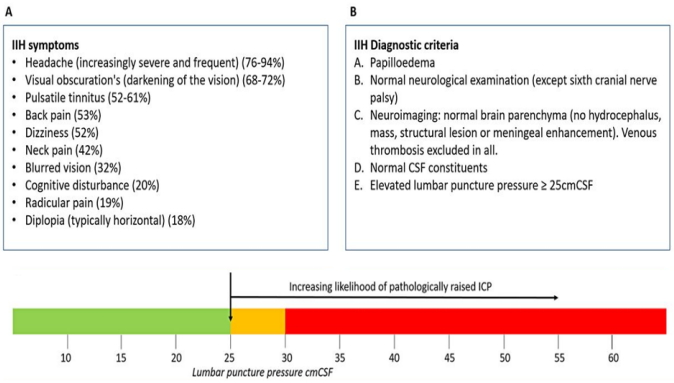
Idiopathic intracranial hypertension (IIH) happens when high pressure around the brain causes symptoms like vision changes and headaches. The high brain pressure likely results from an inbalance in brain fluid (cerebrospinal fluid (CSF). This increases pressure in the brain ("intracranial pressure or ICP") and on the nerve in the back of the eye, called the optic nerve. There is no known cause ("idiopathic"). IIH is predominately associated with females of child bearing age (>90% of cases), but men can be affected as well.



IIH causes disabling long term headaches. Additionally, as fluid builds up around the nerve at the back of the eye, this can cause compression and damage to the optic nerve and if left untreated can lead to permanent blindness. There are a number of other features of the disease, which can be very disabling for example: ringing in the ears, neck and back pain and impaired cognition. Although previously thought to be rare, the number of patients with IIH is increasing each year (the incidence has increased by more than 350% in the last 10 years). For most, unfortunately IIH is a chronic condition and many patients have long term symptoms of disease.

DIAGNOSIS OF IIH

The majority of patients presenting with IIH have symptoms that include a headache that is progressively more severe and frequent. IIH is diagnosed based on the patient's clinical features (Box A) followed by a defined set of criteria (Box B).



Mollan et al., Idiopathic intracranial hypertension: consensus guidelines on management. J Neurol Neurosurg Psychiatry. 2018 Oct;89(10):1088-1100.

Investigation and management depend on symptoms and signs and requires an interdisciplinary team approach. There are clear diagnostic criteria and consensus treatment guidelines (2018), and as a result the awareness of IIH is growing and standardization of care is anticipated to improve.

Current treatments include weight loss management and medical therapies such as acetazolamide, although these are all unlicensed for IIH and have side effects which can be intolerable for patients. For those at risk of irreversible visual loss, urgent neurosurgery / ophthalmic surgery (e.g., CSF shunting) is required to reduce the ICP and preserve vision. There is a need for new safe and effective treatments for IIH. Invex is developing a once per week injectable formulation of Exenatide to treat IIH.

ABOUT PRESENDIN

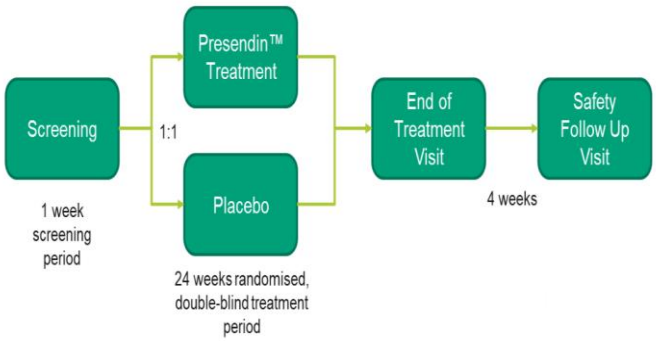
Presendin is a sustained release (SR) formulation of Exenatide in a biodegradable poly (lactic-co-glycolic acid) microsphere (PLGA) delivered via a once per week, sub-cutaneous injection, and moving into Phase III development. This injection would be done at home by the patient (or care giver) once training has taken place. Exenatide is a small peptide and a synthetic version of the GLP-1 agonist exendin-4, which is currently approved for the treatment of type 2 diabetes (but does not cause dangerous lowering of blood sugar levels). Exenatide has been licensed for use in type 2 diabetes since 2005 so there is a wealth of knowledge about the drug safety. Common side effects of Exenatide include nausea, loss of appetite and dizziness, which are typically short lived. Most of these side effects tend to go away within a few days or a couple of weeks and serious side effects are uncommon. Exenatide can also cause weight loss.

ABOUT IIH EVOLVE

IIH EVOLVE is a randomised, placebo-controlled, double-blind Phase III clinical trial that will randomise 240 adult patients with **newly diagnosed IIH with papilloedema** to determine the efficacy and safety of Presendin versus placebo, administered once weekly over 24 weeks. The primary endpoint of IIH EVOLVE will assess efficacy of Presendin to reduce ICP over 24 weeks compared to those on placebo.

Secondary endpoints will assess changes in vision (the visual field: Perimetric Mean Deviation (PMD) and papilloedema) and headache measures (such as Monthly Headache Days (MHD) over 24 weeks). Invex intends to open up to 40 clinical sites across the UK, Europe, Australia, Israel, New Zealand and the USA. Information on the trial is available at clinicaltrials.gov under Identifier **NCT05347147**.

IIH EVOLVE has been designed to meet the requirements for market approval of Presendin for the treatment of IIH in Europe, UK and Australia and to further inform the Food and Drug Administration (FDA) on future drug registration initiatives for the USA market.



GLOBALLY THERE ARE NO CURRENT REGULATORY APPROVED TREATMENTS IN IIH

There are currently no approved drug therapies utilized in the treatment of IIH. Importantly, diagnostic criteria for IIH are well defined and treatment guidelines available. Consensus guidelines co-authored by Prof. Alexandra Sinclair highlight the urgent need for new therapeutic agents, with current methods of treating more severe cases reliant on medical device/surgical interventions with high failure rates and poor outcomes.

GLOBALLY RECOGNISED EXPERT INPUT & INVOLVEMENT

Trial Steering Group Chairperson – Professor Michael Wall - Dr Wall is a Professor of Ophthalmology and Neurology at the University of Iowa College of Medicine and Director of the Iowa Visual Field Reading Center. He is considered a global key opinion leader in IIH, having made a significant contribution to the clinical and scientific literature pertaining to the diagnosis, treatment and management of this disease and has led a significant number of important IIH clinical trials.

Trial Steering Group Member – Associate Professor Clare Fraser – Dr Fraser is a Consultant Neuro-Ophthalmologist, Sydney Eye Hospital, St Vincent's Hospital, Macquarie University Hospital. Dr Fraser served as Vice President of The Neuro-Ophthalmology Society of Australia, is Chair of the North American Neuro-Ophthalmology Society International Committee and is on the committee for the Neuro-Ophthalmology Virtual Education Library and on the editorial boards for several high impact ophthalmology journals.

Trial Steering Group Member – Professor Susan Mollan – Dr Mollan is a consultant Neuro-Ophthalmologist at University Hospital Birmingham. She is the Director of Ophthalmic Research at University Hospital Birmingham and Director of the Ocular Reading Centre. She has published widely on IIH and is a key contributor to current consensus treatment guidelines for IIH.

Trial Steering Group Member – Professor Helen Danesh-Meyer– Dr Danesh-Myer is Professor, Faculty of Medical and Health Sciences, Ophthalmology and holds the Sir William and Lady Stevenson Chair in Ophthalmology and Head of Academic Neuro-ophthalmology and Glaucoma, University of Auckland and Director of the Eye Institute. Dr Danesh-Meyer is an international authority in glaucoma and neuro-ophthalmology.

Trial Steering Group Member – Professor Dr Wolf Lagrèze– Dr Lagrèze Head of Section for Neuro-ophthalmology and Pediatric ophthalmology, Eye Center, Medical Center, Faculty of Medicine, University of Freiburg, Germany. Dr Lagrèze has a strong interest in pediatric ophthalmology, neuro-ophthalmology and orbital diseases.

Trial Steering Group Member – Professor Patricia Pozo-Rosich – Dr Pozo-Rosich is Head of Section in the Neurology Department at Vall d'Hebron University Hospital in Barcelona and Director of the Migraine Adaptive Brain Centre. Dr Pozo-Rosich is also Coordinator of the Brain, Mind & Behaviour eCORE and in charge of the Headache Research Laboratory at the Vall d'Hebron Institute of Research. Dr Pozo-Rosich is the Honorary Secretary of the International Headache Society.

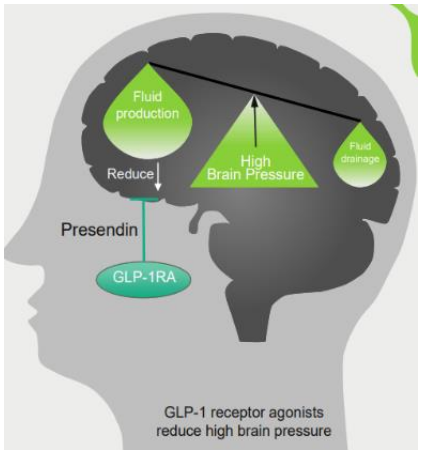
A SIGNIFICANT & COSTLY BURDEN OF ILLNESS

IIH is a rapidly growing disease driven by changing demographics, with incidence growth of 5.2% 2002-2016. By 2030 IIH is projected to cost hospitals in England alone +£400m p.a, with a similar trend in USA.

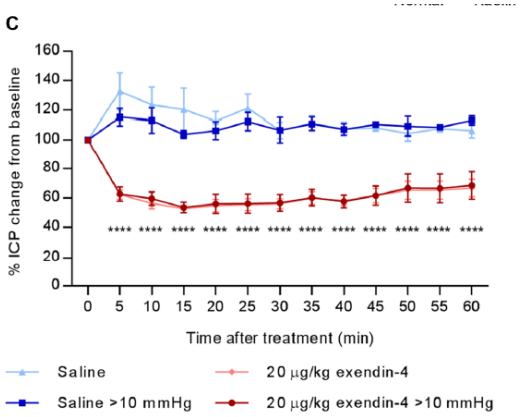
A key cost driver is an estimated 40% of IIH patients have repeat hospital admissions and an average length of stay being 2.7 days. >90% of patients suffer headaches that are progressively more severe and frequent: major cause of morbidity and up to 25% suffer permanent vision loss due to the elevated intracranial pressure (ICP) effect on optic nerve function.

IIH EVOLVE is therefore an important and timely clinical trial to understand the clinical efficacy and safety of the once per week IIH treatment Presendin in **newly diagnosed** IIH patients.

THE EVIDENCE FOR EXENATIDE IN IIH



Prof. Alex Sinclair Invex Executive Director and Chief Scientific Officer and Clinician Scientist and Neurology Consultant in the Metabolic Neurology Group at the Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, The University of Birmingham was the first to demonstrate glucagon like peptide 1 (GLP-1) receptor agonists commonly used in diabetes treatment (Exenatide formulated as Byetta® or Bydureon®) act on the choroid plexus in the brain to lower cerebral spinal fluid secretion and consequently, intracranial pressure (ICP). Exenatide has a well-defined mechanism of action.



STRONG AND SUPPPORTIVE PHASE II CLINICAL DATA

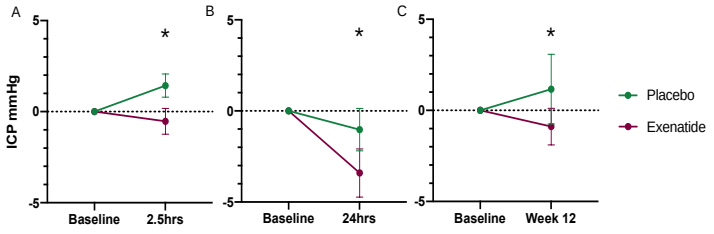
In May 2020, Invex released Phase II trial results in IIH patients. The purpose of the trial, known as the PRESSURE Trial, was to obtain first clinical proof of concept for Exenatide in IIH and provide a basis to move into a pivotal Phase III trial. The design of IIH Pressure was a double blind, placebo-controlled trial of 16 IIH patients randomised to either placebo or Exenatide over 12 weeks.

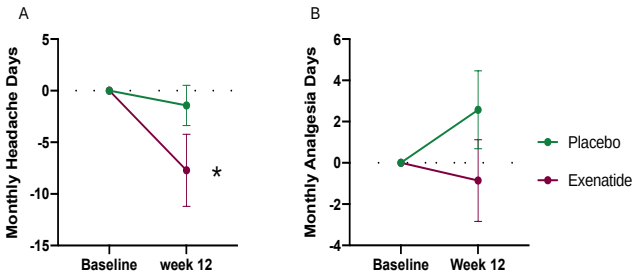
The results were positive.

Primary Endpoint (reduction in ICP) - statistically significant reduction in ICP across three-time points (2.5 hours, 24 hours and 12 weeks post dose).

Secondary Endpoint – statistically significant reduction in headache days (7.7 day reduction p/m).

Secondary Endpoint (Vision) – statistically significant improvement in visual acuity (1 line on the vision chart (LogMar).





IIH PRESSURE: SAFETY & DVERSE EVENTS

No serious adverse events (AE) were observed related to the use of Exenatide. Overall, adverse events were relatively low, with nausea (which settled in the first week) the most common AE seen in >85% of patients treated with Exenatide. Nausea is a known and the most frequent AE of sub-cutaneous administration of this formulation of Exenatide (Byetta®).

Event	Number & Arm*	Description
Serious Adverse Events (SAE)	1,P	Thyrotoxicosis (unrelated, participant continued in study)
Adverse Events (AE)	3, E	Nausea – required treatment
	4, E	Nausea - mild
	1, E 2, P	Minor wound infection (unrelated, participant continued in study)
	1, P	Post-operative swelling

* P = Placebo group, E = Exenatide Group

The results of the PRESSURE trial have been presented at major, relevant medical conferences including at the Annual Meetings for the North American Neuro-Ophthalmology Society (NANOS), The Australian New Zealand Headache Society, European Headache Federation (EHF), the European Neuro-Ophthalmology Society (EUNOS) and the Aerospace Medical Association.

ABOUT INVEX

Invex Therapeutics (Invex) is an Australian Securities Exchange (ASX)-listed biopharmaceutical company focused on the repurposing of an already approved drug, Exenatide, for efficacious treatment of neurological conditions involving raised intracranial pressure. Invex's primary focus is on the disease Idiopathic Intracranial Hypertension (IIH), a condition with no regulatory approved treatments to date. Invex has trademarked its repurposed Exenatide as Presendin.

CONTACT INFORMATION

IIHEVOLVE@invextherapeutics.com. This email address should be used by healthcare professionals either with an interest in or already working on Invex's Phase III IIH-EVOLVE clinical study or for charities seeking further information. Please note that all information on ongoing clinical trials including eligibility criteria and contact information is posted on the https://clinicaltrials.gov/ website under ClinicalTrials.gov Identifier: NCT05347147.

For Further IIH Information:

UK – https://www.iih.org.uk/
For Australia – https://headacheaustralia.org.au or http://www.ihaustralia.org.au