Evidencia de INBRIJA: análisis detallado de los ensayos clínicos

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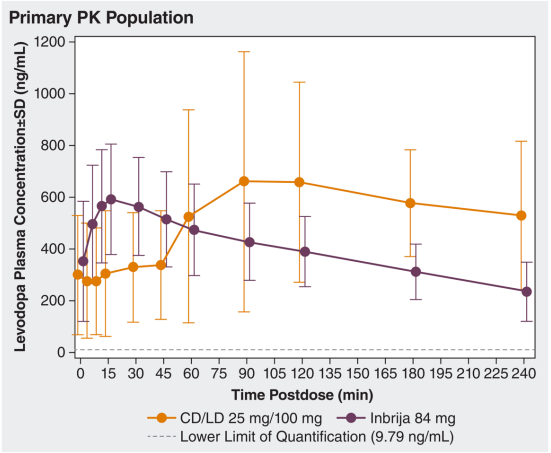

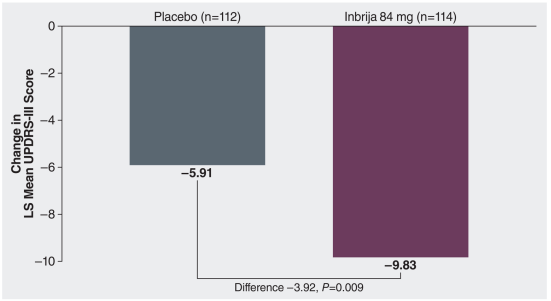

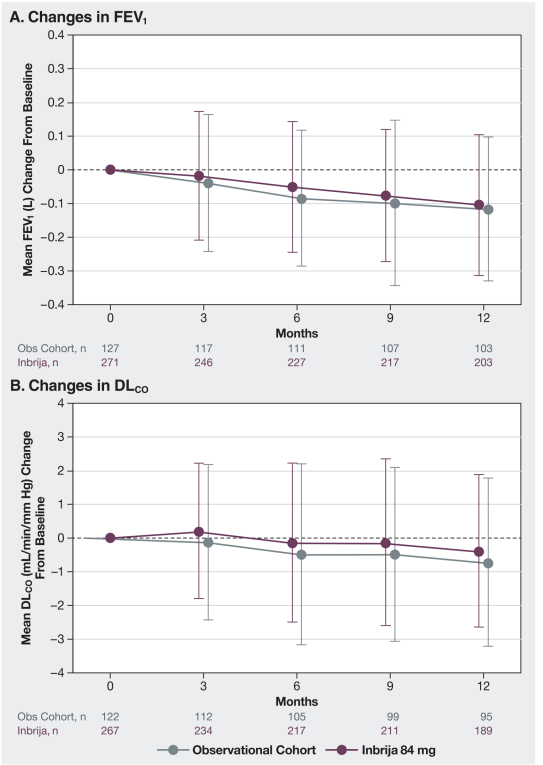

4.1 Indicaciones terapéuticas

"INBRIJA® está indicado para el tratamiento intermitente de fluctuaciones motoras episódicas (**episodios OFF**) en pacientes adultos con **enfermedad de Parkinson** (EP) tratados con un **inhibidor de levodopa/dopa-descarboxilasa**"

Programa de ensayos clínicos de INBRIJA®

Study	Study Type	Purpose	Number of Randomized Subjects	Treatment[a]	Treatment Duration	Reference
Multiple-Dose Studies in PD Subjects						
SPAN-PD CVT-301-004 *Pivotal phase 3 study*	Multicenter, randomized, double-blind, placebo-controlled	Efficacy and safety study	339	• Inbrija 60 mg • Inbrija 84 mg • Placebo	12 weeks	LeWitt PA, et al. *Lancet Neurol.* 2019; 18(2):145-154.
CVT-301-004E	Multicenter, dose-level blinded, long-term extension study[b]	Pulmonary safety, safety	325	• Inbrija 60 mg • Inbrija 84 mg	12 months	Farbman ES, et al. *Neurology.* 2019;92 (15 Supplement): P2.8-048. [abstract]
CVT-301-005	Multicenter, randomized, open-label, with observational cohort control	Long-term pulmonary safety study	408	• Inbrija 84 mg	12 months	Grosset DG, et al. *Parkinsonism Relat Disord.* 2020;71:4-10.
Single-Dose Studies in PD Subjects						
CVT-301-009	Multicenter, randomized, double-blind, placebo-controlled	Safety and tolerability study of Inbrija when administered with the first oral dose of CD/LD of the day to treat early morning OFF symptoms	36	• Inbrija 84 mg • Placebo	2-way crossover: 2 dosing days separated by 1- to 7-day interval	Hauser RA, et al. *Parkinsonism Relat Disord.* 2019;64:175-180.
CVT-301-012	Multicenter, randomized, open-label	Pharmacokinetic evaluation of a single inhaled dose of Inbrija administered with oral CD and a single orally administered dose of CD/LD, under fed conditions	23	• Inbrija 84 mg+ oral 25 mg CD • Oral CD/LD (Sinemet 25 mg/100 mg)	2-way crossover: 2 dosing days separated by 48-hour interval	Safirstein B, et al. *Clin Ther.* In press.

[a]All patients were on a standard oral DDI/LD regimen. [b]Extension of SPAN-PD study, but also enrolled former patients from CVT-301-005, CVT-301-009, and from an earlier study (CVT-301-003), if eligible.
CD, carbidopa; DDI, dopa decarboxylase inhibitor; LD, levodopa; PD, Parkinson's disease.

RESEARCH ARTICLE

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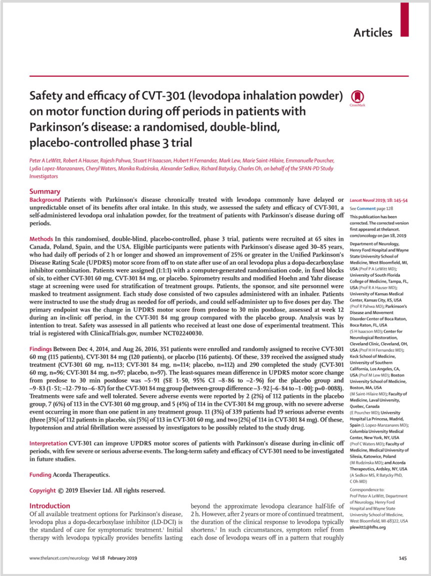

Articles

Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial

Parkinsonism and Related Disorders

A 12-month, dose-level blinded safety and efficacy study of levodopa inhalation powder (CVT-301, Inbrija) in patients with Parkinson's disease

Parkinsonism and Related Disorders

Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease

1. LeWitt PA, et al. **A randomized trial of inhaled levodopa (CVT-301) for motor fluctuations in Parkinson's disease**. Mov Disord 2016;31:1356-1365.
2. LeWitt PA, et al.; SPAN-PD Study Investigators. **Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial**. Lancet Neurol 2019;18:145-154.
3. Farbman ES, et al. A 12-month, dose-level blinded safety and efficacy study of levodopa inhalation powder (CVT-301, Inbrija) in patients with Parkinson's disease. Parkinsonism Relat Disord. 2020;81:144-150.
4. Grosset DG, et al. **Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study**. Parkinsonism Relat Disord 2020;71:4-10.
5. Hauser RA, et al. **Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease**. Parkinsonism Relat Disord 2019;64:175-180.

- En torno a **900 pacientes** han participado en el programa de desarrollo clínico de INBRIJA®
- **22** entradas en **PUBMED** con el término de búsqueda CVT-301

A Randomized Trial of Inhaled Levodopa (CVT-301) for Motor Fluctuations in Parkinson's Disease

Peter A. LeWitt, MD, MMSc,[1]* Robert A. Hauser, MD, MBA,[2] Donald G. Grosset, MD,[3] Fabrizio Stocchi, MD,[4] Marie-Helene Saint-Hilaire, MD,[5] Aaron Ellenbogen, DO, MPH,[6] Mika Leinonen, MSc,[7] Neil B. Hampson, MD,[8] Tia DeFeo-Fraulini, MS,[9] Martin I. Freed, MD, FACP,[9] and Karl D. Kieburtz, MD, MPH[10]

Movement Disorders, Vol. 31, No. 9, 2016

4-week, randomized, double-blind, placebo-controlled, multicenter, parallel-group doce escalation trial.
2 to 4 weeks screening period, 4 weeks treatment period & safety follow-up of 1 week after end of treatment.

Predictable OFF episodes ≥2 hours per day (**excluding early-morning OFF time**).
Exclusion criteria included a history of **chronic respiratory disease** within the preceding 5 years.

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Variable	CVT-301 Group (n = 43)	Placebo Group (n = 43)	*P* Value CVT-301 vs Placebo[a]
Age (years), mean (SD)	62.0 (8.4)	62.7 (9.1)	0.721
Sex, n (%)			0.110[b]
Male	25 (58)	32 (74)	
Female	18 (42)	11 (26)	
Race, n (%)			1.000[c]
White	41 (95)	42 (98)	
Other	2 (5)	1 (2)	
Time since PD diagnosis (years), mean (SD)	9.0 (3.8)	9.8 (4.0)	0.377
Time since emergence of motor fluctuations, years, mean (SD)	4.7 (3.3)	5.0 (3.3)	0.691
UPDRS, Part III score, mean (SD)			
OFF	35.4 (12.0)	36.2 (12.1)	0.741
ON	16.2 (8.1)	18.9 (9.8)	0.170
OFF time, hours/day,[d,e] mean (SD)	5.7 (2.2)	5.8 (1.8)	0.860
OFF episodes, number/day,[d,e] mean (SD)	3.5 (1.1)	3.7 (1.0)	0.380
ON time, hours/day,[d] mean (SD)			
With no dyskinesia	8.2 (3.4)	8.3 (3.5)	0.940
With nontroublesome dyskinesia	1.7 (2.5)	1.6 (2.6)	0.926
With troublesome dyskinesia	0.4 (1.1)	0.3 (1.0)	0.726
Modified Hoehn & Yahr stage when ON, n (%)			0.825
<2.5	27 (63)	26 (61)	
≥2.5	16 (37)	17 (40)	
Duration of LD treatment (years), mean (SD)	7.6 (3.8)	7.9 (4.0)[f]	0.717
LD dosage, mg/day, mean (SD)	687 (276)	852 (315)	0.011
LD doses, number/day, mean (SD)	5.6 (1.4)	6.1 (2.2)	0.261
Other PD drug use, n (%)			
Dopaminergic agonists	31 (72)	26 (61)	0.254[b]
MAO-B inhibitors	23 (54)	14 (33)	0.050[b]
COMT inhibitors	17 (40)	17 (40)	1.000[b]
Amantadine	16 (37)	13 (30)	0.494[b]

Incluyendo early-morning OFF-time

A Randomized Trial of Inhaled Levodopa (CVT-301) for Motor Fluctuations in Parkinson's Disease

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El **14 %** del grupo CVT-301 y **7 %** del grupo placebo tuvieron algunas dificultades en el uso del sistema de inhalación.

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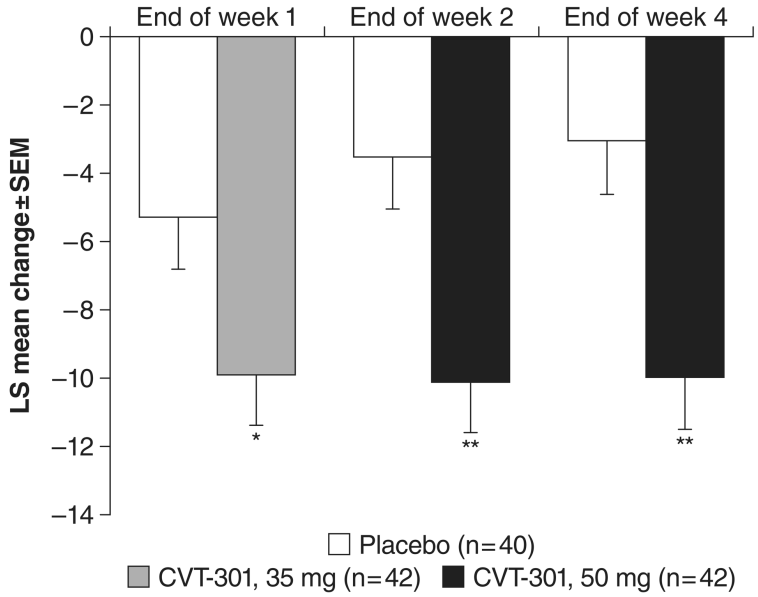

Supplemental Fig. A. LS mean UPDRS Part III score change (from predose to average postdose score) for two CVT-301 dose levels vs placebo (mITT population). *$P < 0.01$, **$P < 0.001$ vs placebo, MMRM. Abbreviations: LS, least-squares; mITT, modified intent to treat; MMRM, mixed model for repeated measurements; SEM, standard error of the mean; UPDRS, Unified Parkinson's Disease Rating Scale.

- 35 mg: -9,9 puntos al final de la semana 1 vs -5,3 puntos para placebo (p = 0,007)
- 50 mg: -10,2 puntos frente a -3,5 puntos placebo (p<0,001)
- 50 mg a la semana 4: –10,0 puntos vs. -3,1 puntos para placebo (p<0,001)

Pacientes con **H&Y <2,5** ⇒ efecto del tratamiento al final de la semana 4 fue de -4,7 puntos (-9,2 a -0,1 pts; p=0,044).

Pacientes con **H&Y ≥2,5** ⇒ efecto del tratamiento al final de la semana 4 fue de -10,2 puntos (-15,7 a -4,6 pts; p<0,001).

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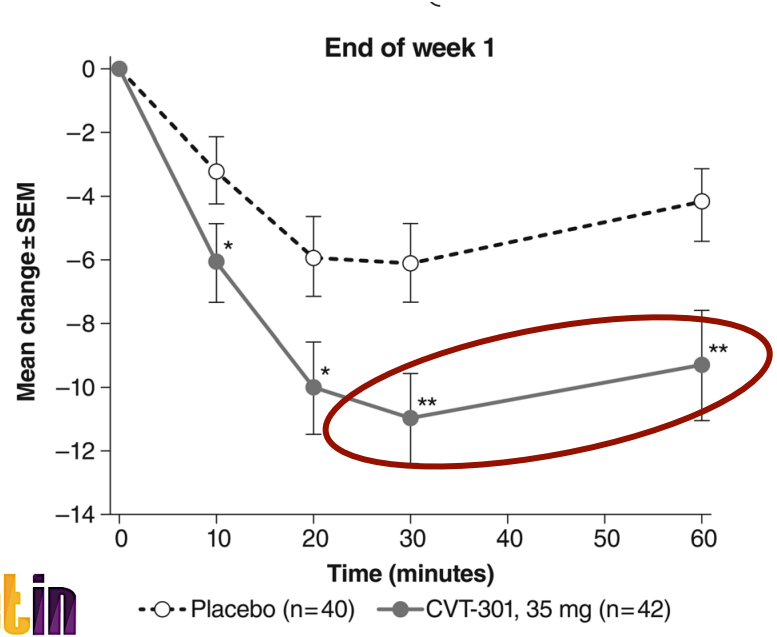
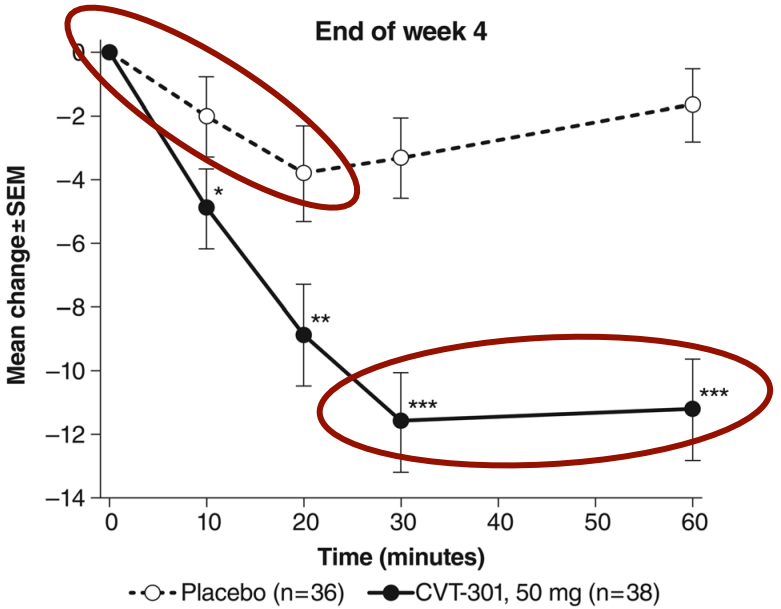
El inicio de la acción en ambas dosis de CVT-301 fue significativo a los **10 minutos** y la mejora media en las puntuaciones motoras siguió siendo significativa frente al placebo **durante los 60 minutos**.





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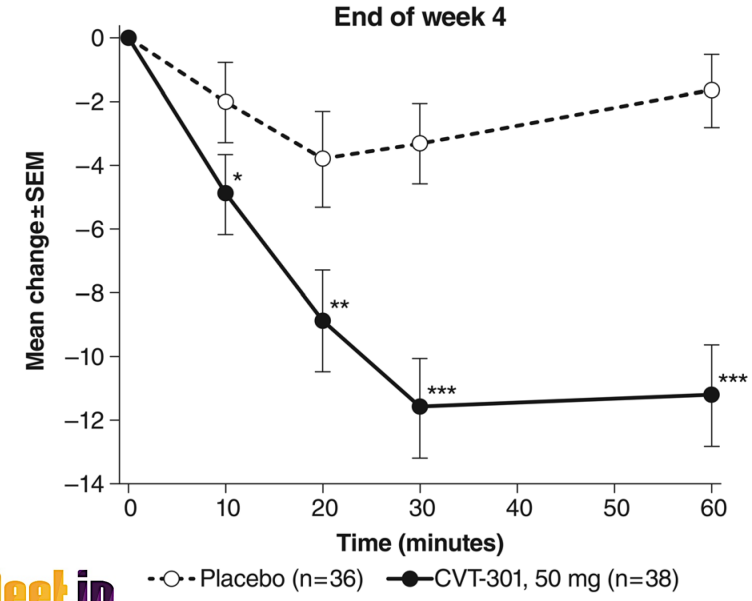

Juicio del examinador:

% de pacientes que lograron un estado ON aumentó del 67 % en la semana 1 al 74 % en la semana 2 y al 78 % en la semana 4.

(Placebo 45 % ➜ 41 % semana 2 ➜ 36 % semana 4).

Juicio de los propios pacientes (PGI-C):

En la semana 4: el 44 % del grupo de placebo calificó su EP como mejorada y el 5 % calificó como peor.

En la semana 4: el 72 % del grupo CVT-301 calificó su EP como mejorada y el 0 % como peor.

Significant difference in OFF time

At week 4 mean decrease of 1.6 hours/day for CVT-301, compared with 0.8 hours/day for placebo (p=0.04).

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Los TEAE con una incidencia >5,0 % en el grupo CVT-301 fueron mareos, tos y náuseas.
Discinesia en 1 paciente (2 %) en cada grupo de tratamiento.
Dos pacientes, **ambos en el grupo de placebo**, experimentaron TEAE severos: ataque de caída y discinesia.

TABLE 2. Treatment-emergent adverse events (safety population)

	CVT-301 Group			
TEAE Incidence,n (%)	At any time (n = 43)	While Using 35 mg (n = 42)	While Using 50 mg (n = 42)	Placebo Group (n = 43)
Summary				
Any TEAE	20 (47)	17 (41)	9 (21)	14 (33)
Any study-drug–related TEAE	10 (23)	8 (19)	6 (14)	9 (21)
Any severe TEAE	0	0	0	2 (5)
Any serious TEAE	0	0	0	1 (2)
Any TEAE leading to study-drug dose adjustment	1 (2)	1 (2)	1 (2)	2 (5)
Any TEAE leading to study-drug discontinuation	2 (5)	1 (2)	1 (2)	3 (7)
Any TEAE leading to death	0	0	0	0
By Preferred Term[a]				
Dizziness	3 (7)	3 (7)	0	2 (5)
Cough	3 (7)	2 (5)	1 (2)	1 (2)
Nausea	3 (7)	1 (2)	2 (5)	0
Headache	2 (5)	2 (5)	0	2 (5)
Edema peripheral	2 (5)	0	2 (5)	1 (2)
Anxiety	2 (5)	0	2 (5)	0
Sputum discolored	2 (5)	0	2 (5)	0

RESEARCH ARTICLE

A Randomized Trial of Inhaled Levodopa (CVT-301) for Motor Fluctuations in Parkinson's Disease

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[5]Boston University School of Medicine, Boston, Massachusetts, USA
[6]Quest Research Institute and Michigan Institute for Neurological Disorders, Farmington Hills, Michigan, USA
[7]4Pharma AB, Stockholm, Sweden
[8]Virginia Mason Medical Center, Seattle, Washington, USA
[9]Acorda Therapeutics, Chelsea, Massachusetts, USA
[10]Clintrex LLC, Rye, New York, USA

ABSTRACT: Background: Although levodopa is the most effective oral PD therapy, many patients experience motor fluctuations, including sudden loss of dose effect and delayed benefit. CVT-301 is a levodopa inhalation powder with the potential for rapid onset of action. The objective of this study was to evaluate CVT-301 self-administered by PD patients to relieve OFF episodes.
Methods: PD patients with ≥2 hours per day of OFF time despite oral levodopa ≥4 times per day were randomized to CVT-301 or placebo for 4 weeks, to be used up to 3 times per day for OFF episodes. After 2 weeks, the study-drug dose was escalated from 35 to 50 mg. The primary end point was mean change in UPDRS Part III score from a predose OFF state to the average of postdose scores obtained at 10, 20, 30, and 60 minutes, as assessed in-clinic at the end of week 4. Home diaries were recorded.
Results: Eighty-six patients used the study drug at an average frequency of 2.1 times per day for CVT-301 and for placebo. At 4 weeks, least-squares mean change in UPDRS Part III score favored CVT-301 by 7.0 points ($P < 0.001$). A treatment effect was evident at 10 minutes. At 4 weeks, least-squares mean OFF-time change from baseline favored CVT-301 by 0.9 hours per day ($P = 0.045$). The most frequently reported adverse events in the CVT-301 group were dizziness, cough, and nausea, each in 7% (3 of 43 patients).
Conclusions: CVT-301 self-administered during OFF episodes provided rapid improvement of motor function, and daily OFF time was significantly reduced at the higher dose. CVT-301 was generally safe and well-tolerated.

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At the time of the study, Dr. Martin I. Freed and Tia DeFeo-Fraulini were employed by Civitas Therapeutics (now wholly owned by Acorda Therapeutics).

Funding agencies: This study was supported by Civitas, now wholly owned by Acorda Therapeutics. Editorial assistance was provided by Jessica Roland at Acorda Therapeutics and by The Curry Rockefeller Group, LLC, which was funded by Acorda Therapeutics.

Relevant conflicts of interest/financial disclosures: Peter A. LeWitt has served as a consultant for Acorda and the Parkinson's Disease and Movement Disorders Program that he directs has received clinical research grant support (for conducting clinical trials) from Acorda. Robert A. Hauser's institution has received research support from Civitas. Donald G. Grosset received compensation for consulting services to Civitas. Marie-Helene Saint-Hilaire's institution has received clinical research grants from Civitas. Mika Leinonen is a biostatistician at 4Pharma AB, a contract research organization that provided compensated statistical consultation services to Civitas and Acorda. Neil B. Hampson worked as a noncompensated pulmonary consultant to Civitas. Tia DeFeo-Fraulini and Martin I. Freed were employees of Civitas. Karl D. Kieburtz is a consultant for Acorda and Civitas. Fabrizio Stocchi and Aaron Ellenbogen have nothing to report. Full author disclosures are listed at the end of the article.

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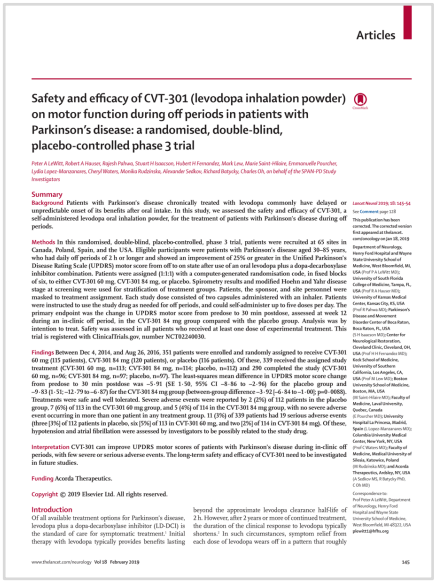
CONCLUSIONES

1. Estudio doble ciego aleatorizado multicéntrico diseñado para conocer la **eficacia** y **seguridad** de CVT-301 (previo 2a con 24 pacientes).
2. Estudio **fase 2b** con un total de **86 pacientes** incluidos (43 por brazo).
3. Ambos grupos con características semejantes, destacando por ser buenos respondedores a la levodopa y presentar casi 6 horas de OFF.
4. Todos ellos recibiendo levodopa con al menos 4 tomas al día.
5. Durante la semana 1 y 2 utilizaron una dosis de partículas finas de levodopa de 35 mg y en la semana 3 y 4 de 50 mg (equivalente a 84 mg, lo finalmente comercializado).
6. **Eficaz frente a placebo con diferencias significativas en la reducción de la UPDRS-III a los 10, 20, 30 y 60 minutos tanto en la semana 1 como en la 4** (50 mg, -7 vs placebo).
7. Mayor respuesta en los pacientes con un estadio de Hoehn&Yahr más avanzado.
8. Reducción significativa del tiempo OFF frente a placebo en 0.8 horas pero sólo con la dosis de 50 mg después de 4 semanas de tratamiento.
9. **Buena tolerabilidad con pocos efectos secundarios (mareos, nauseas y tos, 5% a 7%).**
10. Limitaciones: tamaño muestral pequeño; límite de uso por día en 3 veces (había pacientes con hasta 7 episodios OFF); uso secuencial de dosis pero no comparativas; no se incluyó acinesia matutina.
11. **NECESIDAD DE DESARROLLAR UN ESTUDIO FASE 3.**

1. LeWitt PA, et al. **A randomized trial of inhaled levodopa (CVT-301) for motor fluctuations in Parkinson's disease**. Mov Disord 2016;31:1356-1365.



Articles

Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial

Peter A LeWitt, Robert A Hauser, Rajesh Pahwa, Stuart H Isaacson, Hubert H Fernandez, Mark Lew, Marie Saint-Hilaire, Emmanuelle Pourcher, Lydia Lopez-Manzanares, Cheryl Waters, Monika Rudzinska, Alexander Sedkov, Richard Batycky, Charles Oh, on behalf of the SPAN-PD Study Investigators

Summary

Background Patients with Parkinson's disease chronically treated with levodopa commonly have delayed or unpredictable onset of its benefits after oral intake. In this study, we assessed the safety and efficacy of CVT-301, a self-administered levodopa oral inhalation powder, for the treatment of patients with Parkinson's disease during off periods.

Methods In this randomised, double-blind, placebo-controlled, phase 3 trial, patients were recruited at 65 sites in Canada, Poland, Spain, and the USA. Eligible participants were patients with Parkinson's disease aged 30–85 years, who had daily off periods of 2 h or longer and showed an improvement of 25% or greater in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score from off to on state after use of an oral levodopa plus a dopa-decarboxylase inhibitor combination. Patients were assigned (1:1:1) with a computer-generated randomisation code, in fixed blocks of six, to either CVT-301 60 mg, CVT-301 84 mg, or placebo. Spirometry results and modified Hoehn and Yahr disease stage at screening were used for stratification of treatment groups. Patients, the sponsor, and site personnel were masked to treatment assignment. Each study dose consisted of two capsules administered with an inhaler. Patients were instructed to use the study drug as needed for off periods, and could self-administer up to five doses per day. The primary endpoint was the change in UPDRS motor score from predose to 30 min postdose, assessed at week 12 during an in-clinic off period, in the CVT-301 84 mg group compared with the placebo group. Analysis was by intention to treat. Safety was assessed in all patients who received at least one dose of experimental treatment. This trial is registered with ClinicalTrials.gov, number NCT02240030.

Findings Between Dec 4, 2014, and Aug 26, 2016, 351 patients were enrolled and randomly assigned to receive CVT-301 60 mg (115 patients), CVT-301 84 mg (120 patients), or placebo (116 patients). Of these, 339 received the assigned study treatment (CVT-301 60 mg, n=113; CVT-301 84 mg, n=116; placebo, n=112) and 290 completed the study (CVT-301 60 mg, n=96; CVT-301 84 mg, n=97; placebo, n=97). The least-squares mean difference in UPDRS motor score change from predose to 30 min postdose was −5·91 (SE 1·50, 95% CI −8·86 to −2·96) for the placebo group and −9·83 (1·51; −12·79 to −6·87) for the CVT-301 84 mg group (between-group difference −3·92 [−6·04 to −1·80]; p<0·0003). Treatments were safe and well tolerated. Severe adverse events were reported by 2 (2%) of 112 patients in the placebo group, 7 (6%) of 113 in the CVT-301 60 mg group, and 5 (4%) of 116 in the CVT-301 84 mg group, with no severe adverse event occurring in more than one patient in any treatment group. 11 (3%) of 339 patients had 19 serious adverse events (three [3%] of 112 patients in placebo, six [5%] of 113 in CVT-301 60 mg, and two [2%] of 114 in CVT-301 84 mg). Of these, hypotension and atrial fibrillation were assessed by investigators to be possibly related to the study drug.

Interpretation CVT-301 can improve UPDRS motor scores of patients with Parkinson's disease during in-clinic off periods, with few severe or serious adverse events. The long-term safety and efficacy of CVT-301 need to be investigated in future studies.

Funding Acorda Therapeutics.

Introduction

Of all available treatment options for Parkinson's disease, levodopa plus a dopa-decarboxylase inhibitor (LD-DCI) is the standard of care for symptomatic treatment.[1] Initial therapy with levodopa typically provides benefits lasting beyond the approximate levodopa clearance half-life of 2 h. However, after 2 years or more of continued treatment, the duration of the clinical response to levodopa typically shortens.[2] In such circumstances, symptom relief from each dose of levodopa wears off in a pattern that roughly

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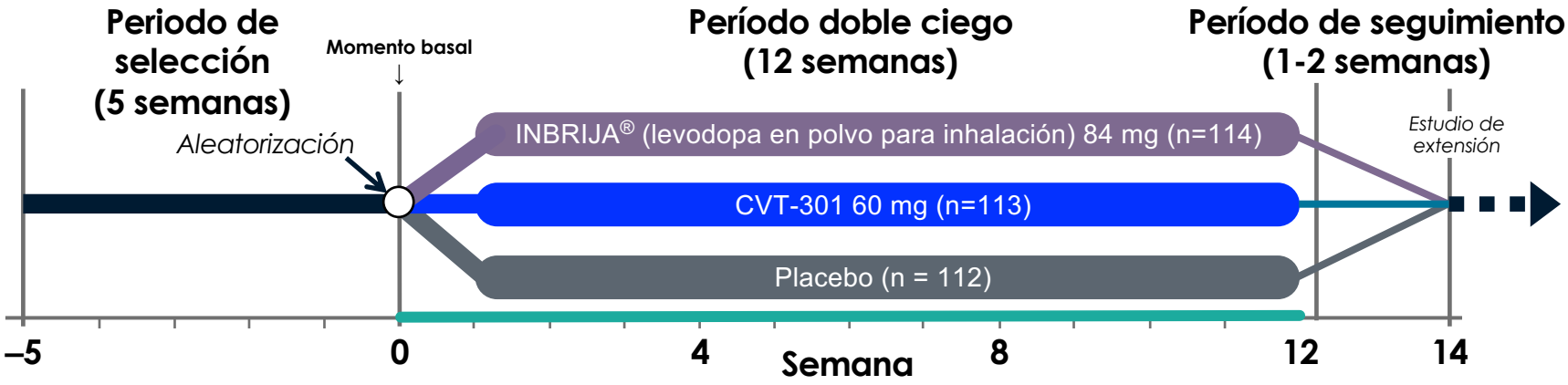
1. LeWitt PA, et al. **A randomized trial of inhaled levodopa (CVT-301) for motor fluctuations in Parkinson's disease**. Mov Disord 2016;31:1356-1365.

2. LeWitt PA, et al.; SPAN-PD Study Investigators. **Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial**. Lancet Neurol 2019;18:145-154.

3. Grosset DG, et al. **Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study**. Parkinsonism Relat Disord 2020;71:4-10.

4. Hauser RA, et al. **Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease**. Parkinsonism Relat Disord 2019;64:175-180.

Ensayo pivotal fase 3 de INBRIJA® (SPAN – PD; CVT-301-04)



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Ensayo pivotal fase 3 de INBRIJA® (SPAN – PD; CVT-301-04)

Variables de valoración	Variables evaluadas en la visita de la semana 12
Variable de valoración principal	**Cambio medio UPDRS III, a los 30 minutos:** cambio entre las puntuaciones antes de la dosis y 30 minutos después de la dosis de INBRIJA® 84 mg en comparación con placebo
Variables de valoración secundarias	**% de pacientes que alcanzaron el estado ON y lo mantuvieron a los 60 minutos:** proporción de pacientes que alcanzaron el estado ON en los 60 minutos posteriores al tratamiento y que se mantuvieron en estado ON a los 60 minutos
	Cambio medio UPDRS III, a los 20 minutos: cambio entre las puntuaciones antes de la dosis y 20 minutos después de la dosis
	PGIC: proporción de pacientes que mejoró en la escala de impresión general de cambio por parte del paciente (PGIC por sus siglas en inglés)
	Cambio medio UPDRS III, a los 10 minutos: cambio entre las puntuaciones antes de la dosis y 10 minutos después de la dosis
	Periodo en OFF en el diario de la EP: cambio respecto a los valores basales en el tiempo total diario en estado OFF

2. LeWitt PA, et al.; SPAN-PD Study Investigators. **Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial**. Lancet Neurol 2019;18:145-154.

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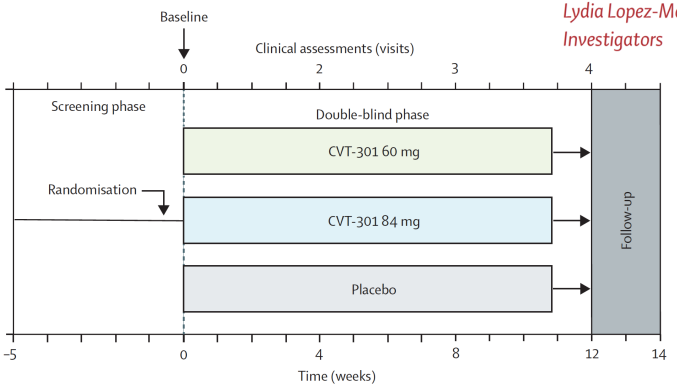


30-85 años con Tº OFF diario ≥2 h (**excluyendo early-morning OFF time**).

Criterios de exclusión:
Discinesia graves, **hipotensión ortostática**, y **enfermedad respiratoria crónica**.

*Todos los pacientes tenían que **ser capaces de usar el inhalador** estando en OFF.*

	CVT-301 84 mg (n=114)	CVT-301 60 mg (n=113)	Placebo (n=112)
Age, years	63·5 (7·97)	63·9 (9·24)	62·6 (8·83)
Time since diagnosis, months	95·7 (46·3)	104·3 (56·4)	97·4 (54·10)
Disease severity			
Modified Hoehn and Yahr stage <2·5	72 (63%)	74 (65%)	74 (66%)
Modified Hoehn and Yahr stage ≥2·5	42 (37%)	39 (35%)	38 (34%)
Smoking history			
Never smoked	65 (57%)	75 (66%)	72 (64%)
Former smoker	44 (39%)	38 (34%)	37 (33%)
Current smoker	5 (4%)	0 (0%)	3 (3%)
Levodopa treatment			
Duration of treatment, months	75·0 (44·6)	84·8 (54·6)	81·6 (53·6)
Levodopa dosage, mg/day	818·6 (401·0)	822·7 (364·1)	841·4 (396·5)
Levodopa doses, number per day	5·0 (1·6)	5·0 (1·7)	5·2 (1·9)
UPDRS part 3 score at screening			
Off state	33·0 (11·0)	35·0 (10·3)	35·4 (12·4)
On state*	14·9 (7·4)	15·8 (8·0)	16·1 (8·3)
Off periods†			
Number per day	3·58 (1·09)	3·54 (1·24)	3·28 (1·10)
Total off time per day, h	5·35 (2·26)	5·60 (1·90)	5·59 (2·25)
Dyskinesia‡			
Patients dyskinetic before baseline	53 (46%)	43 (38%)	46 (41%)
Patients non-dyskinetic before baseline	61 (54%)	70 (62%)	66 (59%)

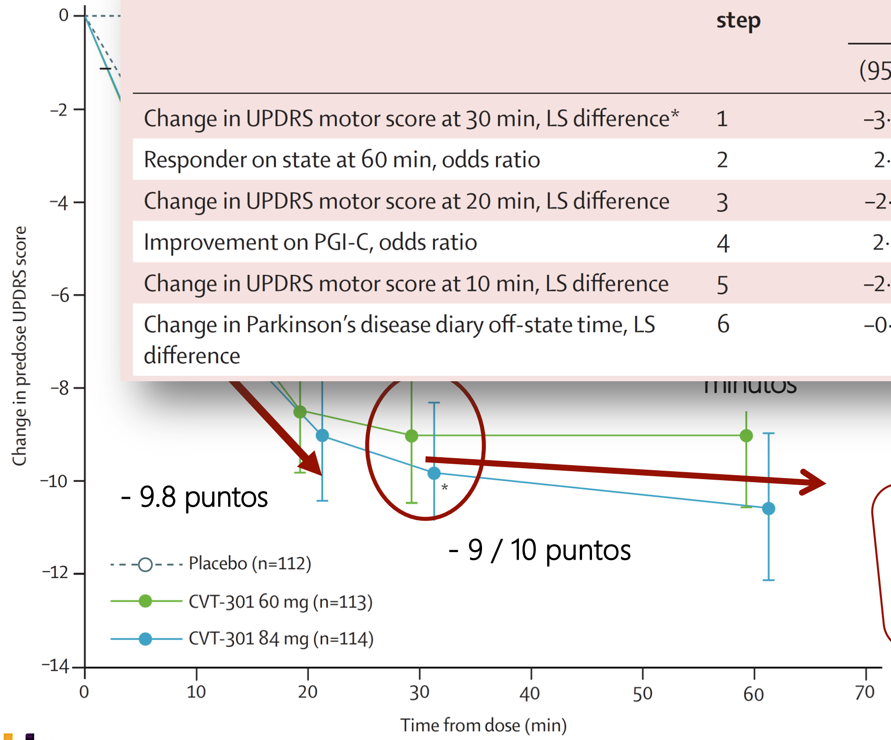
Tº Evol 8,3 años

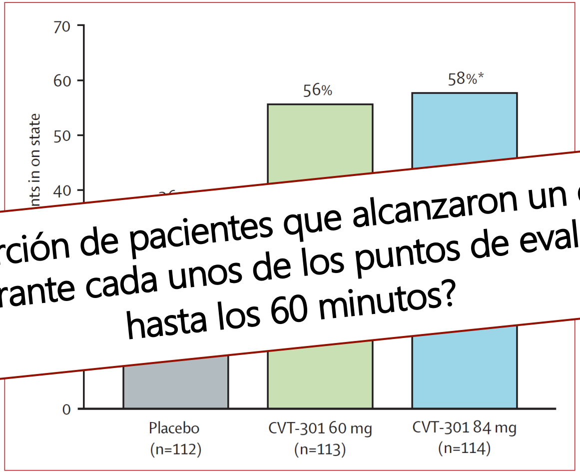
Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial

Lancet Neurol 2019; 18: 145–54

Cambio medio a los 30 minutos fue -5,91 para el placebo & –9,83 (–12,8 a –6,9) para el grupo de 84 mg.

	Hierarchical step	CVT-301 84 mg vs placebo		Hierarchical step	CVT-301 60 mg vs placebo	
		(95% CI)	p value		(95% CI)	p value
Change in UPDRS motor score at 30 min, LS difference*	1	−3·92 (−6·84 to −1·00)	0·0088	7	−3·07 (−5·99 to −0·16)	0·039
Responder on state at 60 min, odds ratio	2	2·65 (1·48 to 4·76)	0·0027	8	2·30 (1·29 to 4·10)	0·006
Change in UPDRS motor score at 20 min, LS difference	3	−2·55 (−5·22 to 0·13)	0·062	9	−1·98 (−4·65 to 0·70)	0·147
Improvement on PGI-C, odds ratio	4	2·94 (1·62 to 5·[illegible]	[illegible]	10	[illegible]	0·026
Change in UPDRS motor score at 10 min, LS difference	5	−2·26 (−4·48 to [illegible]	[illegible]	[illegible]	[illegible]	[illegible]387
Change in Parkinson's disease diary off-state time, LS difference	6	−0·01 (−0·55 to [illegible]	[illegible]	[illegible]	[illegible]	[illegible]722





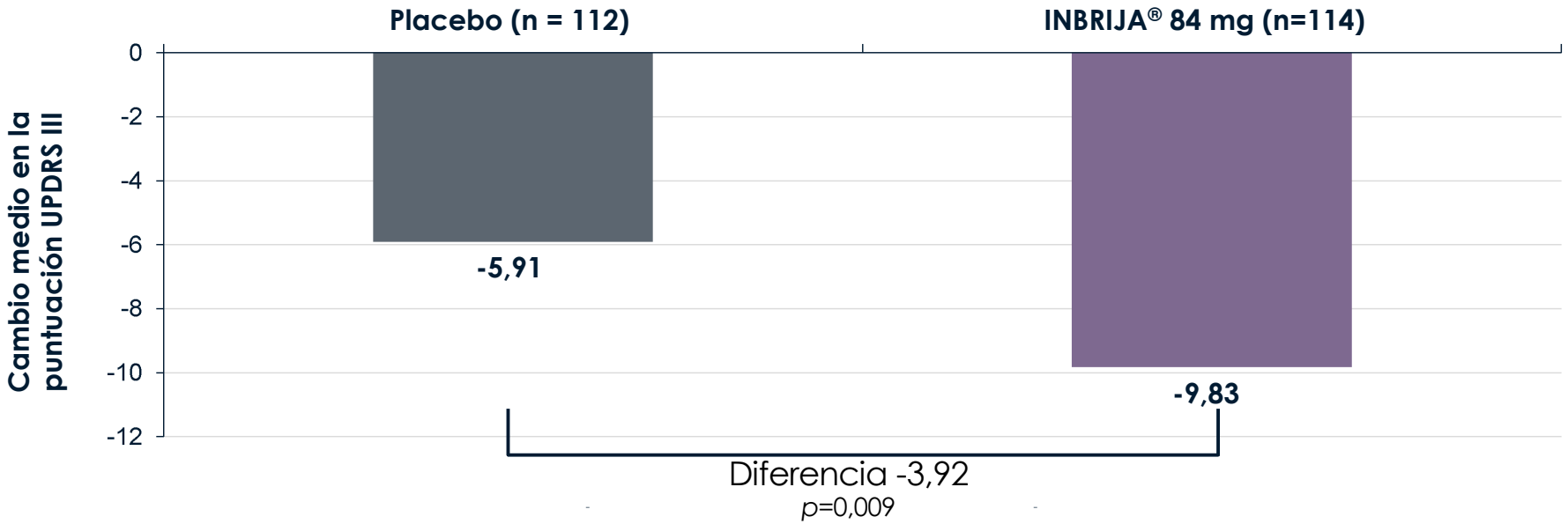
¿Proporción de pacientes que alcanzaron un estado ON durante cada unos de los puntos de evaluación hasta los 60 minutos?

Figure 3: Proportion of patients in an on state at 60 min postdose at week 12
*p=0·0027

Meet in The experts

ESTEVE

Variable de valoración principal: cambio en las puntuaciones UPDRS III antes de la dosis y 30 minutos después de la dosis en la semana 12



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	CVT-301 84 mg (n=114)		CVT-301 60 mg (n=113)		Placebo (n=112)	
	n (%)	Events	n (%)	Events	n (%)	Events
Total	66 (58%)	143	64 (57%)	150	49 (44%)	87
Cough	17 (15%)	18	17 (15%)	20	2 (2%)	2
Upper respiratory tract infection	7 (6%)	7	2 (2%)	2	3 (3%)	3
Nausea	6 (5%)	6	0 (0%)	0	3 (3%)	4
Discoloured sputum	6 (5%)	6	0 (0%)	0	0 (0%)	0
Dyskinesia	4 (4%)	4	5 (4%)	5	0 (0%)	0
Fall	3 (3%)	3	5 (4%)	5	2 (2%)	2
Throat irritation	1 (1%)	1	8 (7%)	8	0 (0%)	0
Dizziness	1 (1%)	1	2 (2%)	2	5 (4%)	5

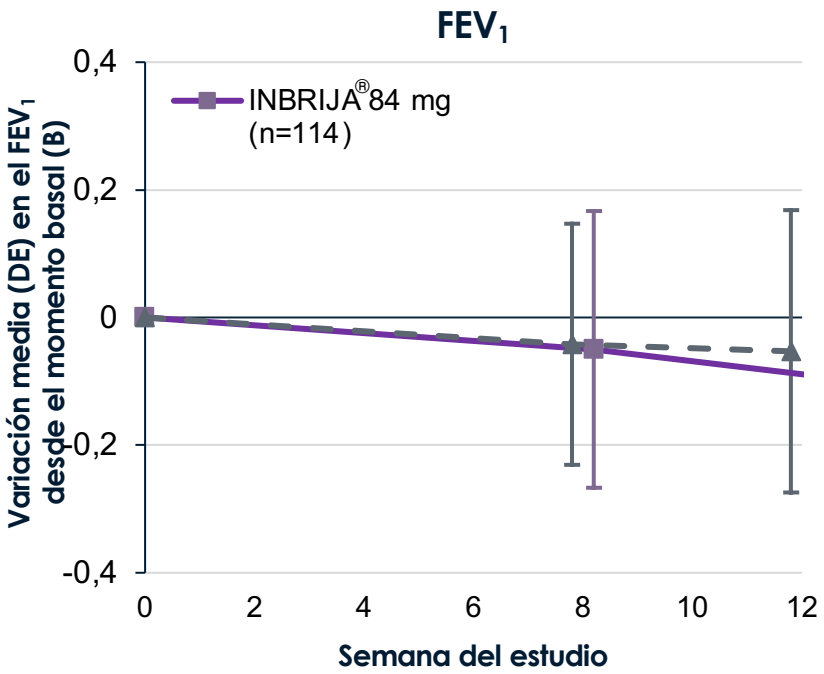
We report all adverse events that occurred in 4% or more patients in any treatment group. Of these, the following led to study withdrawal: cough (one patient in the CVT-301 60 mg group and two in the 84 mg group), throat irritation (one patient in the CVT-301 60 mg group), and dizziness (one patient in the placebo group).

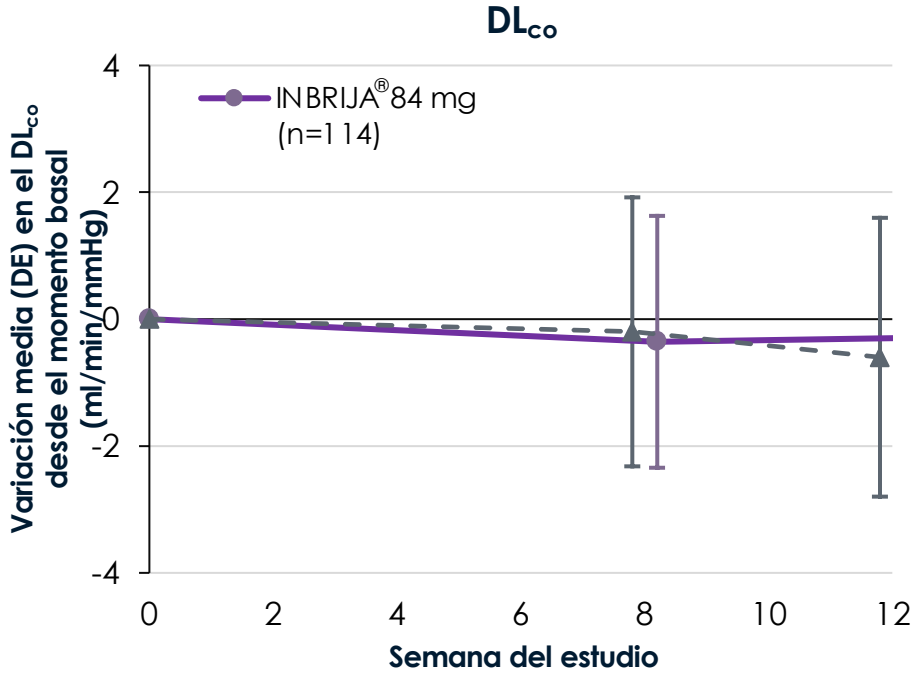
3% efectos secundarios graves
(3% placebo, 5% 60 mg, 2% 84 mg).

✓ Hipotensión (CVT-301 60 mg)
✓ ACxFA (84 mg)

Los únicos 2 efectos adversos graves considerados por los investigadores como relacionados con el fármaco.

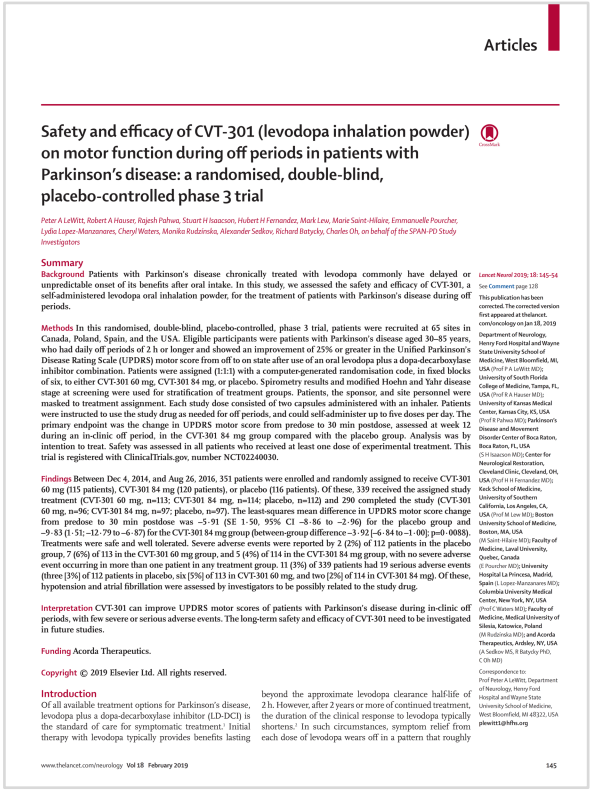
Seguridad: función pulmonar durante 12 semanas





Nota: Los puntos temporales se escalonan para facilitar la lectura.
DL_{CO}, capacidad de difusión pulmonar de monóxido de carbono; FEV_1, volumen espiratorio forzado en el primer segundo.

2. LeWitt PA, et al.; SPAN-PD Study Investigators. **Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial**. Lancet Neurol 2019;18:145-154.



Articles

Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial

Peter A LeWitt, Robert A Hauser, Rajesh Pahwa, Stuart H Isaacson, Hubert H Fernandez, Mark Lew, Marie Saint-Hilaire, Emmanuelle Pourcher, Lydia Lopez-Manzanares, Cheryl Waters, Monika Rudzinska, Alexander Sedkov, Richard Batycky, Charles Oh, on behalf of the SPAN-PD Study Investigators

Summary

Background Patients with Parkinson's disease chronically treated with levodopa commonly have delayed or unpredictable onset of its benefits after oral intake. In this study, we assessed the safety and efficacy of CVT-301, a self-administered levodopa oral inhalation powder, for the treatment of patients with Parkinson's disease during off periods.

Methods In this randomised, double-blind, placebo-controlled, phase 3 trial, patients were recruited at 65 sites in Canada, Poland, Spain, and the USA. Eligible participants were patients with Parkinson's disease aged 30–85 years, who had daily off periods of 2 h or longer and showed an improvement of 25% or greater in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score from off to on state after use of an oral levodopa plus a dopa-decarboxylase inhibitor combination. Patients were assigned (1:1:1) with a computer-generated randomisation code, in fixed blocks of six, to either CVT-301 60 mg, CVT-301 84 mg, or placebo. Spirometry results and modified Hoehn and Yahr disease stage at screening were used for stratification of treatment groups. Patients, the sponsor, and site personnel were masked to treatment assignment. Each study dose consisted of two capsules administered with an inhaler. Patients were instructed to use the study drug as needed for off periods, and could self-administer up to five doses per day. The primary endpoint was the change in UPDRS motor score from predose to 30 min postdose, assessed at week 12 during an in-clinic off period, in the CVT-301 84 mg group compared with the placebo group. Analysis was by intention to treat. Safety was assessed in all patients who received at least one dose of experimental treatment. This trial is registered with ClinicalTrials.gov, number NCT02240030.

Findings Between Dec 4, 2014, and Aug 26, 2016, 351 patients were enrolled and randomly assigned to receive CVT-301 60 mg (115 patients), CVT-301 84 mg (120 patients), or placebo (116 patients). Of these, 339 received the assigned study treatment (CVT-301 60 mg, n=113; CVT-301 84 mg, n=114; placebo, n=112) and 290 completed the study (CVT-301 60 mg, n=96; CVT-301 84 mg, n=97; placebo, n=97). The least-squares mean difference in UPDRS motor score change from predose to 30 min postdose was −5·91 (SE 1·50, 95% CI −8·86 to −2·96) for the placebo group and −9·83 (1·51; −12·79 to −6·87) for the CVT-301 84 mg group (between-group difference −3·92 [−6·84 to −1·00]; p=0·0088). Treatments were safe and well tolerated. Severe adverse events were reported by 2 (2%) of 112 patients in the placebo group, 7 (6%) of 113 in the CVT-301 60 mg group, and 5 (4%) of 114 in the CVT-301 84 mg group, with no severe adverse event occurring in more than one patient in any treatment group. 11 (3%) of 339 patients had 19 serious adverse events (three [3%] of 112 patients in placebo, six [5%] of 113 in CVT-301 60 mg, and two [2%] of 114 in CVT-301 84 mg). Of these, hypotension and atrial fibrillation were assessed by investigators to be possibly related to the study drug.

Interpretation CVT-301 can improve UPDRS motor scores of patients with Parkinson's disease during in-clinic off periods, with few severe or serious adverse events. The long-term safety and efficacy of CVT-301 need to be investigated in future studies.

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CONCLUSIONES

1. Ensayo pivotal doble ciego aleatorizado multicéntrico diseñado para conocer la eficacia y seguridad de CVT-301 84 mg (INBRIJA®).
2. Estudio **fase 3** con un total de **351 pacientes** incluidos (120 con dosis de 84 mg).
3. Predominio de varones (70%), de unos 8 años de evolución, con una media de más de 3 episodios OFF al día y más de 5 horas en OFF, sin demencia ni patología pulmonar, con varios fármacos antiparkinsonianos, y hasta un 40% con discinesias y 1 de cada 5 recibiendo amantadina.
4. Hay 3 brazos con comparación de dos dosis frente a placebo (60 y 84 mg).
5. **Hasta un 85% de los pacientes completaron el estudio (no diferencias entre grupos).** Pocos abandonos por eventos adversos (en torno al 5% o menos).
6. **Se cumple el objetivo principal (dosis de 84 mg), con una reducción a los 30 minutos de 9,83 vs 5,91 puntos en la UPDRS-III (diferencia -3,92; p=0,009). A los 10 minutos la dosis de 84 mg ya es eficaz.**
7. **En la semana 12 casi 6 de cada 10 pacientes que recibían la dosis de 84 mg se encontraban en estado ON 1 hora después de su administración**.
8. Buena tolerabilidad con pocos efectos secundarios. El más destacado con mucho la **tos**, afectando al **15%** con ambas dosis frente a sólo el 2% de placebo.
9. Limitaciones: No se analiza efecto la sobre acinesia matutina; resultado positivo con 84 mg a los 10 minutos pero no a los 20 minutos; máximo de 5 dosis al día (algunos pacientes presentaban 7 episodios de OFF); no mejoría significativa en la reducción en el tiempo OFF; no conocimiento del tiempo de duración del efecto (al menos 60 minutos); dosis de 60 mg eficaz a los 30 minutos también (no comparación directa).
10. **ES EL ENSAYO QUE PERMITE CONSEGUIR LA INDICACIÓN CON LA DOSIS DE 84 MG.**

2. LeWitt PA, et al.; SPAN-PD Study Investigators. **Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial**. Lancet Neurol 2019;18:145-154.

A 12-month, dose-level blinded safety and efficacy study of levodopa inhalation powder (CVT-301, Inbrija) in patients with Parkinson's disease

Parkinsonism and Related Disorders 81 (2020) 144–150

Eric S. Farbman [a,*], Cheryl H. Waters [b], Peter A. LeWitt [c], Monika Rudzińska [d], Michael Klingler [e], Angela Lee [e], Jenny Qian [e], Charles Oh [e], Robert A. Hauser [f]

Baseline demographic, spirometry, and PD characteristics.

Characteristic	CVT-301		
	60 mg (n = 153)	84 mg (n = 159)	Total (n = 312)
Mean age, years	63.9	62.9	63.4
Mean time from diagnosis of PD, months (SD)	103.4 (55.4)	99.3 (47.8)	101.3 (51.6)
Mean duration of LD treatment, months (SD)	86.7 (56.4)	83.7 (46.9)	85.2 (51.7)
Mean daily LD dose, mg (SD)	870.1 (372.7)	895.3 (412.5)	883.0 (393.1)
Mean daily LD doses, n (SD)	5.1 (1.6)	5.1 (1.5)	5.1 (1.5)
Screening PD diary			
Mean number of daily OFF episodes, hrs (includes AM) (SD)	3.46 (1.02)	3.56 (1.10)	3.51 (1.06)
<4.5 h daily OFF time during screening, n (%)	59 (38.6)	57 (35.8)	116 (37.2)
≥4.5 h daily OFF time during screening, n (%)	94 (61.4)	102 (64.2)	196 (62.8)
Mean daily OFF time, hrs (includes AM) (SD)	5.35 (2.11)	5.23 (2.13)	5.29 (2.12)
Mean daily ON time without dyskinesia, hrs (SD)	8.59 (3.42)	8.47 (3.49)	8.53 (3.45)

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	CVT-301		
	60 mg (n = 153)	84 mg (n = 159)	Total (n = 312)
Any TEAE	103 (67.3)	115 (72.3)	218 (69.9)
Serious TEAEs	22 (14.4)	13 (8.2)	35 (11.2)
TEAEs leading to death	0	0	0
TEAEs leading to withdrawal	12 (7.8)	14 (8.8)	26 (8.3)
Drug-related TEAEs[a]	45 (29.4)	51 (32.1)	96 (30.8)
Severe TEAEs	19 (12.4)	12 (7.5)	31 (9.9)
TEAEs > 3% of patients in any treatment group			
Cough	25 (16.3)	23 (14.5)	48 (15.4)
Fall	24 (15.7)	17 (10.7)	41 (13.1)
Upper respiratory tract infection	10 (6.5)	12 (7.5)	22 (7.1)
Dyskinesia	6 (3.9)	10 (6.3)	16 (5.1)
Throat irritation	7 (4.6)	5 (3.1)	12 (3.8)
Nasopharyngitis	8 (5.2)	4 (2.5)	12 (3.8)
Back pain	8 (5.2)	3 (1.9)	11 (3.5)
Constipation	5 (3.3)	7 (4.4)	12 (3.8)
Pain in extremity	6 (3.9)	2 (1.3)	8 (2.6)
Arthralgia	5 (3.3)	4 (2.5)	9 (2.9)
Dizziness	5 (3.3)	4 (2.5)	9 (2.9)
Urinary tract infection	5 (3.3)	4 (2.5)	9 (2.9)
Contusion	5 (3.3)	1 (0.6)	6 (1.9)
Parkinson's disease	5 (3.3)	0	5 (1.6)
Basal cell carcinoma	0	5 (3.1)	5 (1.6)

Efecto INBRIJA® durante 12 meses
Según juicio del paciente y examinador:

- ✓ 68% y 84% resolución de los episodios OFF durante los 60 minutos tras inhalación INBRIJA®
- ✓ Rango de mejoría del 66% → 92% (PGI-C = 1-3) durante todas las visitas hasta los 12 meses.
- ✓ Mejoría SIEMPRE más clara con la dosis de 84 vs 60 mg.

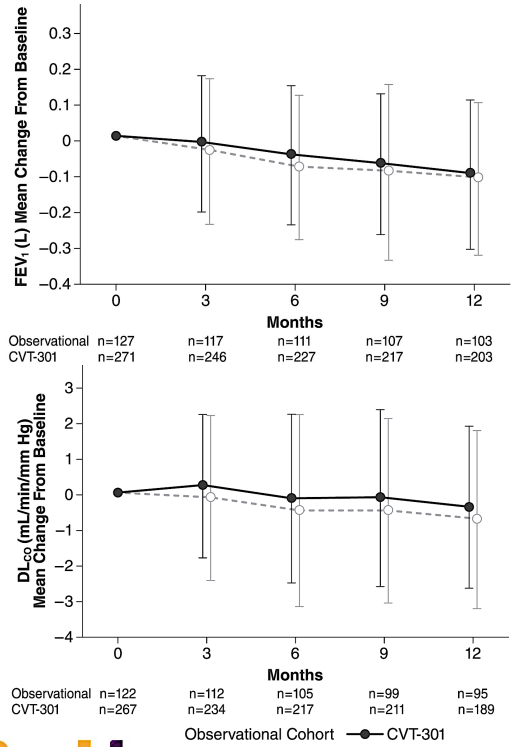
Meet in The experts

ESTEVE

Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study

Parkinsonism and Related Disorders 71 (2020) 4–10

Donald G. Grosset[a,*], Rohit Dhall[b], Tanya Gurevich[c], Jan Kassubek[d], Werner H. Poewe[e], Olivier Rascol[f], Monika Rudzinska[g], Jennifer Cormier[h], Alexander Sedkov[h], Charles Oh[h]



- Estudio prospectivo comparativo y abierto entre CVT-301 84 mg y Cohorte Obervacional (CO), de 12 meses de duración, para evaluar la seguridad pulmonar a largo plazo.

No enfermedad respiratoria crónica y pacientes capaces de realizar espirometría

✓ **NO diferencias significativas** durante los 12 meses en ningún parámetro de función respiratoria (pérdida de fx pulmonar <2,0%).

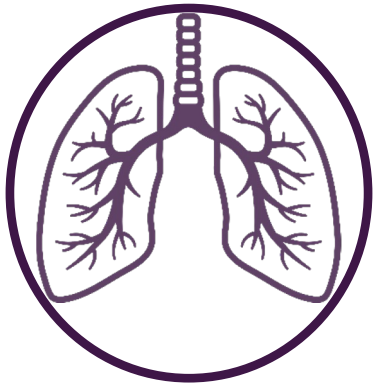
✓ **Discinesias** en cada visita disminuyeron con el tiempo:
20 % a 1 mes ➜ 13 % a los 12 meses.
Discinesias leves o moderadas; Sólo 0,4 % ➜ 1,1 % fueron graves

✓ **Perfil favorable de hipotensión ortostática**
A los 6 meses ➜ 14,5% CVT-301 y 14,9% CO.
A los 9 meses ➜ 10,4% CVT-301 y 15,3% CO.
A los 12 meses ➜ 15,4% CVT-301 y 9,3% CO.

Resultados de ECG normales y similares entre grupos

Meet in The experts

ESTEVE



Después de 1 año,
la reducción media del FEV_1 con respecto a los valores basales fue la misma en ambos grupos (-0,1 L)

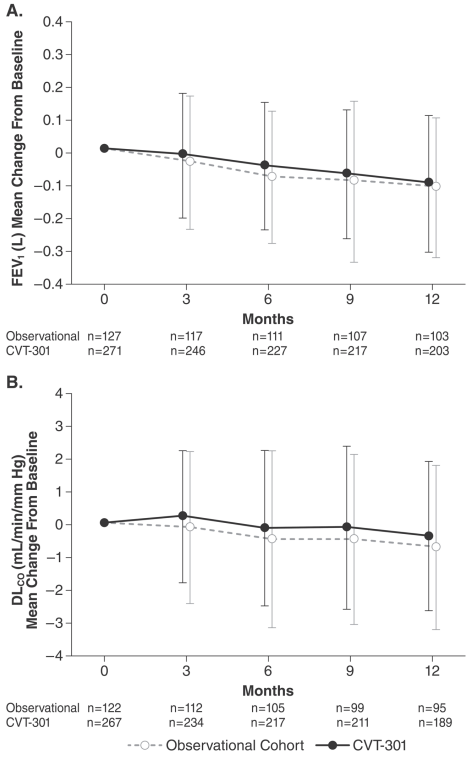


Fig. 2. Mean changes from baseline in FEV_1 (A) and DL_{CO} (B) over 12 months. Note: Error bars represent standard deviation. Time points are staggered for clarity. DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 s.

Table 2
Summary of TEAEs.

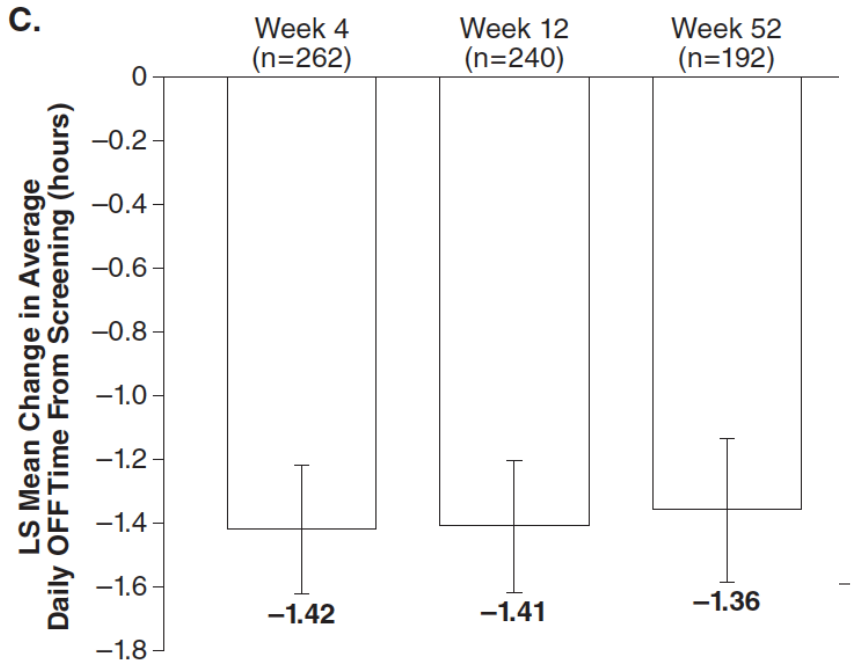
	Observational cohort (n = 127)	CVT-301 84 mg (n = 271)
Any TEAEs		
Patients, n (%)	73 (57.5)	192 (70.8)
Events, n	214	654
Serious TEAEs		
Patients, n (%)	13 (10.2)	42 (15.5)
Events, n	18	61
Severe TEAEs		
Patients, n (%)	9 (7.1)	36 (13.3)
Events, n	14	57
Drug-related TEAEs		
Patients, n (%)	–	102 (37.6)
Events, n	–	209
TEAEs leading to study withdrawal		
Patients, n (%)	0	24 (8.9)
Events, n	0	35
TEAEs occurring in ≥3% patients in any group, patients (%)		
Cough	1 (0.8)	36 (13.3)
Fall	7 (5.5)	22 (8.1)
Nasopharyngitis	7 (5.5)	18 (6.6)
Dyskinesia	5 (3.9)	17 (6.3)
Upper respiratory tract infection	3 (2.4)	13 (4.8)
Back pain	4 (3.1)	12 (4.4)
Nausea	1 (0.8)	10 (3.7)
Hypertension	4 (3.1)	9 (3.3)
Sputum discolored	0	9 (3.3)
Throat irritation	0	9 (3.3)
Arthralgia	3 (2.4)	8 (3.0)
Parkinson's disease[a]	4 (3.1)	8 (3.0)
Vertigo	0	8 (3.0)
Bronchitis	4 (3.1)	7 (2.6)
Orthostatic hypotension	4 (3.1)	7 (2.6)
Influenza	4 (3.1)	4 (1.5)
Insomnia	5 (3.9)	3 (1.1)
Musculoskeletal pain	4 (3.1)	3 (1.1)

PD, Parkinson's disease; TEAEs, treatment-emergent adverse events.
[a] Worsening of PD symptoms.

Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study

Parkinsonism and Related Disorders 71 (2020) 4–10

Donald G. Grosset[a,*], Rohit Dhall[b], Tanya Gurevich[c], Jan Kassubek[d], Werner H. Poewe[e], Olivier Rascol[f], Monika Rudzinska[g], Jennifer Cormier[h], Alexander Sedkov[h], Charles Oh[h]



Variables exploratorias

✓ Mejoría UPDRS-III desde inhalación hasta los 60 minutos → **Hasta -15 puntos!**

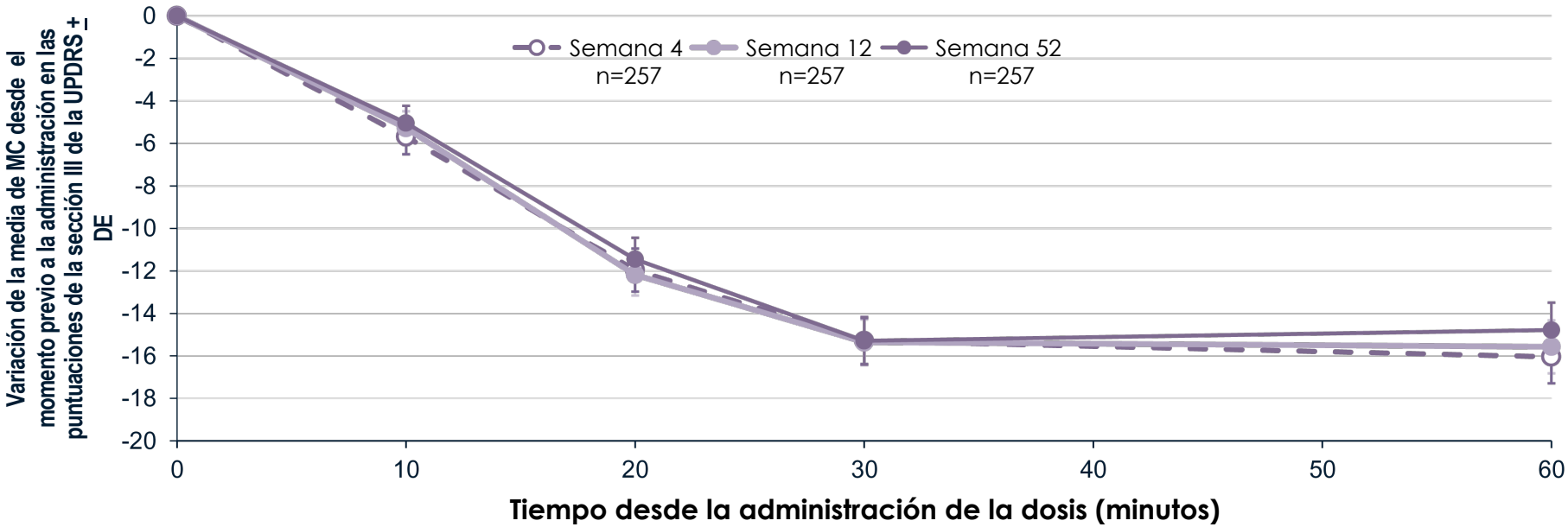
✓ **80%–85%** llegaron al ON durante los 60 min. & mantuvieron el ON a los 60 min.

✓ **>75%** mejoría subjetiva en todas las visitas (PGI-C).

✓ **OFF time** disminuyó en 1,36 – 1,42 h/día

Los diarios de Hauser mostraron ↓Tº OFF total diario durante los 12 meses de seguimiento.

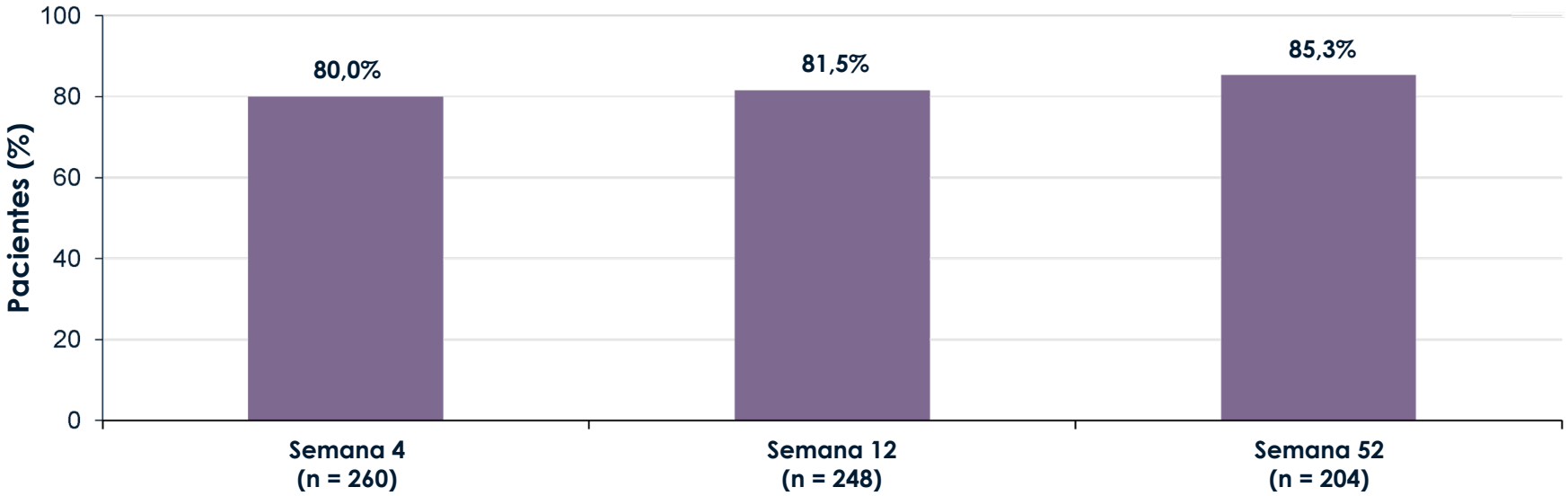
Puntuaciones motoras de la Sección III de la UPDRS después de la administración de INBRIJA®



La eficacia exploratoria se midió sólo en el grupo INBRIJA®, no en la cohorte observacional.
Las tendencias relacionadas con los resultados de eficacia en este estudio de seguridad a largo plazo son de tipo exploratorio.
Como tales, son descriptivas y carecen de poder estadístico. No se pueden extraer conclusiones de los datos.

3. Grosset DG, et al. **Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study**. Parkinsonism Relat Disord 2020;71:4-10.

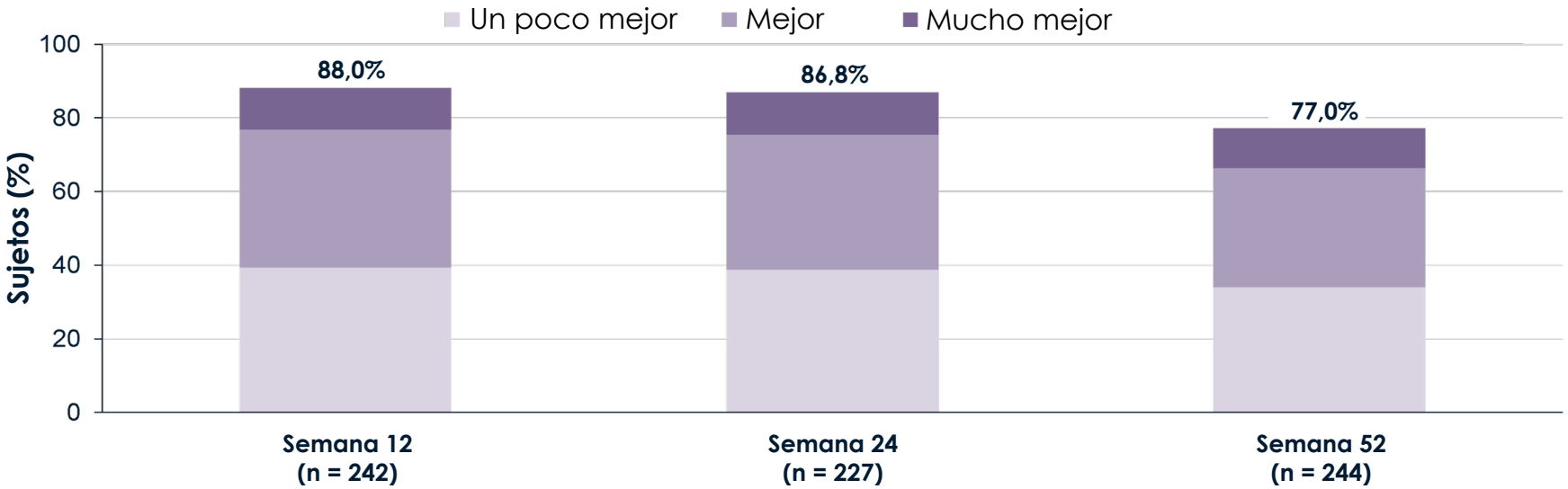
Porcentaje de pacientes que se encontraban en estado ON a los 60 minutos de recibir INBRIJA®



Las tendencias relacionadas con los resultados de eficacia en CVT-301-005 son de naturaleza exploratoria. Como tales, son descriptivas y carecen de poder estadístico. No se pueden extraer conclusiones de los datos.

3. Grosset DG, et al. **Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study**. Parkinsonism Relat Disord 2020;71:4-10.

Porcentaje de pacientes que se encontraban mejor con INBRIJA® (P-GIC)

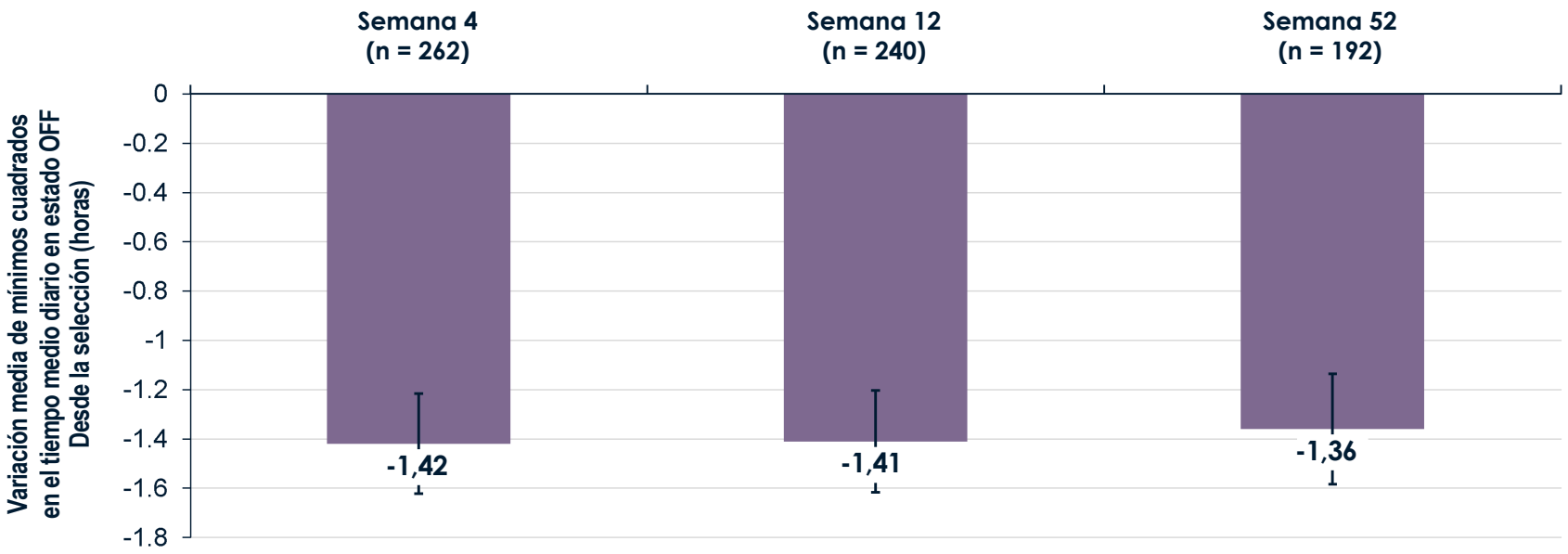


Se asume la imputación de peor caso en los datos que faltan si se produjo la visita.
La finalización prematura se agrupa en la última visita.

Las tendencias relacionadas con los resultados de eficacia en CVT-301-005 son de naturaleza exploratoria. Como tales, son descriptivas y carecen de poder estadístico. No se pueden extraer conclusiones de los datos.

3. Grosset DG, et al. **Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study**. Parkinsonism Relat Disord 2020;71:4-10.

Reducción del tiempo diario OFF con INBRIJA®



Las barras de error representan los errores estándar.
Los pacientes facilitaron los datos de tiempo en estado OFF a través de un diario de EP en el domicilio (3 últimos días antes de la visita). Las tendencias relacionadas con los resultados de eficacia en INBRIJA son de naturaleza exploratoria. Como tales, son descriptivas y carecen de poder estadístico.
No se pueden extraer conclusiones de los datos.

3. Grosset DG, et al. **Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study**. Parkinsonism Relat Disord 2020;71:4-10.

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Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study

Donald G. Grosset[a,*], Rohit Dhall[b], Tanya Gurevich[c], Jan Kassubek[d], Werner H. Poewe[e], Olivier Rascol[f], Monika Rudzinska[g], Jennifer Cormier[h], Alexander Sedkov[h], Charles Oh[h]

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ARTICLE INFO

Keywords:
Inhaled levodopa
Motor fluctuations
Off periods
Safety
Efficacy

ABSTRACT

Introduction: CVT-301 is an orally inhaled levodopa therapy approved for the intermittent treatment of OFF episodes in Parkinson's disease patients who are taking a standard oral levodopa regimen. This open-label, randomized, controlled study over 12 months characterizes the safety, including pulmonary safety, of CVT-301 84 mg (nominal respirable levodopa fine-particle dose, 50 mg).

Methods: Patients experiencing motor fluctuations were randomized 2:1 to CVT-301 or an observational cohort (OC) receiving oral standard of care. Pulmonary safety was assessed using spirometry and carbon monoxide diffusion capacity (DL_{CO}). Exploratory efficacy endpoints, assessed only for CVT-301, included change in Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), patients achieving ON within 60 min and remaining ON at 60 min, Patient Global Impression of Change (PGIC) scale, and total daily OFF time.

Results: Of 408 patients randomized, 310 completed the study (204 in CVT-301 and 106 in OC). Mean 12-month changes from baseline for CVT-301 were −0.105 L (FEV_1) and −0.378 mL/min/mm Hg (DL_{CO}), and for OC were −0.117 L and −0.722 mL/min/mm Hg, respectively. Between-group comparisons were not statistically significant. For FEV_1/FVC the 12-month change was −0.3 and −1.6, respectively, which was a significant between-group difference. However, between-group differences were not significant at 3 and 9 months and all changes from baseline were small (< 2.0%). UPDRS-III scores improved from predose to 60 min postdose at all assessments; 80%–85% of patients switched ON within 60 min and remained ON; and > 75% reported improvement in PGIC. OFF time decreased by 1.32–1.42 h/day.

Conclusion: CVT-301 84 mg induced no clinically significant differences in pulmonary function compared with the OC. Improvements in motor scores, OFF time, and patient-reported outcomes support clinical efficacy for up to 12 months.

1. Introduction

Levodopa (LD) administered orally with a dopa decarboxylase inhibitor (DDI) such as carbidopa is the most effective treatment for managing the motor symptoms of Parkinson's disease (PD) [1–3]. However, ON-OFF fluctuations become increasingly frequent with chronic LD exposure and disease progression [3–5].

CVT-301 (Inbrija™) is a self-administered, orally inhaled therapy approved for the intermittent treatment of OFF-period symptoms in patients with PD who are taking an oral carbidopa/LD regimen [6–8]. Inhaled LD, which bypasses the gastrointestinal route, enters the bloodstream rapidly and predictably [8]. In a double-blind, placebo-controlled phase 3 study in patients on standard PD therapy, CVT-301 84 mg (nominal respirable LD fine-particle dose, 50 mg) significantly

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1353-8020/

CONCLUSIONES

1. Estudio abierto con seguimiento a 1 año de seguridad de CVT-301 sobre la función pulmonar.
2. 271 pacientes tratados con CVT-301 a dosis de 84 mg que se compararon con una cohorte observacional de 127 pacientes de características similares.
3. Características similares a las del ensayo fase 3. Predominio de varones (60%), de unos 9 años de evolución, con una media de más de 3 episodios OFF al día y más de 5 horas en OFF, sin demencia ni patología pulmonar, con varios fármacos antiparkinsonianos, y hasta un 70% recibiendo un agonista dopaminérgico y un 30% amantadina.
4. La tasa de abandonos en el grupo tratado fue de un 27% frente al 18% en la cohorte observacional. Del total del grupo tratado (N=271), un 10% abandonaron por efectos adversos.
5. **Después de 1 año de seguimiento, la reducción media del FEV1 con respecto a los valores basales fue la misma en ambos grupos (-0,1 L).**
6. **La tos fue el efecto secundario más frecuente, 13%** en el grupo tratado con 84 mg de CVT-301.
7. **Respuesta similar al mes, 3 meses y 12 meses**, con **reducción de en torno a 15 puntos en la escala UPDRS-III a los 30 minutos**. Este efecto se mantiene después de 60 minutos.
8. **8 de cada 10 pacientes en estado ON a los 60 minutos** de administración de CVT-301, tanto al mes, 3 meses como 12 meses, que se acompañó de similar percepción de mejoría (77% al año).
9. **Reducción del tiempo OFF en algo menos de 1,5 horas después de 1 año de seguimiento**.
10. Limitaciones: No se analiza efecto la sobre acinesia matutina; 6,6% de los pacientes no completaron la espirometría correctamente; el grupo comparativo sólo fue para la función pulmonar; de nuevo, no sabemos cuanto puede durar el efecto más allá de los 60 minutos.
11. **ESTUDIO IMPORTANTE QUE DEMUESTRA BENEFICIO Y SEGURIDAD A CORTO Y LARGO PLAZO.**

3. Grosset DG, et al. **Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study**. Parkinsonism Relat Disord 2020;71:4-10.

Parkinsonism and Related Disorders 64 (2019) 175–180

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Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease

Robert A. Hauser[a,*], Stuart H. Isaacson[b], Aaron Ellenbogen[c], Beth E. Safirstein[d], Daniel D. Truong[e,f], Steven F. Komjathy[g], Deena M. Kegler-Ebo[g], Ping Zhao[g], Charles Oh[g]

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[b] Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL, USA
[c] Quest Research Institute, Bingham Farms, MI, USA
[d] MD Clinical, Hallandale Beach, FL, USA
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Carbidopa
Inhalation
Inbrija

ABSTRACT

Background: CVT-301 (Inbrija) is a self-administered orally inhaled levodopa approved for the intermittent treatment of OFF episodes in patients with Parkinson's disease (PD) treated with carbidopa/levodopa. Prior studies only evaluated CVT-301 after the first ON of the day.

Objective and methods: The objective of this study was to evaluate the safety and tolerability of CVT-301 for early morning OFF. Using a randomized, double-blind, 2-way crossover design, eligible patients in the morning OFF state (having not received PD medication overnight) received a single dose of CVT-301 84 mg or placebo on 2 dosing days, immediately after their first morning oral carbidopa/levodopa dose. Safety assessments included treatment-emergent adverse events, vital signs, and patient- and examiner-reported dyskinesia. An exploratory efficacy assessment was examiner-rated time-to-ON with carbidopa/levodopa + CVT-301 vs carbidopa/levodopa + placebo.

Results: Of the 36 patients (mean age 62.9 years) who enrolled and completed the study, 9 (25.0%) reported treatment-emergent adverse events following CVT-301 administration; 4 (11.1%) reported treatment-emergent adverse events following placebo. The most common adverse event was cough (4 [11.1%] for CVT-301 vs 1 [2.8%] for placebo), which was typically mild and transient. Incidence of asymptomatic orthostatic hypotension (CVT-301, 6; placebo, 7) and examiner-rated dyskinesia were similar for both (36–39% mild, 3–4% moderate, and 0% severe). Median time-to-ON was 25.0 min following carbidopa/levodopa + CVT-301 and 35.5 min following carbidopa/levodopa + placebo ($P = 0.26$). At 30 min, more patients had turned ON following carbidopa/levodopa + CVT-301 administration (66.7%), compared with carbidopa/levodopa + placebo (44.5%) ($P = 0.046$).

Conclusion: Single doses of CVT-301 84 mg administered with oral carbidopa/levodopa for early morning OFF symptoms were well-tolerated, with no notable safety concerns.

1. Introduction

CVT-301 (Inbrija™) is a self-administered, orally inhaled levodopa (LD) formulation approved in the US for the intermittent treatment of OFF episodes in patients with Parkinson's disease (PD) treated with carbidopa (CD)/LD. Prior studies only evaluated CVT-301 in patients on oral CD/LD therapy after the first ON of the day, when CD levels are presumed to be adequate to afford sufficient decarboxylase inhibition to minimize peripheral dopamine side effects from LD such as nausea/vomiting and orthostatic hypotension. The purpose of this study was to evaluate the acute safety and tolerability of CVT-301 given with the first oral CD/LD dose of the day, during early morning OFF, when plasma levels of CD may be low or nonexistent following an overnight break in oral CD/LD administration.

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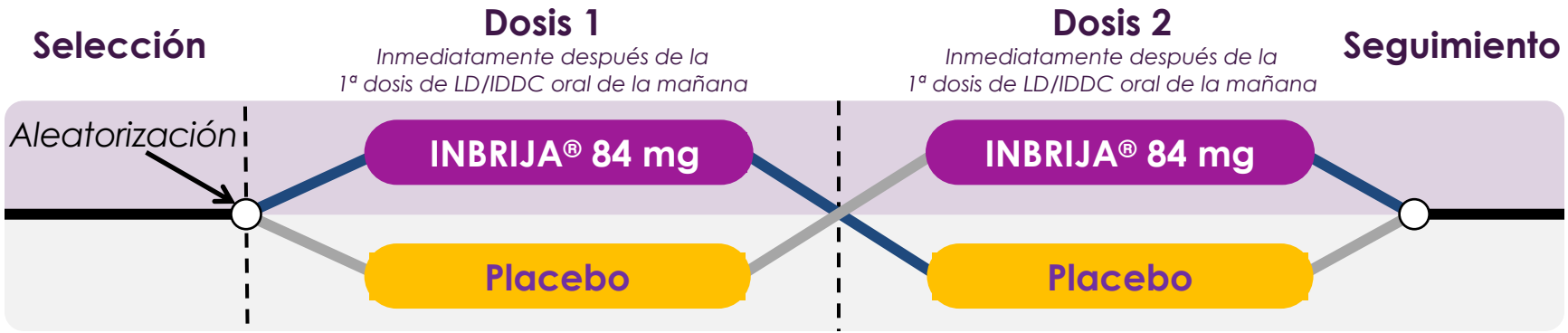
2. LeWitt PA, wt al.; SPAN-PD Study Investigators. **Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial**. Lancet Neurol 2019;18:145-154.

3. Grosset DG, et al. **Inhaled levodopa in Parkinson's disease patients with OFF periods: A randomized 12-month pulmonary safety study**. Parkinsonism Relat Disord 2020;71:4-10.

4. Hauser RA, et al. **Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease**. Parkinsonism Relat Disord 2019;64:175-180.

Estudio de INBRIJA® para la acinesia matutina (CVT-301-009)



- Necesidad de evaluar eficacia y seguridad de CVT-301 a primera hora de la mañana (niveles bajos de carbidopa)
- Estudio doble ciego, aleatorizado, controlado con placebo y bidireccional de grupos cruzados realizado en **36 pacientes** con enfermedad de Parkinson y fluctuaciones motoras
- **Objetivo principal: seguridad y tolerabilidad de INBRIJA® cuando se administra para tratar el periodo OFF a primera hora de la mañana en pacientes con enfermedad de Parkinson.**
- **Objetivo secundario: tiempo hasta el estado ON evaluado por el examinador comparando INBRIJA® frente placebo administrados con la primera dosis oral de LD/IDDC del día.**

4. Hauser RA, et al. **Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease**. Parkinsonism Relat Disord 2019;64:175-180.

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Parkinsonism and Related Disorders 64 (2019) 175–180

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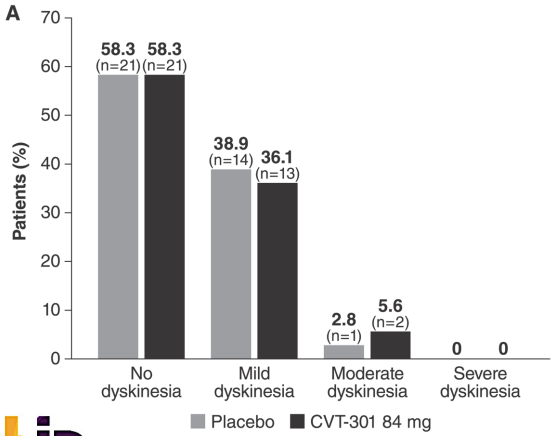
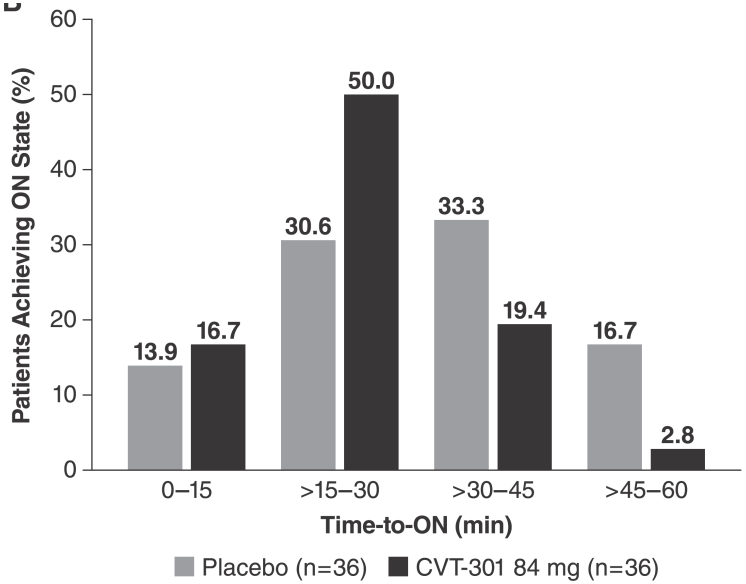
Duration of PD (y), mean (range)	7.9 (1.4–15.3)
LD daily dose (mg), mean (SD)	727.5 (272.0)
LD morning dose (mg), mean (SD)	183.8 (124.4)[a]
Hoehn & Yahr stage, n (%)	
1	2 (5.6)
2	16 (44.4)
2.5	8 (22.2)
3	10 (27.8)





✓ A los 30 minutos ⇒ 66,7% (n=24) alcanzaron el ON tras **84 mg CVT-301** > 44,5% (n=16) con placebo (p=0,04).

Parkinsonism and Related Disorders 64 (2019) 175–180

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Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease

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ABSTRACT

Background: CVT-301 (Inbrija) is a self-administered orally inhaled levodopa approved for the intermittent treatment of OFF episodes in patients with Parkinson's disease (PD) treated with carbidopa/levodopa. Prior studies only evaluated CVT-301 after the first ON of the day.

Objective and methods: The objective of this study was to evaluate the safety and tolerability of CVT-301 for early morning OFF. Using a randomized, double-blind, 2-way crossover design, eligible patients in the morning OFF state (having not received PD medication overnight) received a single dose of CVT-301 84 mg or placebo on 2 dosing days, immediately after their first morning oral carbidopa/levodopa dose. Safety assessments included treatment-emergent adverse events, vital signs, and patient- and examiner-reported dyskinesia. An exploratory efficacy assessment was examiner-rated time-to-ON with carbidopa/levodopa + CVT-301 vs carbidopa/levodopa + placebo.

Results: Of the 36 patients (mean age 62.9 years) who enrolled and completed the study, 9 (25.0%) reported treatment-emergent adverse events following CVT-301 administration; 4 (11.1%) reported treatment-emergent adverse events following placebo. The most common adverse event was cough (4 [11.1%] for CVT-301 vs 1 [2.8%] for placebo), which was typically mild and transient. Incidence of asymptomatic orthostatic hypotension (CVT-301, 6; placebo, 7) and examiner-rated dyskinesia were similar for both (36–39% mild, 3–6% moderate, and 0% severe). Median time-to-ON was 25.0 min following carbidopa/levodopa + CVT-301 and 35.5 min following carbidopa/levodopa + placebo ($P = 0.26$). At 30 min, more patients had turned ON following carbidopa/levodopa + CVT-301 administration (66.7%), compared with carbidopa/levodopa + placebo (44.5%) ($P = 0.040$).

Conclusion: Single doses of CVT-301 84 mg administered with oral carbidopa/levodopa for early morning OFF symptoms were well-tolerated, with no notable safety concerns.

1. Introduction

CVT-301 (Inbrija®) is a self-administered, orally inhaled levodopa (LD) formulation approved in the US for the intermittent treatment of OFF episodes in patients with Parkinson's disease (PD) treated with carbidopa (CD)/LD. Prior studies only evaluated CVT-301 in patients on oral CD/LD therapy after the first ON of the day, when CD levels are presumed to be adequate to afford sufficient decarboxylase inhibition to minimize peripheral dopamine side effects from LD such as nausea/vomiting and orthostatic hypotension. The purpose of this study was to evaluate the acute safety and tolerability of CVT-301 given with the first oral CD/LD dose of the day, during early morning OFF, when plasma levels of CD may be low or nonexistent following an overnight break in oral CD/LD administration.

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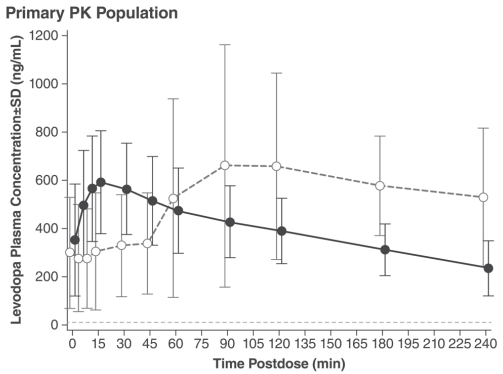
CONCLUSIONES

1. Estudio doble ciego cruzado que demuestra que CVT-301 84 mg es segura y bien tolerada para tratar la acinesia matutina.
2. Se incluyeron un total de 36 pacientes.
3. Predominio de varones (58%), con buena función pulmonar, con casi 8 años de evolución de enfermedad, tratados con varios fármacos y una dosis diaria de levodopa de más de 700 mg y matutina en torno a 180 mg.
4. **Efectos secundarios en casi el 20% de los pacientes al recibir CVT-301 84 mg frente al 5% al recibir placeo (son los mismos pacientes).**
5. **La tos fue nuevamente el efecto secundario más frecuente (11,1%).**
6. **No hubo diferencias en cuanto a las discinesias que no parecen un problema**, no apareciendo en hasta casi el 60% de los pacientes con ambas terapias y siendo sólo moderadas en menos del 6% de los paciente. No hubo ningún paciente que desarrollara discinesias severas.
7. **A los 16 a 30 minutos, el 50% de los pacientes alcanzaban el ON con CVT-301 frente al 30% cuando recibieron placebo.** Por contra, menos del 3% después de 45 minutos.
8. Limitaciones: No se diseñó para analizar la respuesta sino la tolerabilidad y seguridad; se desconoce la respuesta que podría haber incrementando la dosis de levodopa/carbidopa de la mañana; baja sensibilidad de los diarios para detectar diferencias en el tiempo OFF en las 3 horas post-administración; efecto del placebo considerable y más prolongado que el de CVT-301 (a los 46 a 60 minutos, 16,7% frente a 2,8%).
9. **ESTUDIO QUE DEMUESTRA que INBRIJA® podría utilizarse en acinesia matutina.**

4. Hauser RA, et al. **Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease**. Parkinsonism Relat Disord 2019;64:175-180.



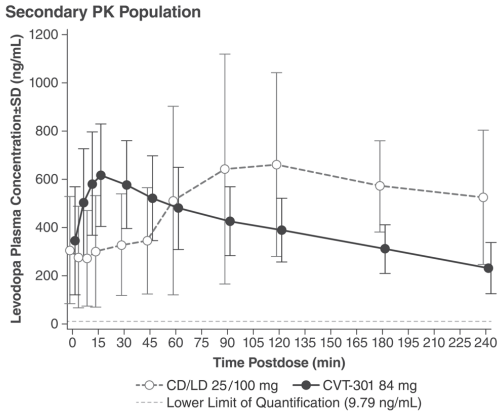
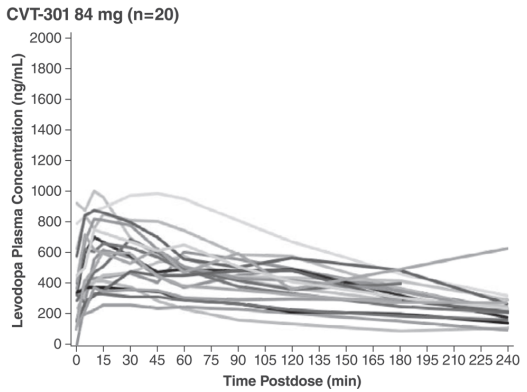


Figure 3. Mean (SD) plasma levodopa concentrations after a single inhaled dose of CVT-301 84 mg and after a single ingested dose of CD/LD 25/100 mg, by study population. Data points are staggered for clarity. CD = carbidopa; LD = levodopa; PK = pharmacokinetics.



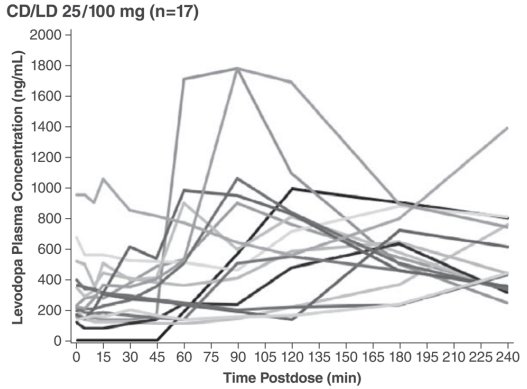


Figure 4. Individual plasma levodopa profiles after a single inhaled dose of CVT-301 84 mg and after a single ingested dose of CD/LD 25/100 mg (primary PK population). CD = carbidopa; LD = levodopa; PK = pharmacokinetics.

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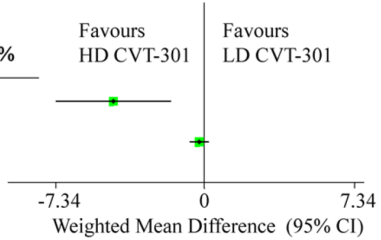
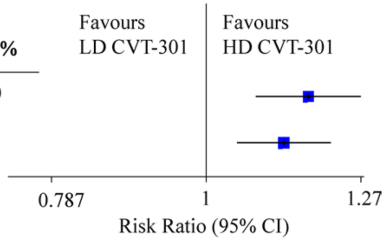
Efficacy	No. of Studies	HD CVT-301 Total	Mean	SD	LD CVT-301 Total	Mean	SD	Weighted Mean Difference (95% CI)	P value	I^2, %
A.UPDRS PartIII(30 minutes post-dose)	4	578	-14.18	26	198	-9.67	13.45	-4.51(-7.34, -1.68)	0.002	0
D.Change in Average Daily OFF Time	3	564	-1.29	3.06	137	-1.00	2.37	-0.29(-0.76, -0.18)	0.227	0



Efficacy	No. of Studies	HD CVT-301 Events	Total	Rate, %	LD CVT-301 Events	Total	Rate, %	Risk Ratio (95% CI)	P value	I^2, %
B.Patients who achieved and maintained an ON state up to 60 minutes post-dose	5	664	868	76.50	254	389	65.30	1.17(1.08, 1.27)	<0.001	0
C.Patients with improved PGIC score	4	777	1003	77.47	289	421	68.65	1.13(1.05, 1.21)	0.001	0



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Can Patients with Parkinson's Disease Use Dry Powder Inhalers during Off Periods?

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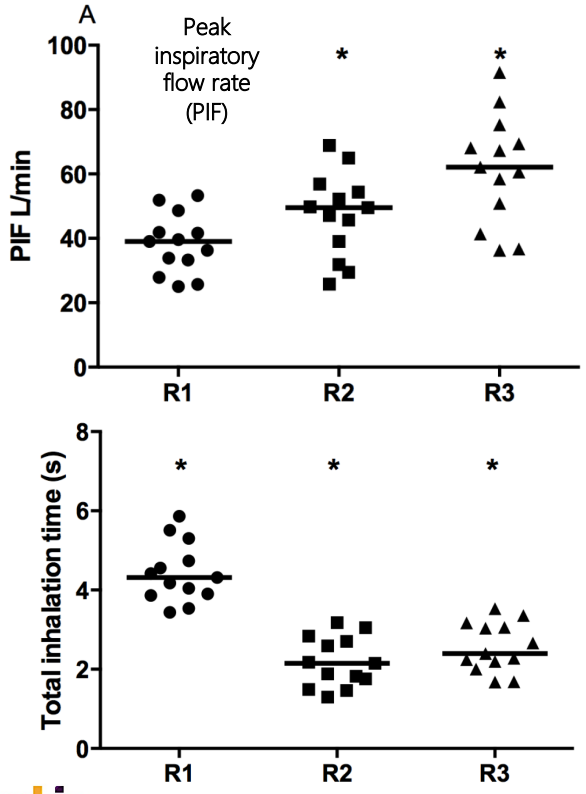

- Inhaladores con 3 resistencias de flujo de aire diferentes:
  R1 = 0,061 kPa → R2 = 0,048 kPa → R3 = 0,037 kPa.
- Dificultades para una inhalación correcta la primera vez.
- Particularmente difícil seguir las acciones en el orden correcto.
- Después de la práctica, todos los pacientes obtuvieron mejoría excepto uno (12/13), que mostró la tendencia a espirar a través del inhalador, incluso después del ejercicio repetido.
- Los 13 pacientes pudieron generar presiones >2 kPa, incluso en R3, y 10 pacientes lograron ≥4 kPa.
- 12/13 pacientes pudieron contener la respiración durante al menos 5 segundos después de la inhalación y 9 pudieron mantenerla hasta los 10 segundos.
- La presencia de temblor durante el uso del dispositivo no fue problemático para sostener el inhalador en la posición correcta.

Estos datos indican que los pacientes con EP consiguen utilizar un inhalador de polvo seco durante los períodos de descanso.

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