

Clinical Trial Highlights – Infusion Therapies

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INTRODUCTION

Advancing Parkinson's Disease (PD) is marked by the appearance of motor and non-motor complications some of which are related to chronic levodopa therapy. These complications can be disabling and negatively impact the quality of life. The motor complications associated with chronic levodopa therapy include early morning OFFs, wearing off, delayed ON, ON-OFF phenomenon, dose failures, and dyskinesias.

Motor complications result from the combination of multiple underlying factors. Reduced striatal dopaminergic terminal function plays a pivotal role in the variable response to levodopa therapy. With advancing dopaminergic terminal and dopamine transporter loss, striatal neurons slowly lose the ability to store dopamine in terminal vesicles. This, in turn, affects the neuron's ability to buffer the synaptic dopamine levels with exogenous levodopa use [1, 2].

Additionally, intermittent oral levodopa leads to pulsatile stimulation of the degenerating striatal neurons. Such pulsatile delivery leads to changes at the receptor level that contribute towards fluctuations in clinical response. The oral levodopa bioavailability is also affected by its short half-life and unpredictable absorption. Other factors include delayed gastric emptying and impaired absorption across the intestine and blood-brain barrier [1, 2].

One potential solution aims to develop therapies that could deliver steady or continuous dopaminergic stimulation at the striatal level. Though controlled release forms of levodopa are available, they do not prevent or provide significantly prolonged benefit for motor complications [2,3]. This creates space for the development of infusion therapies. Advanced therapies currently available on the market include Levodopa-Carbidopa intestinal gel (LCIG), Deep Brain Stimulation (DBS) and Apomorphine pump.

Advanced therapies including DBS are recommended to relatively younger PD patients with motor complications who have no significant comorbidities that could increase the risk of surgical procedure. While indications for infusion therapies including LCIG and apomorphine are generally the same they are specifically recommended for older patients, patients with impaired cognition and other contraindications to DBS [4]. For the purpose of this issue, we will focus on infusion therapies.

LCIG is currently approved in Europe and Japan as Duodopa® and recently in the USA as Duopa®. LCIG has been efficacious in reducing OFF time, improving dyskinesia and quality of life over the long term [2, 5]. LCIG requires placement of a percutaneous endoscopic gastrostomy-jejunal tube (PEG-J) which is then attached to the pump. LCIG is available in cassettes that the patient or caregiver changes every morning. Due to the direct delivery of the medication to the jejunum, LCIG has an added advantage of bypassing the gastric emptying and being able to provide a steadier levodopa delivery. There is strong evidence of continued improvement in OFF

times and quality of life. Though there is limited data, there is a positive impact of LCIG on dyskinesia and non-motor symptoms [2]. Though the therapy provides relief to patients with Parkinson's (PwPs) with motor complications, there is also a higher rate of adverse events (AE). Pooled analysis in 2016 reported a high rate (~75%) of device or procedure related AE, a small percentage leading to therapy discontinuation [2]. However, recent data from the GREENFIELD study reports only 16% device related AE [5]. Though variable, device related AE like tube blockage and replacement can be inconvenient to PwPs.

Apomorphine subcutaneous (s.c.) infusion is the other infusion therapy currently available on the market in Europe and being studied in the US. Apomorphine is a potent broad-spectrum dopamine agonist exerting its effect on all dopaminergic receptors. It has a very short half-life and is not absorbed orally. It is one of the oldest dopamine agonists and has been shown to be efficacious in alleviating OFF symptoms. It has been available for a while as a rescue drug used as an injectable. A large number of open-label studies have supported the use of s.c. apomorphine infusions as monotherapy or add on therapy by demonstrating a significant reduction in daily OFF time and dyskinesia, and improved motor functions [6].

Despite being available on the European market for a while, the first ever multicenter, double-blinded, placebo-controlled TOLEDO trial of apomorphine infusion was completed only recently [7]. It was shown to reduce the daily OFF time by 2 hr as compared to the placebo arm and was well tolerated. The drug is delivered subcutaneously via an infusion pump that has to be replaced daily [7]. Despite the availability of current advanced therapies, there is room for the development of more sophisticated alternatives for drug delivery to expand the pool of patients and scenarios, reduce device related AE and possibly be more user friendly for PwPs. For this issue, we will highlight the infusion therapies currently in development.

References

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Experimental Infusion Therapies In Clinical Trials

Overview

There are six programs in clinical trial phases for infusion therapies, four in Phase 3 and two in Phase 1.

All the therapies in the clinic use either levodopa/carbidopa (LD/CD) or apomorphine and all use sub-cutaneous (s.c.) administration, although Dizlin is developing both s.c. and intra-venous (i.v.) versions of Infudopa.

The table below summarises the key elements of each project.

ORGANISATION	PROJECT NAME	DRUG	PHASE	TARGET COMPLETION	NCT NUMBER
Abbvie	ABBV-951	LD/CD	3	March 2021	03781167
Mitsubishi Tanabe/ Neuroderm	ND0612	LD/CD	3	April 2021	04006210
Rennes University	EARLY-PUMP	Apomorphine	3	March 2023	02864004
US WorldMeds	INFUS-ON	Apomorphine	3	September 2021	02339064
Mitsubishi Tanabe/ Neuroderm	ND0701	Apomorphine	1	N/A	N/A
Dizlin	Infudopa	LD/CD	1	Early 2020	03419806

The targets for infusion therapies are people with moderately advanced PD in all cases except EARLY-PUMP. This project is built on the hypothesis that intervention with continuous infusion of apomorphine is best initiated before motor complications develop.

Dizlin is comparing Infudopa, both i.v. and s.c., to Abbvie's intra-jejunal gel, Duodopa. ABBV-951 and INFUS-ON have an open-label single arm only design with no active comparator. Due to the nature of the trial cohort, the comparator in the Rennes University study is optimised medical treatment. ND0612 is being compared to placebo, both s.c., and in tablet form.

The duration of treatment for the Phase 3 trials is 12 weeks with the exception of Abbvie which runs for 52 weeks.

Both primary and secondary outcomes are focused on efficacy for ND-0612, EARLY-PUMP and INFUS-ON whereas the primary outcome for ABBV-951 is safety; secondary outcome measures will assess efficacy. The outcome measures of the Infudopa study reflect its focus on pharmacokinetics, although some secondary measures use the Parkinson Kinetigraph to quantify symptoms.

Mitsubishi Tanabe/Neuroderm's ND0701, a continuous s.c. pump delivering apomorphine, is in Phase 1 as reported on the company website. There is no NCT entry on clinicaltrials.gov, nor a listing on EudraCT, but a paper outlining a Phase 1 study in healthy volunteers has been published [1]. ND0701 was safe and well-tolerated, with bioavailability equivalent to APO-go (s.c. apomorphine, Britannia Pharmaceuticals).

Lobsor's LECIGon is an intra-jejunal gel formulation of levodopa, carbidopa, and entacapone, similar to Abbvie's Duodopa but with the addition of entacapone. LECIGon's Phase 1 study in 11 patients reported in 2015 (NCT02448914) and was used as a pivotal study to gain approval in Sweden, where it was recently launched. Valeritas is in the pre-clinical stage with the h-Patch aiming to deliver s.c. apomorphine.

Given the surgical and maintenance challenges of intra-jejunal gel for continuous delivery of LD/CD, the therapies in development using s.c. delivery offer the potential for consistent levels of dopaminergic therapy with fewer side effects. The prospect of self-administration for patients is also attractive. Dizlin's Infudopa i.v. also has the potential to add another option for in-patient therapy.

References

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Abbvie- ABBV-951

Background: Abbvie already has a presence in the PD market via its infusion therapy, Duodopa® (EU, Japan) and Duopa® (US). The company is focusing on developing newer treatments and delivery systems for PD. Abbvie has been working on developing a novel solution of LD/CD that can be administered continuously via the less invasive s.c. route [1].

They recently published data regarding the single dose escalating phase 1 study looking at the pharmacokinetic (PK) and safety profile of ABBV-951. The molecule was administered subcutaneously to 6 healthy volunteers over a 72-h period. The study demonstrated rapid conversion of the prodrug to levodopa and stable levodopa exposure over 72-h. The main AE were infusion site reactions including infusion site edema and transient pain [2]. The results allowed for initiation of the current study described below.

Title: A 52-Week, Open-label, Single-arm Study to Evaluate the Safety and Tolerability of 24-hour Daily Exposure of Continuous Subcutaneous Infusion of ABBV-951 in Subjects With Parkinson's Disease

Phase: 3

Objective: A phase 3 interventional study designed to assess the safety and tolerability of ABBV-951 in participants with Parkinson's Disease (PD)

Status: Recruiting

Clinicaltrials.gov Identifier: NCT03781167

Sponsor: AbbVie

Estimated Enrolment: 130 participants

Estimated Primary Completion Date: March, 2021

Study Design: This is a phase 3, 52-week, open-label, a single-arm interventional study evaluating the safety and tolerability of continuous s.c. infusion of the active drug ABBV-951.

The study is including participants 30 years or older with levodopa responsive idiopathic PD inadequately controlled by their current therapy and having recognizable motor fluctuations, with a minimum of daily 2.5 hrs of OFF time. Standard exclusionary criteria are applied including cognitive impairment that will prevent the

participant to safely and effectively adhere to the study requirements. The study is being conducted across multiple international centers.

The study includes a screening period, a dose optimization period of 4 weeks followed by 48 weeks of the maintenance period. The study requires a daily 24 hr infusion via a s.c. pump.

Outcome Measures:

The primary objective of the study overall focuses on the safety profile of the drug. It monitors the following from the day of the infusion through 30 days after the last infusion device is removed.

1. Treatment emergent AE with a focus on AE of special interest defined as any AE of polyneuropathy or weight loss.
2. Effect on blood and urine parameters from baseline to the end of the study.
3. Effect on blood pressure, pulse rate and abnormal electrocardiogram up to 56 weeks.

The secondary outcomes focus on the clinical outcome looking at the change from baseline to the end of the study, which is up to 56 weeks.

1. Average normalized daily OFF time and ON time.
2. Parkinson's symptoms as assessed by the MDS-UPDRS parts I-IV.
3. Quality of life using the PDQ-39 and EQ-5D-5L scores.
4. Sleep symptoms using the Parkinson's Disease Sleep Scale-2.

Comments:

Since these are initial studies, their focus is on the safety and tolerability profile. It will be important to demonstrate equal, if not superior, long-term PK profile of the prodrug with similar clinical efficacy as compared to LCIG. The newer drug, if successful, may provide a less invasive alternative to appropriate candidates in comparison to LCIG via PEG-J tube and potentially bypass gastric related complications. The trial is still ongoing and design for the study was recently presented during the 2019 Movement Disorder Society – International Congress [3].

References:

- [1] <https://www.abbvie.com/our-science/pipeline/abbv-951.html>
- [2] M. Rosebraugh, P. Kym, W. Liu, M. Facheris, J. Benesh, A Novel Levodopa/Carbidopa Prodrug (ABBV-951) 24-Hour Continuous Subcutaneous Infusion Treatment for Parkinson's Disease (P3.8-037), *Neurology*. 92 (2019).
- [3] Safety and Tolerability in Parkinson's Disease Patients Treated with a Continuous Subcutaneous Infusion of ABBV-951: Design of a 52-Week Phase 3 Study - MDS Abstracts, (n.d.). <https://www.mdsabstracts.org/abstract/safety-and-tolerability-in-parkinsons-disease-patients-treated-with-a-continuous-subcutaneous-infusion-of-abbv-951-design-of-a-52-week-phase-3-study>.

Mitsubishi Tanabe Pharma/Neuroderm ND0612

Background: Neuroderm is a wholly owned subsidiary of Mitsubishi Tanabe Pharma, who acquired the company in 2017. They are developing ND0612, a continuous s.c. infusion of LD/CD together with a higher dose version for more advanced patients (ND0612H). The formulation is delivered using either a discrete infusion patch-pump or a s.c. pump.

A phase I dose-escalating study on 54 healthy volunteers showed good tolerability and safety, with s.c. dose ranging from 0.08 to 0.24 ml/h (corresponding to 120 to 360 mg/day of LD) and stable plasma concentrations from 400 to 500 ng/ml [1]. Direct s.c. delivery reduced oral LD/CD intake, in the case of the Phase 2a study by 80% [2].

ND0612H was evaluated in a Phase 2 trial (NCT02577523) comparing two regimens; 24h continuous infusion (720mg/90mg LD/CD) and 14h infusion (538mg/68mg LD/CD) supplemented by oral LD/CD [3]. Both regimens were well tolerated with the 24h approach significantly reducing OFF time and increasing ON time ahead of regimen 2.

Following these trials and further successful studies in Phase 1a (NCT01486628), Phase 1/2a (NCT01725802) and Phase 2a (NCT01883505), Neuroderm have started the BouNDless Phase 3 trial.

Title: A Clinical Trial Investigating the Efficacy, Safety and Tolerability of Continuous Subcutaneous ND0612 Infusion in Comparison to Oral IR-LD/CD in Subjects With Parkinson's Disease Experiencing Motor Fluctuations (BouNDless).

Phase: 3

Status: Recruiting

Clinicaltrials.gov ID: NCT04006210

Sponsor: Neuroderm Ltd

Enrolment: 300

Completion: April 2021

Study Design: The BouNDless study is a multi-center (4 locations), randomized, active-controlled, double-blind, double-dummy, parallel-group design. After screening, subjects will start on an open label immediate release (IR) LD/CD adjustment period, followed by a ND0612 open-label adjustment period. Once optimised, patients will be randomised to receive either ND0612 or matching placebo, both accompanied by IR LD/CD. There is an option to move to an open-label extension study (NCT02726386) lasting for a further year.

Neuroderm plans to recruit patients with moderate to advanced PD, between the ages of 30 and 80. They must have a good response to levodopa, with a modified Hoehn & Yahr score of ≤ 3 when ON. There must be at least 2 hours of OFF time per day. The patient must be taking ≥ 4 levodopa doses/day (≥ 3 doses/day of Rytary) at a total daily dose of ≥ 400 mg.

Outcome Measures: The primary outcome measure is the change in daily ON time without troublesome dyskinesia (sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia) using a patient diary over 12 weeks.

The secondary outcome measure is the change in OFF time using a patient diary, also over 12 weeks.

Comments

Together with Abbvie's ABBV-951, ND0612 will offer an alternative to intra-jejunal gels, potentially with more control of dosage to obtain optimal symptom relief. This mode of delivery of LD/CD is likely to be much more acceptable to patients, hopefully at a lower overall cost. The disadvantage of ND0612 is a limit of levodopa dose that can be delivered via the pump over 24 hours which will require use of add on oral medications by most patients.

References

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Rennes University – EARLY PUMP Study

Background: Apomorphine infusion solution is already available in France as Apokinin by Aguetant pharmaceuticals and its use is approved for motor fluctuations in PD. The Rennes University team has been actively studying the impact of the apomorphine pump on various aspects of PD. The group has published data on the effect of continuous s.c. apomorphine pump on the dynamics of cognitive action control in patients with mild to moderate PD and effect on the motor, cognition, psychiatric symptoms and quality of life in PD patients without cognitive impairment [1, 2]. The university is now studying the effects of starting the continuous pump early in patients with mild signs of motor fluctuations described below.

Title: Apomorphine Pump in Early Stage of Parkinson's Disease (EARLY-PUMP)

Objective: The objective of the study is to assess the impact on the quality of life with using apomorphine pump early on in PD participants as soon as they develop the motor fluctuations compared to oral medications or best medical therapy

Phase: 3

Status: Recruiting

Clinicaltrials.gov Identifier: NCT02864004

Sponsor: Rennes University Hospital

Estimated Enrolment: 192 participants

Estimated Primary Completion Date: March 2023

Study Design: This is a phase 3, randomized, parallel arm, interventional study designed to assess whether the use of apomorphine pump in relatively early motor fluctuation stage of PD positively impacts the social and occupational functioning of the PD participants, by improving their quality of life and delaying the appearance of severe disabling motor complications.

The study is including adults aged 65 years old or below with idiopathic PD with a disease duration of more than 4 years. They should have the presence of fluctuations and/or dyskinesia but for not more than 3 years. Participants must demonstrate impairment in activities of daily living or impairment of social and occupational functioning due to PD symptoms despite medical management. Standard exclusionary criteria apply. Participants with deep brain stimulation or lesional surgery or with LCIG are excluded. The study is currently recruiting across multiple centers in France.

The participants will be recruited over a period of 36 months and randomly assigned to one of the two arms to either receive apomorphine pump with an individually optimized dose or receive the best medical treatment, which could be the best single or combination therapy according to the guidelines of European Federation of Neurological Sciences. Participants will be followed for a year with clinical evaluations at months 6 and 12. The pump will be installed and adjusted at baseline during the first hospitalization and further pump adjustment and readjustment of oral medications are allowed every month. Additionally, there will be another 3-day hospitalization visit at month 3 for pump adjustment. The study will also collect data throughout the study for medico-economic evaluation.

Outcome Measures:

The study kept the primary outcome as the change in the quality of life using the PDQ39 questionnaire from baseline to 12 months follow up. The secondary outcomes focus on the change in score over the course of 12 months from baseline and include various parameters including patient and neurologist's global impression of change, MDS-UPDRS I-IV scales, non-motor symptoms scales, change in the best ON, ON with dyskinesia and OFF periods, adverse events. The secondary outcomes also explore changes in sleep, psychosocial functioning, depression, anxiety, and apathy scales.

Comments:

Whether early initiation of infusion therapies can delay or alleviate the negative impact on PwP's social and economic aspect of life is a critical question that remains unanswered. This study hopes to answer the question. Interestingly apomorphine has been shown to have an anti-dyskinetic effect and as such, will be interesting to find if early infusion delays the onset of the same.

References:

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USWorldMed's INFUS-ON

Background: US WorldMeds manufacture APOKYN, a s.c. injectable formulation of apomorphine. The INFUS-ON trial investigates continuous s.c. infusion of apomorphine *via* a portable external electronic device as a registration study to enable drug approval in the US.

Title: Infusion of Apomorphine: Long-term Safety Study (INFUS-ON)

Phase: 3

Status: Active, not recruiting

Clinicaltrials.gov ID: NCT02339064

Sponsor: US WorldMeds

Enrolment: 99

Completion: September 2021

Study Design: This is a Phase 3, multicentre (18 locations), open-label, safety and tolerability study of continuous apomorphine infusion in subjects with advanced Parkinson's Disease (PD) whose motor fluctuations remain unsatisfactory with levodopa (or levodopa/carbidopa) and at least one other class of drugs or mode of therapy for PD.

Outcome Measures: The primary outcome is the percentage of OFF time during the waking day at week 12 compared to baseline. Secondary outcome measures are all based on efficacy:

1. Percent of daily "on" time without troublesome dyskinesias during waking day, baseline to Week 12
2. Percent of daily "off" time during the waking day, baseline to weeks 2, 4, 8, 20, 28, 36, 44, and 52; and all treatment extension period visits.
3. Percent of daily "on" time without troublesome dyskinesias during the waking day, baseline to weeks 2, 4, 8, 20, 28, 36, 44, and 52; and all treatment extension period visits.
4. Percent of daily "on" time without dyskinesias, baseline visit to treatment weeks 2, 4, 8, 20, 28, 36, 44, and 52; and all treatment extension period visits.
5. UPDRS - Motor Score, baseline visit to week 12.
6. Clinical Global Impression of Severity (CGI-S) and Change (CGI-C) Scale, baseline visit to treatment weeks 2, 4, 8, 20, 28, 36, 44, and 52; and all treatment extension period visits.
7. Patient Global Impression of Severity (PGI-S) and Change (PGI-C) Scale, baseline visit to treatment weeks 2, 4, 8, 20, 28, 36, 44, and 52; and all treatment extension period visits.
8. Parkinson's Disease Questionnaire, baseline visit to treatment weeks 2, 4, 8, 20, 28, 36, 44, and 52; and all treatment extension period visits.
9. UPDRS - Activities of Daily Living Score, baseline visit to treatment weeks 2, 4, 8, 20, 28, 36, 44, and 52; and all treatment extension period visits.
10. Proportion of responders, baseline visit to treatment weeks 2, 4, 8, 20, 28, 36, 44, and 52; and all treatment extension period visits.
11. Frequency and total dose of average daily intermittent injection of APOKYN for subjects on APOKYN treatment at study entry, baseline visit to treatment weeks 2, 4, 8, 20, 28, 36, 44, and 52; and all treatment extension period visits.

Comments

The INFUS-ON trial is aiming to recruit patients with advanced idiopathic PD, with unsatisfactory motor control despite optimised treatment and OFF periods ≥ 3 hours per day.

Apomorphine is well accepted as efficacious in the treatment of OFF episodes in advanced PD and the rationale for continuous s.c. delivery makes sense. Hopefully, this study will enable drug approval in the US after many years of successful utilization in Europe.

Dizlin- INFUDOPA

Background: Dizlin is developing infusion solutions of levodopa and carbidopa labelled as Infudopa. Infudopa can be administered via three routes – intravenous (i.v.) injection, short term i.v. infusion (Infudopa IntraV) and long-term s.c. injection (Infudopa SubC) [1].

The shelf life is 24 months refrigerated and 3 months at room temperature for the s.c. solution. SubC is also designed to minimize skin-related adverse effects. Since the uptake is fast, continuous infusion treatment can be started early with the use of a bolus dose in the morning and throughout the day as needed. The i.v. infusion is being developed for short term use, for example, being used peri-operatively.

Title: Levodopa Pharmacokinetics in Patients With Parkinson's Disease and Symptom Fluctuation: A Phase I, Open-label, Randomized, Multicentre, Crossover Study Comparing Intravenous and Subcutaneous Infudopa With Intestinal Duodopa

Objective: The objective of the study is to compare the pharmacokinetic profile of Infudopa, i.v. and s.c. infusions, to intestinal Duodopa infusions.

Phase: 1

Status: Recruiting

Clinicaltrials.gov Identifier: NCT03419806

Sponsor: Vastra Gotaland Region

Collaborator:

The Swedish Research Council

Dizlin Medical Design AB

Goteborg University

Estimated Enrolment: 28 participants

Estimated Primary Completion Date: According to Dizlin's website, the study will be finalised early in 2020 [2]

Study Design: The current study is a prospective, 3-period-cross-over, open-label multicentre trial comparing i.v. and s.c. administration of the study drug, Infudopa, to Duodopa.

The study is including advanced Parkinson's patients who are already on a stable regimen of LCIG for at least 30 days with a dose between 685mg to 4000mg and be using it for 16- or 24-h. Standard exclusionary criteria apply.

The study is being conducted in Sweden and requires three treatment visits. The study has a cross-over design with a minimum of 3 days of Duodopa in between the treatment visits. At each visit, the participant will receive either standard Duodopa infusion, Infudopa intravenously or Infudopa subcutaneously over a 16-h period. The order of the treatment will be non-blinded but randomized. A pre-study optimum dose of Duodopa will be established that will determine the dose of the i.v. and s.c. Infudopa that will yield a corresponding serum levodopa level. The Infudopa i.v. will be dosed at 75% of participant's individual pre-study Duodopa dose and administered via an indwelling catheter in the arm as a morning rapid constant dose followed by continuous i.v. infusion up to 16-h. Similarly, Infudopa s.c. will be administered over 16-h as a morning rapid constant rate followed by continuous infusion dosed similarly to pre-study Duodopa dose for the participant.

Outcome Measures: The primary objective focuses on demonstrating two major pharmacokinetic points.

1. To demonstrate that a steady state plasma concentration of levodopa and carbidopa, equivalent to that of Duodopa, can be achieved after the i.v. and s.c. infusion of Infudopa.
2. To demonstrate that peak-trough fluctuations of levodopa and carbidopa plasma concentrations during the dosage interval of both i.v. and s.c. Infudopa will be comparable to that of Duodopa.

Secondary objectives are designed to look at the

1. Safety profile, particularly focusing on local skin reactions,
2. Expanded pharmacokinetic profile of both levodopa and carbidopa after s.c. and i.v. administration compared to Duodopa. The parameters being checked include bioavailability, maximum plasma concentration, time to maximum plasma concentration, area under the curve, and elimination half-life.
3. Effect on clinical parameters focusing on bradykinesia, dyskinesia, and tremors using the clinical rating scale UPDRS and objective assessments via Parkinson's Kinetigraph.

Comments:

Infudopa aims to demonstrate an equally efficacious alternative s.c. delivery of carbidopa/levodopa compared to LCIG. If the results are positive, it will be another alternative to LCIG. The Infudopa IntraV, if successful in demonstrating meaningful clinical benefit, will be a potentially interesting addition for use in peri-operative scenarios. Since these are still early phase studies, they rightly aim to demonstrate clinically acceptable PK and safety profile of the active drugs.

References:

- [1] <http://www.dizlin.se/pipeline-products/>
- [2] <https://www.dizlin.se/clinical-trials/>

Phase 3 in focus – Amneal's IPX203

Background: There is a clear clinical need for oral formulations of levodopa that deliver optimal levels in the bloodstream for extended periods of time. Whilst such formulations exist and are used, for example, Sinemet CR and Rytary, there is still considerable room for improvement. Impax Laboratories, acquired by Amneal in 2018, sells Rytary, but are also developing IPX203, aimed to have a longer half-life than Rytary. Both drugs are manufactured as capsules containing different particle forms of levodopa and carbidopa (LD/CD). The mix of particles enables the combination of immediate release (IR) of LD/CD together with sustained release LD/CD over an extended period of time.

IPX203 has been tested in two Phase 2 studies. The first (NCT02271503) evaluated a single dose of IPX203 in 26 patients in an open-label, a rater-blinded trial designed to evaluate pharmacokinetics and pharmacodynamics, in comparison to IR LD/CD and Rytary. As expected, IPX203 showed superior duration of effect to IR LD/CD, but it also produced a longer duration of symptom relief than Rytary, with almost an hour less OFF time per day [1].

The second (NCT03007888) Phase 2 study used the same design principles but over a two-week period, in comparison to IR LD/CD, with 28 subjects. The superiority of IPX203 was confirmed, with 2.3 hours less OFF time compared to IR LD/CD, with most of that labeled as good ON time [2].

Following the success of the Phase 2 trials, Impax/Amneal initiated a Phase 3 study in 2018. There is also a nine-month safety extension trial planned (NCT03877510).

Title: A Study to Evaluate the Safety and Efficacy of IPX203 in Parkinson's Disease Patients With Motor Fluctuations

Phase: 3

Status: Recruiting

Clinicaltrials.gov ID: NCT03670953

Sponsor: Impax Laboratories LLC (now Amneal)

Enrolment: 510

Completion: July 2020

Study Design: This is a multi-center (89 locations), randomized, double-blind, double-dummy, active-controlled, parallel-group study. It will consist of a 3-week, open-label IR CD-LD dose adjustment period; a 4-week, open-label period for conversion to IPX203; followed by a 13-week double-blind treatment period with subjects randomized in a 1:1 ratio, stratified by center, to receive either IPX203 (with matching IR CD-LD placebo) or IR CD-LD (with matching IPX203 placebo).

Outcome Measures: The primary outcome is the change in “good ON” time. Secondary outcome measures are the change in OFF time; patients rated as “much improved” or “very much improved” in Patient Global Impression of Change (PGI-C); change in UPDRS Part III; and change in UPDRS Parts II and III.

All the outcome measures will be assessed at the end of the double-blind study period at 13 weeks.

Comments

While symptomatic therapies for PD are easier to develop than drugs to modify the course of the disease, easier does not mean easy. This reality is underlined by the recent failure of the previously featured Phase 3 study of Intec Pharma’s Accordion Pill to reach its primary outcome objectives [3]. The Accordion Pill LD/CD containing both immediate and controlled release forms, presented with a unique gastric retentive drug delivery system which allowed for slow release of LD/CD in the stomach. According to the company website, on preliminary review, the study failed to demonstrate a statistically significant difference in OFF times as compared to the IR CD/LD arm. Further analysis and publication of data are pending [4].

The Phase 3 trial of IPX203 is thus a large and comprehensive program with a randomized, double-blind, double-dummy, active-controlled, parallel-group study design. The company’s experience with Rytary (codenamed IPX066 when in development) will be invaluable for the successful implementation of this pivotal Phase 3 study. While not groundbreaking, if successful, a new oral formulation of LD/CD with a longer duration of action will be a welcome addition to the armamentarium of available treatment options for PwPs.

References

- [1] Modi, Nishit B *et al* (2019) Single dose pharmacokinetics and pharmacodynamics of IPX203 in patients with advanced Parkinson Disease; a comparison with immediate-release Carbidopa-Levodopa and with extended-release Carbidopa-Levodopa capsules. *Clin Neuropharmacol* 42 4-8.
- [2] Modi, Nishit B *et al* (2019) Pharmacodynamics, efficacy and safety of IPX203 in Parkinson Disease patients with motor fluctuations. *Clin Neuropharmacol* 42 149-156.
- [3] McFarthing K, Prakash N, Simuni T (2019) Clinical trial highlights: 1. Gene therapy for Parkinson’s, 2. Phase 3 study in focus - intec pharma’s accordion pill, 3. Clinical trials resources. *J. Parkinsons. Dis.* 9, 251–264.
- [4] <https://www.intecpharma.com/pipeline/ap-cd-ld/>

CLINICAL TRIALS HIGHLIGHTS - RESOURCES

PARKINSON'S THERAPIES IN DEVELOPMENT

The Hope List - <http://bit.ly/ParkinsonsHopeList>

FINDING A CLINICAL TRIAL

ClinicalTrials.gov from the US National Library of Medicine - <https://clinicaltrials.gov>

PD Trial Tracker; analysing ClinicalTrials.gov for Parkinson's specific trials - <http://www.pdtrialtracker.info>

Fox Trial Finder - <https://foxtrialfinder.michaeljfox.org>

European Parkinson's Disease Association - <https://www.epda.eu.com/about-parkinsons/treatments/clinical-trials/>

Parkinson's UK - <https://www.parkinsons.org.uk/research/take-part-research>

UK NHS Clinical Trials Gateway - <https://www.ukctg.nihr.ac.uk>

Cure Parkinson's Trust - <https://www.parkinsonsmovement.com/clinical-trials/>

Parkinson's Study Group - <http://www.parkinson-study-group.org/clinical-trials>

American Parkinson Disease Association - <https://www.apdaparkinson.org/resources-support/living-with-parkinsons-disease/clinical-trials/>

CenterWatch - <https://www.centerwatch.com/clinical-trials/listings/condition/117/parkinsons-disease/>

WHAT DOES IT MEAN TO PARTICIPATE IN A PARKINSON'S CLINICAL TRIAL?

Michael J Fox Foundation, Clinical Trial Companion – <https://www.michaeljfox.org/pdcompanion.html>

Parkinson's Foundation - <https://www.parkinson.org/Understanding-Parkinsons/Treatment/Clinical-Trials>