Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Vyalev

Active ingredients: Foslevodopa and Foscarbidopa

Sponsor: Abbvie Pty Ltd.

October 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The TGA assesses applications to enter therapeutic goods in the Australian Register of Therapeutic Goods (ARTG).
- Australian Public Assessment Reports (AusPARs) provide information on the evaluation of prescription medicines and the considerations that led the TGA to approve or not approve their entry in the ARTG. AusPARs are an important part of the transparency of the TGA's decision-making process.
- AusPARs are compiled and published by the TGA, using extracts from scientific evaluations and risk-benefit assessments. They contain detailed research findings and specialised terminology.
- Each AusPAR relates to a prescription medicine application at a particular point in time. A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine.
- More information can be found in Australian Public Assessment Report (AusPAR) guidance.

Contents

List of abbreviations

Abbreviation	Meaning
ABBV-951	foslevodopa / foscarbidopa or Vyalev
ACM	(Australian) Advisory Committee on Medicines
ADR	adverse drug reaction
AE (SI)	adverse event (of special interest)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA	Australian Specific Annex (to the RMP)
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
AUC_{0-last}	area under the concentration-time curve from time 0 to time of the last measurable concentration
$AUC_{tau\ or\ \tau}$	area under the concentration-time curve within a dosing interval
BA	bioavailability
BE	bioequivalence
bpm	beats per minute
BW	bodyweight
CARBIDOPA (CD)	carbidopa
CER	clinical evaluation report
CFB	change from baseline
CI	confidence interval
C_{max}	maximum observed concentration
CMI	Consumer Medicines Information
CNS	central nervous system
CO	clinical overview
COMT	catechol-O-methyltransferase
CSCI	continuous subcutaneous infusion
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	percentage of coefficient of variation
CYP	cytochrome P450
DB	double-blind

Abbreviation	Meaning
DBP	diastolic blood pressure
DDCI	DOPA decarboxylase inhibitor
DDI	drug-drug interaction
DDS	dopamine dysregulation syndrome
ECG	electrocardiogram
E-R	exposure-response
EQ-5D-5L	EuroQol 5-dimensions
EU	European Union
FAS	full analysis set
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLNT	Great Lakes NeuroTechnologies
HR	heart rate
IA	interim analysis
ICARBIDOPA	impulse control disorders
IEC	independent ethics committee
IIV	inter-individual variability
IRB	independent review board
ISES	Infusion Site Evaluation Scale
ITT	intention-to-treat
KPPS	King's Parkinson's Disease Pain Scale
LCIG	levodopa/carbidopa intestinal gel
LC-MS/MS	liquid chromatography tandem mass spectrometry
LEVODOPA (LD)	levodopa
LE	levodopa equivalents
LLN	lower limit of normal
LLOQ	lower limit of quantification
LS	least square
(MDS) UPDRS	(Movement Disorder Society) Unified Parkinson's Disease Rating Scale
mRNA	messenger ribonucleic acid
msec	millisecond
NMS	neuroleptic malignant syndrome

Abbreviation	Meaning
OL	Open label
3-OMD	3-O-methyLevodopaopa
PCS	potentially clinically significant
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire-39 items
PDSS-2	Parkinson's Disease Sleep Scale-2
PEG	percutaneous endoscopic gastrostomy
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetic(s)
PP	per protocol
PT	Preferred Term
QoL	quality of life
QTcF	QT interval corrected relative to heart rate using Fridericia's formula
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
Rd	Round
RMP	Risk Management Plan
SAE	serious adverse event
SAS	Safety Analysis Set
SBP	systolic blood pressure
SC	subcutaneous or subcutaneously
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SD	standard deviation
SOC	system organ class
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent AE
TGA	Therapeutic Goods Administration
t_{max}	time to reach maximum observed concentration
ULN	upper limit of normal
USA	United States of America

Abbreviation	Meaning
UTI	urinary tract infection
VAS	visual analogue scale

Product submission

Submission details

Type of submission:	New fixed dose combination medicine Vyalev, containing 2 new chemical entities (foslevodopa and foscarbidopa)
Product name:	Vyalev
Active ingredients:	foscarbidopa, foslevodopa
Decision:	Approved
Date of decision:	1 March 2024
Date of entry into ARTG:	27 March 2024
ARTG number:	372902
, *Black Triangle Scheme for the current submission:*	Yes
Sponsor's name and address:	Abbvie Pty Ltd Locked Bag 5029, BOTANY, NSW, 1455 Australia
Dose form:	Injection, solution
Strength:	foslevodopa 2400 mg/10 mL and foscarbidopa 120 mg/10 mL
Container:	Vial Glass Type I Clear
Pack size:	7 x 10 mL vials
Approved therapeutic use for the current submission:	For the treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimised alternative pharmacological treatment
Route of administration:	Subcutaneous
Information on use:	For information on the use of Vyalev (such as dosage, pregnancy category, contraindications, and precautions etc.) refer to the Product Information (PI) document or contact a doctor or pharmacist. Use the TGA PI/CMI search facility to view the current Product Information (PI) and Consumer Medicines Information (CMI).

Product background

This AusPAR provides information on the assessment of Vyalev (foslevodopa 2400 mg/10 mL and foscarbidopa 120 mg/10 mL) for the proposed indication:[1]

> *For the treatment of idiopathic Parkinson's disease with severe motor fluctuations despite optimised alternative pharmacological treatment.*

Parkinson's disease (PD)

Parkinson's disease (PD) is the most common form of parkinsonism, a group of neurological disorders with Parkinson disease-like movement problems such as rigidity, slowness, and tremor.[2] More than 6 million individuals worldwide have Parkinson's disease. The prodromal features are rapid eye movement sleep behaviour disorder, hyposmia, constipation, along with characteristic movement difficulty (tremor, stiffness, slowness), and psychological or cognitive problems (cognitive decline, depression, anxiety).

Advanced Parkinson's disease stage 4 or 5 of the Hoehn and Yahr Scale is characterised by very limited mobility without assistance, severe motor deficits, risk of falls, and cognitive and psychotic problems. The mean time from disease onset to wheelchair-dependence is estimated at 14 years, although about a third of patients seem to have a relatively mild disease and remain stable for many years.

Current treatment options

PD has no cure and the aim of currently available therapy is to manage symptoms, improve quality of life and restore functional capability.[2] Levodopa remains the gold standard in dopamine (DA) replacement therapy.[2] The mechanism of action for levodopa as dopamine replacement therapy in the central nervous system involves the enzymatic decarboxylation of levodopa (a DA prodrug) by central dopa decarboxylase.[2] The main pharmacological treatment approach for PD consists of re-establishing dopaminergic stimulation in the striatum, primarily through oral administration of the dopamine precursor levodopa with a dopa decarboxylase inhibitor (DDCI), such as carbidopa, to prevent peripheral metabolism of levodopa to dopamine (to significantly reduce the levodopa dose required for a therapeutically effective response).[3]

Advanced PD is managed with surgery and pump-delivered dopaminergic therapy. Surgery is most successful in patients with severe motor fluctuations and dyskinesias. Continuous dopaminergic therapy via portable, programmable pumps is available for levodopa patients or when surgery is unsuitable. Levodopa+carbidopa (duodopa) intestinal gel is administered continuously through a permanent tube, directly into the duodenum or upper jejunum. Apomorphine is delivered subcutaneously. For both drugs, adjusting infusion rates and giving bolus doses helps smooth out motor fluctuations and dyskinesias.

Despite its efficacy, as the disease progresses, oral levodopa loses its effectiveness and patients develop disabling motor fluctuations such as 'On' and 'Off' phenomena, defined as a sudden switch between periods of good motor system control ('On' time) and periods of poor mobility, tremor, slowness, and stiffness ('Off' time). Pharmacological management of PD also includes

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Armstrong, M.J. and M.S. Okun, *Diagnosis and Treatment of Parkinson Disease: A Review.* Jama, 2020. **323**(6): p. 548-560

[3] Cacabelos, R., *Parkinson's Disease: From Pathogenesis to Pharmacogenomics.* Int J Mol Sci, 2017. **18**(3).

dopamine agonists, anticholinergics, amantadine, monoamine oxidase B (MAO-B) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors.

The inability to adequately control motor complications with oral treatment is characteristic of advanced PD and necessitates alternative therapeutic approaches. One approach for the treatment of advanced PD is the continuous delivery of individually titrated doses of levodopa/carbidopa directly into the intestine, such as with levodopa-carbidopa intestinal gel (LCIG) or with levodopa-entacapone-carbidopa intestinal gel.

Other treatments of motor fluctuations in advanced PD include deep brain stimulation and continuous subcutaneous (SC) apomorphine infusion.

Clinical rationale

The Applicant's rationale for the product development:

> *Foslevodopa/foscarbidopa is administered SC using a lighter infusion pump compared to Duodopa (LCIG) and delivers a much smaller volume of highly concentrated drug product over a 24-h period relative to Duodopa (over 16 h), with an overnight break.*
>
> *Unlike oral administration, continuous delivery of foslevodopa/foscarbidopa results in less variability in LEVODOPA and CARBIDOPA plasma concentrations, to provide continuous rather than intermittent stimulation of dopaminergic receptors in the brain, ultimately reducing motor complications and improving QoL in patients with advanced PD.*

Regulatory status

Australian regulatory status

This is a new product containing 2 new chemical entities not currently included in the Australian Register of Therapeutic Goods (ARTG), either individually or in combination.

The initial application relied on extrapolation of efficacy data and, in part, safety data from the TGA approved medicine for advanced PD, Duodopa (levodopa and carbidopa monohydrate gel).

International regulatory status

Foslevodopa and foscarbidopa were under evaluation in the European Union (EU) at the time the TGA commenced evaluation of this submission.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 1: Timeline for application PM-2021-03724-1-1

Description	Date
Application dossier accepted and first round evaluation commenced	6 October 2021
First round evaluation completed	23 March 2023
Second round evaluation completed	21 July 2022

Description	Date
Delegate's[4] benefit-risk assessment and request for Advisory Committee on Medicines (ACM) advice	September 2022
First ACM Meeting (Meeting 35)	October 2022
Sponsor's submission of additional safety and efficacy data	9 November 2022 to 15 September 2023
Delegate's benefit-risk assessment of additional safety and efficacy data and request for ACM advice	July 2023
Second ACM Meeting (Meeting 40)	August 2023
Registration decision	1 March 2024
Administrative activities and registration in the ARTG completed	27 March 2024
Number of working days from submission dossier acceptance to registration decision*	232

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk-benefit assessment

A summary of the TGA's assessment of Vyalev is provided below.

Manufacturing and quality evaluation summary

The quality evaluator recommended registration approval of the proposed product from a pharmaceutical chemistry perspective.

Key findings

- The infusion contains2 'new chemical entities': foslevodopa and foscarbidopa. These are phosphate ester prodrugs that are converted *in vivo* by alkaline phosphatases to levodopa and carbidopa respectively.
- Dopamine doesn't significantly cross the blood-brain barrier, but levodopa (also known as 'L DOPA') does cross, via the transporter LAT1. In the brain, L-DOPA is converted to dopamine by the enzyme aromatic amino acid decarboxylase. Carbidopa, which does not cross the blood-brain barrier, inhibits the extracerebral decarboxylation of levodopa, so that more levodopa reaches the brain and is converted into dopamine. Foslevodopa is, thus, a prodrug of a prodrug.
- The proposed infusion has foslevodopa and foscarbidopa in a 23 to 1 mole ratio (= 20:1 w/w). The TGA approved Duodopa has levodopa and carbidopa in a 5:1 mole ratio.

[4] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

(Registered 200/25 mg and 100/25 mg tablets have levodopa and carbidopa monohydrate in a 10:1 or in a 5:1 mole ratio respectively.)

- The foscarbidopa concentration was selected to maintain a 20:1 (w/w) ratio of foslevodopa to foscarbidopa, which had been shown in vivo to provide an equivalent levodopa:carbidopa exposure ratio to oral levodopa/carbidopa formulations at the 4:1 (w/w) ratio (e.g. 100/25 mg).
- Foslevodopa and foscarbidopa drug substances are highly water soluble.
- Foscarbidopa is susceptible to pH dependent oxidative degradation in the infusion solution to 'DHPPA-P', 'HydrazoneAB', and hydrazine:
- Hydrazine
  - The existence of hydrazine as a potential impurity in the finished product is noted in the PI ("up to 0.5 mg/day").
  - Hydrazine is a reagent typically used in the synthesis of carbidopa and a degradation impurity in both carbidopa and foscarbidopa. Hydrazine is controlled in the precursor carbidopa to 20 ppm. The proposed finished product limits for hydrazine are ≤ 0.035% (release); ≤ 0.100% (Shelf-life) ≤ 0.175% (Clinical In-Use), where % limits relate to the foscarbidopa content.
  - The Sponsor stated that hydrazine is a non-mutagenic carcinogen.
  - The evaluator noted in the proposed PI that VYALEV could have a maximum hydrazine dose of *0.5 mg* (i.e. the clinical in-use limit at maximum daily dose of foscarbidopa: 0.175%*300 mg = 0.525 mg). The current Australian Duodopa PI references hydrazine as an impurity but does not quantify levels. The Duodopa specifications limit hydrazine in the intestinal gel at the end of shelf-life to NMT 40 µg/g gel consistent with overseas (UK and USA) product information documentation detailing a maximum hydrazine exposure of *8 mg*.
  - The evaluator concluded: Hydrazine is a degradant of concern. The levels in this product are lower than in Duodopa. Pharmacopoeial reference limits for hydrazine in carbidopa products are still evolving.
- Uranium
  - The evaluator stated that Foslevodopa and foscarbidopa are made from levodopa and carbidopa using a phosphorylating reagent itself made from phosphate salts. Those salts can contain uranium as an impurity and they are used in the last synthetic step in preparation of the drug substances. Thus, uranium is a risk associated with foslevodopa and foscarbidopa and not Duodopa (or most other drugs).
  - Appropriate control of such contamination is best maintained with specifications for the reagent.
  - Five metals are controlled in the foslevodopa and foscarbidopa drug substance specifications (V, Mn, Fe, Co, Cu), but not uranium. Uranium is not explicitly addressed in ICH Q3D.
  - The Sponsor responded that AbbVie states that it has now confirmed the capability of updated analytical methodologies for uranium determination and can now commit to a control strategy to meet the 0.12 µg/day U PDE. AbbVie states that time is required to fully develop, validate and implement this control strategy and update the relevant documentation. AbbVie has proposed that tightening of the uranium PDE to 0.12 µg/day be accepted as a post-approval commitment: AbbVie commits to filing a variation in Q1

2023 to tighten the PDE limit of uranium from 1.2 µg/day to 0.12 µg/day and to update relevant dossier sections related to the uranium control strategy.

– The TGA toxicology evaluation recommended a lower uranium PDE of 0.12 µg/day. Information from Abbvie on levels in the 2 drug substances shows that foslevodopa is the significant source of potential uranium contamination. Batch analyses for seven recent foslevodopa batches all had uranium at not detected levels (currently < 0.18 ppm). If present at the limit of detection used in those analyses (0.18 ppm), a maximum daily dose of foslevodopa (6 g) would contain 1.1 µg of uranium. To control uranium exposure to below 0.12 µg per day, uranium in foslevodopa should be limited to 0.02 ppm.

Drug delivery system

Administration of the foslevodopa/foscarbidopa infusion requires a drug delivery system, which is to be evaluated and supplied separately. This consists of both a pump and fluid path components. The infusion solution will be supplied alone, separately from the other components.

The pump is a software-controlled pump developed by Phillips-Medisize A/S (Struer, Denmark). The drug delivery system will use components already commercially available (vial adapter, syringe, infusion sets).

The physicochemical compatibility of the drug delivery system with the foscarbidopa/foslevodopa infusion solution has been established.

Nonclinical (toxicology) evaluation summary

The non-clinical evaluator concluded there were no nonclinical objections to the registration of foslevodopa/foscarbidopa provided issues regarding impurities are adequately addressed.

Key findings

- The rapid metabolism of the prodrugs to levodopa and carbidopa supports the product's use for the proposed indication.
- At a concentration of 10 µM (10-foslevodopa and 230-foslevodopa the maximum clinical C_{ss}), foslevodopa and foscarbidopa showed no significant binding to other receptors, ion channels or transporters, and no enzyme inhibition. No off-target effects are expected with these new actives.
- Foslevodopa and foscarbidopa showed low protein binding in all the animal species and in humans.
- CYP450 enzymes are not involved in the metabolism of foslevodopa or foscarbidopa and these drugs did not inhibit or induce CYP enzymes at clinically relevant concentrations. Neither foslevodopa nor foscarbidopa inhibited the activities of drug transporters at clinically relevant concentrations. Drug interactions are expected to be those known for levodopa and carbidopa.
- Repeat dose toxicity studies by continuous IV infusion were conducted in rats (up to 4 weeks) and Cynomolgus monkeys (up to 4 weeks) and by continuous SC infusion were conducted in dogs (up to 13 weeks). These species are considered to be appropriate animal models. CNS clinical signs were a major feature and were the dose-limiting toxicity in rats and monkeys. The effects were seen at clinically relevant exposures, were consistent with those seen with levodopa/carbidopa and can be attributed to dopamine-related effects in

the CNS. No new toxicities with foslevodopa/foscarbidopa were seen with regards to the toxicity profile of levodopa/carbidopa.

- Foslevodopa and foscarbidopa (tested individually) were not mutagenic in the bacterial reverse mutation assay or clastogenic in vitro (in human lymphocytes), except for foscarbidopa in bacterial mutation assay which was positive in E. coli WP2 uvrA (-S9). This single case of a positive result is considered acceptable within the context of the available knowledge on the genotoxicity of levodopa and carbidopa for which there is some evidence, for both compounds, of genotoxic potential. Foslevodopa/foscarbidopa was negative in an in vivo rat micronucleus test.
- No carcinogenicity studies were conducted, which was considered acceptable (levodopa/carbidopa were not found to be carcinogenic).
- No reproductive toxicity studies were conducted, which was considered acceptable.
- Several local tolerance studies were conducted in dogs using continuous SC infusion. The concentration of foslevodopa/foscarbidopa in the formulation was 200/50 ng/mL (cf. 240/12 mg/mL for the clinical formulation). Continuous SC infusion was technically difficult in laboratory animals, with a baseline inflammatory response associated with the implantation of the catheters. Foslevodopa/foscarbidopa appeared to aggravate this baseline inflammation (with the most severely affected dogs also showing septic changes), but not induce any specific local adverse changes.
- Hydrazone
  - The clastogenic potential of the foscarbidopa-related impurity, hydrazone AB had not been assessed. The Sponsor provided justifications to substantiate that the clastogenic potential of Vyalev is no greater than that of Duodopa, and therefore, the proposed limit for the foscarbidopa-related impurity, hydrazone AB, should be considered acceptable. In consideration of the Sponsor's justifications, the evaluator concluded:

    The clastogenic risk with VYALEV is not considered to be higher than that with DUODOPA, and for this reason, the proposed shelf-life limit for the foscarbidopa-related impurity, hydrazone AB, is considered acceptable from a toxicological perspective.
- Hydrazine
  - The evaluator recommended that hydrazine, which was considered as a mutagenic and carcinogenic impurity, should be controlled to ensure levels were as low as possible.
- Uranium
  - Uranium was identified as a possible impurity in materials used in the synthesis of foslevodopa.
  - The evaluator recommended a Permissible Daily Exposure (PDE) of 0.12 µg/day for uranium. Batch analyses for seven recent foslevodopa batches all had uranium at not detected levels (currently < 0.18 ppm). If present at the limit of detection used in those analyses (0.18 ppm), a maximum daily dose of foslevodopa (6 g) would contain 1.1 µg of uranium. To control uranium exposure to below 0.12 µg per day, uranium in foslevodopa should be limited to 0.02 ppm.
  - The Sponsor agreed to the PDE for uranium of 0.12 µg/day. The Sponsor confirmed that they adopted the required control strategy to achieve the level of uranium (0.02 ppm or 0.12 µg/day) as stipulated by the toxicology evaluator. However, the Sponsor had not yet developed and validated an analytical method that could detect levels that would comply with the PDE of 0.12 µg/day.

- Uranium had not been detected in 7 batches of the product with an analytical method that could detect concentrations that would result in 1 µg/day. As it will take some time to develop and validate a sufficiently sensitive analytical method, the Sponsor proposed an interim PDE of 1.2 µg/day and commits to submitting a variation submission in Q1 2023 that would comply with the PDE of 0.12 µg/day.
- The interim limit for uranium should not be referred to as "PDE", which infers a "permissible daily exposure", but should be referred to as an interim limit based on practicality.
- There should also be mechanisms in place to ensure the Sponsor complies with their post-marketing commitments. The limit of 1.2 µg/day is an interim limit applicable for 6 months. However, the issue should be rectified as soon as possible to further minimise the risk.

Overall, the nonclinical safety profile of foslevodopa/foscarbidopa was largely the same as that observed with levodopa/carbidopa, except for the finding of uranium.

Clinical evaluation summary

Pharmacology

Foslevodopa/foscarbidopa is a highly soluble formulation of levodopa-4´-monophosphate (foslevodopa) and carbidopa-4´-monophosphate (foscarbidopa).

The 2 drug substances in ABBV-951, foslevodopa and foscarbidopa, function as prodrugs that rapidly and almost completely (> 90%) undergo enzymatic bioconversion via intrinsic alkaline phosphatase to release levodopa (LD) and Carbidopa (CD), respectively, *in vivo*.

Pharmacokinetics (PK)

Absorption

Following subcutaneous infusion into the abdomen, foslevodopa/foscarbidopa was rapidly absorbed and converted to the active moieties, levodopa and carbidopa, by alkaline phosphatase. Levodopa and carbidopa were detected in plasma at 30 minutes following a single bolus foslevodopa/foscarbidopa dose. Systemic levodopa and carbidopa exposures were similar following foslevodopa/foscarbidopa SC infusion to the abdomen, arm and thigh.

Two main BA/BE studies (M17-220 and M20-141), and a 'pilot' BA study (M18-764) were submitted in support of the application.

Study M18-764 reported relative BA at 16 h post infusion initiation between foscarbidopa/foslevodopa 35 mg/700 mg CSCI, using the commercial formulation, and LCIG carbidopa/levodopa 87.5 mg/350 mg infusion.

The evaluator highlighted:

> *the results from the pilot study need to be interpreted with caution since the design was open-label (OL), there was no crossover in treatment arms and a 'period effect' between treatment sequences could not be excluded.*

Study M17-220

Study design: Phase I, randomised, open label study administered in a standard 2-sequence, 2-treatment, 2-period crossover design.

The objective of the study was to compare LEVODOPA PK from 24 h foscarbidopa/foslevodopa infusion to the LEVODOPA PK from Duodopa (LCIG) infused over 16 hours plus night-time oral CARBIDOPA/LEVODOPA doses in healthy adults.

A 24-hour delivery of foscarbidopa/foslevodopa was compared to 16-hour delivery of LCIG plus nighttime oral LD/CD tablets. The oral LD night-time doses were chosen to represent all sources of LD taken during a 24-hour period as an example of a typical treatment day in patients with advanced PD who use LCIG for their motor and nonmotor fluctuations but continue to experience symptoms (such as nocturnal akinesia, morning akinesia, early morning dystonia, and difficulty turning in bed) once the infusion of LCIG is suspended for the night.

Results

Table 2: Relative bioavailability and 90% Confidence Intervals of levodopa for subjects who completed both levodopa/carbidopa intestinal gel and foslevodopa/foscarbidopa regimens

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen B vs. Regimen A	$C_{max,0-16}$	606	656	0.923	0.873, 0.975
	AUC_{0-16}	7810	8220	0.951	0.893, 1.012
	AUC_{∞}	14900	14700	1.009	0.969, 1.049

Regimen A: Levodopa/carbidopa intestinal gel (12.5/50 mg carbidopa/levodopa loading dose followed by 87.5/350 mg carbidopa/levodopa over 16 hours followed by two 25/100 mg carbidopa/levodopa oral doses at 18 and 21 hours after the start of infusion). Levodopa/carbidopa intestinal gel was delivered via a portable infusion pump through a nasojejunal tube.

Regimen B: ABBV-951 (4/80 mg foscarbidopa/foslevodopa loading dose followed by 35/700 mg foscarbidopa/foslevodopa over 24 hours). ABBV-951 was delivered via a portable infusion pump subcutaneous into the abdomen.

For the foslevodopa/foscarbidopa 35/700 mg infusion over 24 hours, levodopa Cmax0-16 and AUC0-16 exposures were 8% and 5% lower, respectively, and AUC∞ exposure was 0.9% higher relative to LCIG CARBIDOPA/LEVODOPA 87.5/350 mg infusion over 16 hours. The point estimates were close to 1 and the 90% CI within the acceptable range of 80%-125%.

Study M20-141

A phase I, randomised, open label study administered in a standard 2-sequence, 2-treatment crossover design.

The aim of the study was to assess PK of CD and LD from foscarbidopa/foslevodopa relative to Duodopa LCIG in healthy adults.

Foscarbidopa/foslevodopa and LCIG were infused for 24 hours in healthy adults.

Regimen A: LCIG (15 mg/60 mg CD/LD loading dose over approx. 30 minutes followed by 168 mg/672 mg CD/LD over 24 h). LCIG was delivered via a portable infusion pump through a nasojejunal tube.

Regimen B: Foslevodopa/foscarbidopa (4.8 mg/96 mg CARBIDOPA/LDP loading dose over approx. 4 minutes followed by 43.2 mg/864 mg CDP/LDP over 24 h). Foslevodopa/foscarbidopa was delivered SC into the abdomen via a portable infusion pump.

Formulations: Foscarbidopa/foslevodopa CDP/LDP 12/240 mg per mL, solution for infusion in 10 mL i.e., proposed commercial strength preparation, as well as the commercial pack size (10 mL vial) was compared to the commercially available LCIG (Intestinal gel suspension CD 5 mg/mL and LD 20 mg/mL in 100 mL bag).

Results

Table 3: Mean PK parameters of levodopa for subjects who completed both LCIG and foslevodopa/foscarbidopa regimens

Pharmacokinetic Parameters (units)		Regimen A (N = 20)	Regimen B (N = 20)
C_{max}	ng/mL	1260 (1300, 25)	831 (841, 16)
T_{max}[a]	h	0.5 (0 – 2.0)	18.0 (1.0 – 24.5)
AUC_t	ng•h/mL	17400 (17800, 21)	18800 (19100, 17)
AUC_∞	ng•h/mL	17500 (17900, 21)	18900 (19200, 17)
$t_{1/2}$[b]	h	1.73 (0.27)	2.14 (0.39)
AUC_{0-24}	ng•h/mL	16100 (16400, 22)	16000 (16200, 18)

Table 4: Mean PK parameters of carbidopa for subjects who completed both LCIG and foslevodopa/foscarbidopa regimens

Pharmacokinetic Parameters (units)		Regimen A (N = 20)	Regimen B (N = 20)
C_{max}	ng/mL	158 (168, 34)	113 (115, 16)
T_{max}[a]	h	4.0 (1.5 – 28.0)	20.0 (1.5 – 24.5)
AUC_t	ng•h/mL	2640 (2750, 27)	2670 (2720, 19)
AUC_{inf}	ng•h/mL	2750 (2860, 27)[c]	2790 (2830, 18)
$t_{1/2}$[b]	h	2.09 (0.55)[c]	2.97 (0.60)
AUC_{0-24}	ng•h/mL	2180 (2270, 28)	2270 (2310, 18)

- Cmax for LDP (831 ng/mL) was low compared to LD (1260 ng/mL). The evaluator considered that this finding could be due to the rapid conversion of prodrug.
- The 90% CIs were between 0.80 and 1.25 for AUC.

The Cmax was for LDP was 34% lower, compared to LD and 90% CIs were not within the acceptable range. The Sponsor states attributes the raised Cmax with LD due to an error with administration of levodopa during the treatment period:

> *It was determined that the NJ tube used to deliver LCIG for the study was incorrectly listed as 10.02 mL priming volume while the actual volume was approximately 5 mL. The incorrect listed priming volume of the NJ tube caused approximately 5 mL (100 mg LD) to be delivered during the LCIG priming phase prior to when dosing was intended to start and explains the difference in Cmax observed.*

Table 5: Relative bioavailability comparison

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen B vs. Regimen A	C_{max}	831	1256	0.662	0.599, 0.731
	AUC_t	18840	17421	1.081	1.043, 1.122
	AUC_{inf}	18943	17513	1.082	1.043, 1.122

The evaluator highlighted that M17-220 and M20-141 both conducted 36 h of PK sampling. The evaluator has referred to the bioequivalence guideline that recommended a minimum 72-h sampling period. The evaluator considered that *given the rapidity of conversion of the parent moieties to the active moieties and the relatively short mean elimination half-lives of all of these moieties, a 36-h sampling period is not expected to adversely affect the relative BA assessment;* and The relative bioA carry-over effect between foslevodopa/foscarbidopa and LGIC treatments could be evaluated in the BA/BE studies, M17-220 and M20-141.

In response to the clinical evaluator's questions regarding the relative comparability of LD vs LDP and CD vs CDP, the Sponsor clarified that:

> *The relative bioavailability of foslevodopa/foscarbidopa compared to LCIG could not be determined since the phosphate prodrugs were not delivered in the LCIG regimen. However, the relative bioavailability of LD and CD could be determined. Overall, the relative bioavailability (foslevodopa/foscarbidopa compared to LCIG) was similar for LD and much higher for CD.*
>
> a. *The LD relative bioavailability for foslevodopa/foscarbidopa compared to LCIG was slightly higher (see iii above); and*
>
> b. *For CD, 35 mg of foscarbidopa was delivered over 24 h for the foslevodopa/foscarbidopa regimen. For the first 16 h, 23 mg of foscarbidopa was delivered. Using the molecular weight conversion (foscarbidopa to CARBIDOPA = 0.73) approx. 17 mg of CD was delivered for the first 16 h of the foslevodopa/foscarbidopa infusion regimen. The comparison arm with LCIG infused 87.5 mg of CD to the jejunum over the same 16-h time period. Overall, for the CD component, foslevodopa/foscarbidopa has approx. 5 times higher bioavailability compared to LCIG. This difference in CD bioavailability is the reason the foslevodopa/foscarbidopa ratio was optimised to 20:1 foslevodopa to foscarbidopa for subsequent clinical studies, including all phase III studies, and for the final commercial formulation. CD AUC values for both LCIG and foslevodopa/foscarbidopa were very similar in the study, demonstrating that the 20:1 foslevodopa to foscarbidopa dosing ratio is appropriate.*

Dose proportionality

Following foslevodopa/foscarbidopa infusions in Study M15-738, based on PK parameters, LD and CD exhibited a dose-proportional increase in exposure from 960 mg/48 mg to 4800 mg/240 mg foslevodopa/foscarbidopa.

Distribution

No volume of distribution data was provided for foslevodopa and foscarbidopa.

The evaluator considered it reasonable to extrapolate the volume of distribution LD and CD to foslevodopa and foscarbidopa as these prodrugs will eventually be converted to LD and CD.

Plasma protein binding

No clinical studies assessed protein binding.

In vitro studies A-1591706 (foslevodopa) and A-1610308 (foscarbidopa) demonstrated 28% plasma protein binding in human tissue. No concentration-dependent protein binding was observed for either foslevodopa or foscarbidopa. The low protein binding values for foslevodopa and foscarbidopa were considered as generally consistent with low LD and CD protein binding values reported following LGIC administration.

Tissue distribution

Steady state LD exposure was achieved within 2 hours after foslevodopa/foscarbidopa infusion as a loading dose and followed by continuous infusion or achieved after 12 to 16 h without a loading dose.

Metabolism

Foslevodopa and foscarbidopa are prodrugs that are rapidly converted by ALP into LD and CD, respectively. Since LD is co-administered with CD, LD is not eliminated via metabolism of the aromatic amino-acid decarboxylase enzyme. Instead, metabolism occurs predominantly via the catechol-O-methyl transferase enzyme system. Other routes of metabolism are transamination and oxidation.

Excretion

LD, CD and their metabolites are primarily excreted in urine.

Pharmacokinetics in the target population

Findings from Study M15-738 in PD patients suggest that stable LD and CD exposures were observed and maintained for the duration of the study, including at steady-state.

PK results from healthy volunteers (M15-733, Part 4) and PD patients (M15-738, Group 5), who were administered with the same foslevodopa/foscarbidopa SC loading dose and SC maintenance dose over a 72-h period had comparable steady-state LD and CD exposures.

PK of foslevodopa/foscarbidopa in subjects with renal or hepatic impairment has not been established.

Specific correlation between age and exposure following foslevodopa/foscarbidopa infusion was not explored in the clinical development programme.

The Delegate has noted that a BE study with foslevodopa/foscarbidopa and Duodopa LCIG conducted in patients with PD is lacking in this submission.

Pharmacodynamics (PD)

Mechanism of action

Foslevodopa and foscarbidopa are converted *in-vivo* to LD and CD, respectively. LD relieves symptoms of Parkinson's disease following decarboxylation to dopamine in the brain. CD, which does not cross the blood-brain barrier, inhibits the extracerebral decarboxylation of LD to dopamine, which means that a larger amount of LD becomes available for transportation to the brain and transformation into dopamine.

QT Assessment was an Exposure-Response (E-R) analysis using time-matched baseline correction from the oral LD/CD period of dosing assessed mean change in QTcF following initiation of foslevodopa/foscarbidopa. Based on linear mixed effects regression analysis, the estimate at the maximum predicted LD exposure (the upper one-sided 95% confidence bound) was shown to be less than the 10 msec threshold.

No apparent effect on cardiac repolarisation was observed for patients who switched from oral LD/CD to foslevodopa/foscarbidopa.

The evaluator concluded that Foslevodopa/foscarbidopa did not show a clinically meaningful QT prolongation effect relative to oral CD/LD dosing at the observed LD plasma concentration range.

Dose-finding

Findings from M15-733 Group 2 suggested that the 20:1 foslevodopa/foscarbidopa dosing ratio resulted in a LD:CD AUC exposure ratio similar to oral LD/CD dosed at a 4:1 ratio. The 20:1 dosing ratio was selected for the final foslevodopa/foscarbidopa formulation.

The recommended starting dose of foslevodopa/foscarbidopa in the phase III studies was based on each patient's daily oral LD intake. This was based on all LD-containing medications, and an adjustment for COMT inhibitors. During the treatment period, the dose of foslevodopa/foscarbidopa were optimised to reach a clinical response that maximised functional 'On' time and minimised the number and duration of 'Off' episodes and 'On' episodes with troublesome dyskinesia.

Efficacy

No pivotal studies with efficacy as a **primary** endpoint were included in this application. Exploratory efficacy data were reviewed from the following studies:

- Study M15-741 (ongoing phase III, interim CSR; 30 March 2021)
- Study M15-737 (ongoing phase III, extension, interim CSR; 30 March 2021)
- Study M15-739 (completed phase I)

At the time of this application, a phase III controlled clinical study, M15-736, titled '*Randomized, Double-Blind, Double-Dummy, Active-Controlled Study Comparing the Efficacy, Safety and Tolerability of ABBV-951 to Oral Carbidopa/Levodopa in Advanced Parkinson's Disease Patients*' and its extension study, M20-098 were ongoing in the USA and Australia. Data were not submitted from these studies as part of this application.

Study M15-741

An open-label single arm study with the primary objective to assess the local and systemic safety and tolerability of foslevodopa/foscarbidopa delivered as a Continuous Sub-cutaneous Infusion (CSCI) for 24 h daily for up to 52 weeks. Assessment of efficacy was a secondary objective. It was noted that efficacy and safety data for up to 26 weeks was included in this application as interim analysis.

Subjects ≥ 30 years of age who were diagnosed with a LD-responsive idiopathic PD and have motor symptoms with fluctuations inadequately controlled by oral medications were recruited. Subjects were also required to have identifiable 'Off' and 'On' states (motor fluctuations) and report a minimum of
2.5 h of 'Off' time per day, as assessed by PD diaries, prior to study entry.

Study treatments: 52-week treatment period (4-weeks optimization followed by 48-weeks maintenance).

An initial loading dose of foslevodopa/foscarbidopa was administered based on the daily levodopa intake.

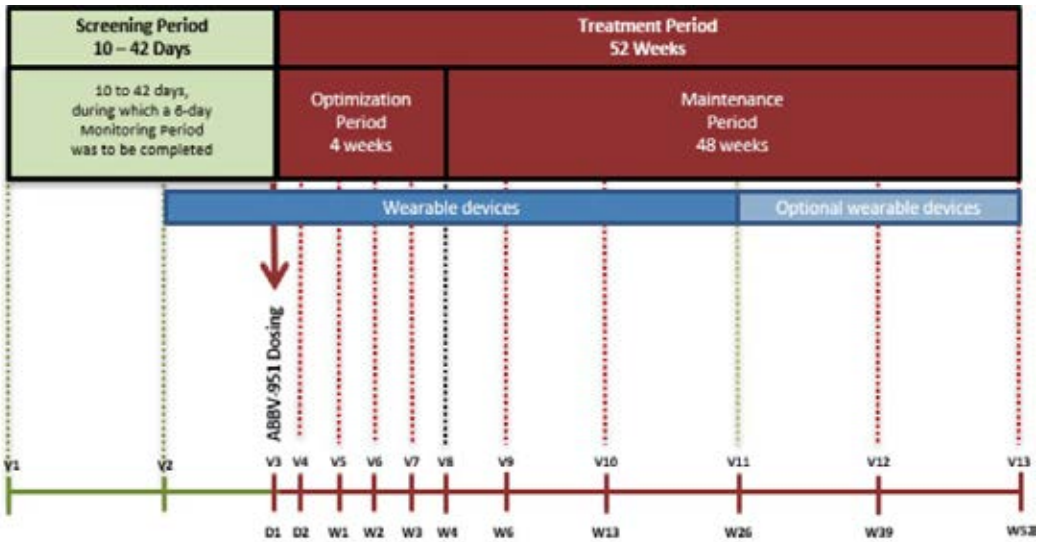
The to-be-marketed formulation of foslevodopa/foscarbidopa was initiated close to the patient's usual first morning dose and delivered continuously 24 h per day via an infusion set connected to a pump.

Base infusion rate was adjusted at any time to achieve and maintain an optimal therapeutic response to maximise functional 'On' time during the day by minimising the number and duration of 'Off' episodes (bradykinesia) and minimising 'On' time with troublesome dyskinesia.

During the optimisation period, concomitant PD medications were tapered down or suspended, as and when needed. During the maintenance period, concomitant PD medications were to remain stable unless medically indicated.

The continuous infusion rates of foslevodopa/foscarbidopa were able to be customised to deliver doses ranging from approximately 600 to 4100 mg of levodopa over a 24-hour period. Conversion from oral levodopa to foslevodopa/foscarbidopa were achieved in in an average of 3.5 outpatient visits.

Figure 1: Study design for M15-741



D = Day; V = Visit; W = Week

Baseline characteristics

223 subjects were enrolled. Most subjects were male (60.1%). The mean (SD) age was 63.8 (9.29) years. A comparable proportion of subjects were aged above and below 65 years. Around 46% of subjects had ≥ 10 years since the diagnosis of PD.

223 subjects were categorised into 2 'exploratory' modal dose-groups i.e., a low-dose category with modal total daily dose < 1800 mg LD or a high-dose category with modal total daily dose ≥ 1800 mg LD. 119 subjects were in the low-dose category and 104 subjects in the high-dose category.

Table 6: Baseline demographics

Parameter		ABBV-951 Dose Category		
		Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Sex, n (%)	Male	60 (50.4)	74 (71.2)	134 (60.1)
	Female	59 (49.6)	30 (28.8)	89 (39.9)
Race, n (%)	White	90 (75.6)	96 (92.3)	186 (83.4)
	Black or African American	0	1 (1.0)	1 (0.4)
	Asian	27 (22.7)	7 (6.7)	34 (15.2)
	American Indian or Alaska Native	1 (0.8)	0	1 (0.4)
	Multiple	1 (0.8)	0	1 (0.4)
Ethnicity, n (%)	Hispanic or Latino	8 (6.7)	12 (11.5)	20 (9.0)
	Not Hispanic or Latino	111 (93.3)	92 (88.5)	203 (91.0)
Age, years	Mean (SD)	63.4 (8.97)	64.2 (9.67)	63.8 (9.29)
	Median (min, max)	65.0 (34, 83)	64.0 (43, 86)	65.0 (34, 86)
Age category, n (%)	< 65 years	58 (48.7)	53 (51.0)	111 (49.8)
	≥ 65 years	61 (51.3)	51 (49.0)	112 (50.2)
Weight, kg	Mean (SD)	68.20 (17.283)	77.37 (16.480)	72.47 (17.488)
	Median (min, max)	67.30 (34.1, 120.7)	78.35 (41.4, 110.9)	72.85 (34.1, 120.7)
Geographic region, n (%)	North America	39 (32.8)	51 (49.0)	90 (40.4)
	Europe and Australia	58 (48.7)	48 (46.2)	106 (47.5)
	Japan	22 (18.5)	5 (4.8)	27 (12.1)
Duration of PD since diagnosis, n (%)	< 10 years	62 (52.1)	58 (55.8)	120 (53.8)
	≥ 10 years	57 (47.9)	46 (44.2)	103 (46.2)

max = maximum; PD = Parkinson's disease; SD = standard deviation

Subjects

A high proportion (39.9%) of subjects discontinued from the study.

The Sponsor conducted an interim analysis at 12 weeks of treatment period (before 8th July 2020). The analysis showed that difficulties with using the drug delivery system and infusion site skin AEs were the commonest causes for discontinuation. As a risk mitigation strategy, study sites and subjects underwent retraining, with a specific focus on the correct use and application of the infusion set cannula and aseptic techniques. In addition, Neria™ guard, the primary intended commercial infusion set for delivery of foslevodopa/foscarbidopa, was added in protocol Version 6. Subjects who enrolled under protocol Version 6 were required to begin the study using the neria guard infusion set rather than the Cleo 90 infusion set. The analysis of human factor study at later time points suggested that the Neria guard infusion set showed fewer local manipulations and increased patient compliance.

Table 7: Subject disposition

Disposition	Number (%) of Subjects		
	ABBV-951 Dose Category		
	Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Total subjects enrolled	119 (100)	104 (100)	223 (100)
Subjects who previously received ABBV-951 (in Phase 1 studies)	2 (1.7)	5 (4.8)	7 (3.1)
ABBV-951 ongoing	35 (29.4)	22 (21.2)	57 (25.6)
ABBV-951 prematurely discontinued	46 (38.7)	43 (41.3)	89 (39.9)
Primary reason for premature ABBV-951 discontinuation[a]			
Adverse event	23 (19.3)	23 (22.1)	46 (20.6)
Infusion site related infections	5 (4.2)	6 (5.8)	11 (4.9)
Infusion site related non infection reactions	10 (8.4)	6 (5.8)	16 (7.2)
Polyneuropathy	0	0	0
Weight loss	0	0	0
Hallucinations/psychosis	6 (5.0)	4 (3.8)	10 (4.5)
Somnolence	0	0	0
Falls and associated injuries	0	0	0
Withdrew consent	15 (12.6)	10 (9.6)	25 (11.2)
Lost to follow-up	0	1 (1.0)	1 (0.4)
Lack of efficacy	3 (2.5)	4 (3.8)	7 (3.1)
COVID-19 infection	0	0	0
COVID-19 logistical restrictions	0	0	0
Difficulty with drug delivery system	1 (0.8)	2 (1.9)	3 (1.3)
Other	4 (3.4)	3 (2.9)	7 (3.1)
ABBV-951 completed	38 (31.9)	39 (37.5)	77 (34.5)

A comparative analysis of subject disposition across the subsets of patient population treated before and after the protocol change is shown in Table 8.

Table 8: Comparative analysis of subject disposition across the subsets of patient population treated before and after the protocol change

Disposition	Number (%) of Subjects		
	Sample 1[a] N = 157	Sample 2[b] N = 66	All Subjects N = 223
ABBV-951 prematurely discontinued within first 12 weeks	49 (31.2)	8 (12.1)	57 (25.6)
Primary reason for premature ABBV-951 discontinuation[c]			
Adverse event	26 (16.6)	4 (6.1)	30 (13.5)
Infusion site related infections	8 (5.1)	0	8 (3.6)
Infusion site related non infection reactions	9 (5.7)	1 (1.5)	10 (4.5)
Polyneuropathy	0	0	0
Weight loss	0	0	0
Hallucinations/psychosis	6 (3.8)	1 (1.5)	7 (3.1)
Somnolence	0	0	0
Falls and associated injuries	0	0	0
Withdrew consent	14 (8.9)	2 (3.0)	16 (7.2)
Lost to follow-up	1 (0.6)	0	1 (0.4)
Lack of efficacy	4 (2.5)	1 (1.5)	5 (2.2)
COVID-19 infection	0	0	0
COVID-19 logistical restrictions	0	0	0
Difficulty with drug delivery system	1 (0.6)	1 (1.5)	2 (0.9)
Other	3 (1.9)	0	3 (1.3)

a. Sample 1 = subjects enrolled before 08 July 2020.
b. Sample 2 = subjects enrolled on or after 08 July 2020.
c. One subject can be only counted once.

Results

At week 26, there was an overall improvement in the "exploratory efficacy endpoints". There was an improvement in the "On-time" with and without dyskinesia, along with a reduction in the "Off-time". Improvements in sleep symptoms and health-related quality of life were achieved. A similar improvement in "motor aspects of experiences of daily living and quality of life endpoints were not reported.

Table 9: Efficacy endpoints

Measure	N	Baseline Mean (SD)	Week 26 Mean (SD)	Mean Change (SD)
"Off" time (hours)[a]	97	5.79 (2.35)	2.85 (3.02)	−2.94 (3.16)
"On" time without troublesome dyskinesia (hours)[a]	97	9.62 (2.42)	12.87 (3.08)	3.24 (3.16)
"On" time without dyskinesia (hours)[a]	97	7.01 (3.39)	11.02 (4.23)	4.00 (4.42)
Motor aspects of experiences of daily living[b]	104	15.9 (7.17)	12.7 (7.65)	−3.2 (6.82)
Sleep symptoms[c]	104	20.6 (9.93)	15.0 (9.64)	−5.7 (11.20)
Quality of life[d]	104	34.5 (14.93)	27.3 (15.05)	−7.2 (11.36)
Health-related quality of life[e]	86	0.662 (0.184)	0.744 (0.1375)	0.082 (0.1712)
Measure	**N**	**Baseline (%)**	**Endpoint (%)**	**Difference (%)**
Morning akinesia (%)[f]	77	77.8%	20.8%	−57.0%

SD = standard deviation
a. Parkinson's disease (PD) diary.
b. Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II score.
c. Parkinson's Disease Sleep Scale 2 (PDSS-2) total score.
d. Parkinson's Disease Questionnaire-39 item (PDQ-39) summary index.
e. EQ-5D-5L summary index.
f. Percentage of subjects with early morning "Off" status based on the first morning symptom upon awakening derived from the PD diary.

Study M15-739

A phase Ib, single-arm, open-label, outpatient study.

The primary objective was to assess local and systemic safety and tolerability of foslevodopa/foscarbidopa over 4 weeks in an outpatient setting. The secondary objective was to assess steady-state LD levels. The exploratory objectives were to assess the efficacy of foslevodopa/foscarbidopa in subjects whose motor complications were inadequately controlled by current therapy.

21 subjects were recruited. 14 subjects completed the study. Mean subject age was 61.6 y (Range: 35-77 years). 62% of the subjects were males.

Table 10: Demographic summary

	Mean ± SD (N = 21)	Min – Max
Age (years)	61.6 ± 10.3	35 – 77
Weight (kg)	80.6 ± 15.8	57 – 110
Height (cm)	170 ± 8.4	155 – 182
Sex	13 Males (62%), 8 Females (38%)	
Race	21 White (100%)	

Exploratory efficacy results

17 of the 20 subjects had improvement in "Off" time. The mean (SD) reduction of "Off" time from baseline to study end was 3.24 (3.65) hours across subjects (46.2% improvement). Four subjects reported > 90% reduction of daily "Off" time at the end of the study. There was an overall reduction in normalized "Off" time and "On" time with non-troublesome dyskinesia. and A mean improvement of 3.99 (5.37) hours was reported for "On" time with troublesome dyskinesia.

The Sponsor considered that the overall exploratory efficacy data associated with reduction of "Off" time and improvement in "On" time were consistent with data reported from previous Duodopa studies.

The Delegate noted there were wide standard deviations for the efficacy endpoints. The low number of participants and the natural variability of these endpoints might have contributed to this observation.

Safety

Safety endpoints were assessed as primary endpoints in studies M15-741 and M15-737. Both these studies were ongoing at the time of clinical evaluation. Data from an interim cut-off of 30th March 2021 were included in the application.

In the safety analysis, data was categorised as two 'exploratory' modal dose-groups i.e., a low-dose category with modal total daily dose < 1800 mg LD or a high-dose category with modal total daily dose ≥ 1800 mg LD. It was noted that the ongoing open-label phase III studies were not designed or powered to determine differences in efficacy or safety between dose-groups.

At clinical cut-off (30 March 2021), 36 subjects were included in controlled studies with foslevodopa and foscarbidopa and 518 subjects dosed across the clinical program.

Table 11: Exposure to foslevodopa/foscarbidopa across clinical studies

Study type/ Parkinson's disease	Controlled studies				Uncontrolled studies	Total Foslevodopa and Foscarbidopa
	Foslevodopa and Foscarbidopa	**Placebo**	***Control A**	***Control B**	Foslevodopa and Foscarbidopa	
Clinical pharmacology	**36**	**36**	**0**	**0**	**187**	**223****
Other (phase III)	0	0	0	0	295	295***
TOTAL	**36**	**36**	**0**	**0**	**482**	**518**

At the time of data cut-off (30 March 2021), 515 subjects had received ≥ 1 dose of foslevodopa and foscarbidopa and 144 subjects with advanced PD had been exposed ≥ 12 months.

In Study M15-737, the mean exposure to foslevodopa/foscarbidopa was 236.2 days and 144.2 person-years. As of the data cut-off date for the interim report (30 March 2021), only 12 subjects had reached Week 24. Hence safety data from this study does not add much to support the overall evidence.

Treatment emergent adverse events (TEAE)

In Study M15-741, 92.4% of subjects experienced some form of a TEAE. Highest incidence of TEAEs occurred in the General Disorders and Administration Site Conditions (80.7%) followed by nervous system disorders (44.4%), infections and infestations (42.6%) and psychiatric disorders (42.6%).

In Study M15-737, 45.8% of subjects experienced some form of a TEAE. TEAEs were evenly distributed between modal dose-categories. Administration Site Conditions (16.7%) were the commonest events. Infections and Infestations were reported in around 11% subjects. Most AEs were non- serious, and mild or moderate in severity. Most infusion site skin AEs resolved with or without treatment.

Treatment-related adverse events

Across studies, the administration site conditions were the commonest events reported. Other commonly reported events were related to the underlying clinical condition PD, such as psychiatric disorders and nervous system disorders (each 31.4%).

Deaths

In Study M15-741, 5 deaths were reported. All patients were in the high-dose category.

Three deaths were considered TEAEs, as they occurred within 30 days after the last dose of foslevodopa/foscarbidopa:

1. Cardio-respiratory arrest: Day 108, 70-75-year-old female (deterioration in general health)
2. Cerebrovascular accident: Day 117, 60-65-year-old male (complex medical history that included an inferior myocardial infarction, emphysema and abdominal aortic aneurysm)

3. Acute large right cerebral subdural haematoma and intracranial mass: Day 289, 65-70-year-old female (secondary to a fall from her bed without assistance)

Two deaths occurred more than 30 days after the last dose of foslevodopa/foscarbidopa:

4. Multiple organ failure from Day 119 in a 70-75-year-old female

5. Cachexia from Day 311 in a 35-40-year-old female (in context of urinary infection, 2 respiratory infections and prolonged immobility)

The study investigator did not consider any of the reported deaths as treatment related.

Serious adverse events (SAEs)

In Study M15-741, SAEs were reported for 55 (24.7%) subjects, with similar incidence between modal dose-categories. The most frequently reported SAEs were infusion site cellulitis (4.5%), infusion site abscess and hallucination (each 2.7% overall), psychotic disorder and PD (each 2.2% overall). Most SAEs were considered possibly treatment-related, with no general trend with regards to modal dose-category. Eight (3.6%) subjects had SAEs that led to premature discontinuation of study drug, including infusion site abscess in 3 subjects, infusion site cellulitis in 2 subjects, PD in 2 subjects and hallucination in 1 subject.

In Study M15-737: 5 (6.9%) subjects experienced an SAE, 4 in the high-dose category but none were considered treatment-related. Three (4.2%) subjects experienced a severe TEAE, all from the high-dose category.

Discontinuations due to AEs

In Study M15-741, 54 (24.2%) subjects experienced AEs that lead to study drug discontinuation, with similar distribution between modal dose-categories overall and by PT. Overall AEs reported in ≥ 3 subjects that lead to study drug discontinuation by PT, included: Infusion site events (infusion site cellulitis, 4.0%; infusion site erythema, 3.6%; infusion site nodule and infusion site oedema; each 1.8%; and infusion site reaction and infusion site abscess).

Since a higher than anticipated number of treatment discontinuations were observed in M15-741, irrespective of modal dose-category, most within the first 12 weeks of treatment, the Sponsor undertook an internal investigation. The main causes of treatment discontinuations appeared to be infusion site AEs and difficulties with using the drug delivery system.

The following mitigation measures were implemented: (a) Retraining of study sites and subjects, with specific focus on the correct use of the infusion set and cannula, and on aseptic techniques; (b) The Neria™ guard, the primary intended commercial infusion set for delivery of foslevodopa/foscarbidopa, was added as an alternative infusion set. These mitigation measures were fully implemented by 08 July 2020 (Protocol v6). The effect of these measures was evaluated by comparing key safety parameters for subjects enrolled before 08 July 2020 (Sample 1 [n = 157]) to those enrolled after 08 July 2020 (Sample 2 [n = 66]).

- The percentage of subjects who discontinued foslevodopa/foscarbidopa was lower in Sample 2 (12.1%) vs. Sample 1 (31.2%).
- The percentage of subjects with infusion site reactions was lower in Sample 2 (53.0%) vs. Sample 1 (83.4%). A similar pattern was observed in the percentage of subjects who discontinued foslevodopa/foscarbidopa because of infusion site reactions, with 1.5% in Sample 2 vs. 5.7% in Sample 1.
- The percentage of subjects with infusion site infections was lower in Sample 2 (16.7%) vs. Sample 1 (26.1%). A similar pattern was observed in the percentage of subjects who

discontinued foslevodopa/foscarbidopa because of infusion site infections, with none in Sample 2 vs. 5.1% in Sample 1.

- The percentage of subjects with TEAEs associated with product complaints was lower in Sample 2 (48.5%) vs. Sample 1 (75.8%).

In study M15-737, at data-cut off, no subject had treatment discontinued or interrupted due to a TEAE following foslevodopa/foscarbidopa infusion.

AEs related to product complaints

In Study M15-741, one-hundred and sixty-four (73.5%) subjects reported TEAEs associated with product complaints, with similar distribution between modal dose-categories. The incidence rates were: Cleo-90 infusion set (39.5%), the Neria™ guard infusion set (10.8%) and the infusion pump (7.2%), with no notable differences between modal dose-categories.

In Study M15-737, at data cut-off, 12 (16.7%) subjects reported TEAEs associated with product complaints, with a higher proportion in the high-dose category (19.6%) vs. the low-dose category (11.5%). Most complaints (6.9%) related to the infusion set, with a higher proportion in the high-dose category (8.7%) vs. the low-dose category (3.8%). Four (5.6%) subjects from the high-dose category, reported AEs associated with foslevodopa/foscarbidopa. The evaluator has highlighted that the results should be interpreted with caution since available data were limited by the low number of participants.

Infusion site infections

In Study M15-741, incidence of infusion site infections following foslevodopa/foscarbidopa infusion was 32.3% (n = 72), with higher incidence in subjects from the high dose-category (39.4%) compared with the low dose-category (26.1%). Sixty-six (29.6%) TEAEs were considered treatment-related following foslevodopa/foscarbidopa exposure. Infusion site cellulitis (23.8%; 'dose-related'); infusion site abscess (8.5%; 'dose-related'); and infusion site infection (5.8%; 'dose-related'). Twelve (5.4%) events were considered severe, 14 (6.3%) events serious (infection site cellulitis, 4.5%; and infusion site abscess, 2.7%) and 11 (4.9%) events led to study drug discontinuation (10 of which were considered treatment-related). The evaluator highlighted that 4 subjects experienced systemic complications of sepsis and/or metabolic encephalopathy, which required hospitalised treatment.

In Study M15-737, 6 (8.3%) subjects experienced infusion site infections, all treatment-related. Infusion site cellulitis accounted for 5 (6.9%) events, 4 of which occurred from the high-dose category. None were severe, serious or resulted in discontinuation. Most resolved or recovered.

Hallucinations and psychosis

In Study M15-741, most of these TEAEs (21.1%) were considered treatment-related. Of the TEAEs reported, treatment-related events following foslevodopa/foscarbidopa exposure were reported for: Hallucination (16.6%); hallucination, visual (5.8%); psychotic disorder (2.2%); and hallucination, auditory (2.2%), with similar distribution between modal dose-categories.

Polyneuropathy (peripheral neuropathy)

No events of Guillain-Barré syndrome were reported in the foslevodopa/foscarbidopa clinical development program. No polyneuropathy events were reported in the phase I studies or in M15-737, at the time of data cut-off. In M15-741, 5 (2.2%) subjects experienced at least 1 polyneuropathy event, 4 in the high-dose category. Two cases of treatment-related peripheral

polyneuropathy were reported (both high-dose category) and 1 severe event (in the high-dose category). No events led to study drug discontinuation.

Somnolence

No somnolence events were reported in the phase I studies or in M15-737, at the time of data cut-off. In M15-741, incidence of somnolence following foslevodopa/foscarbidopa infusion was 4.9%, with lower incidence of somnolence reported in subjects categorised as high-dose (1.9%) compared with low-dose (7.6%).

Falls and associated injuries

In Study M15-741, the incidence of falls and associated injuries following foslevodopa/foscarbidopa infusion was 15.7%, with higher incidence of falls and associated injuries reported in subjects categorised in the high modal dose-category (19.2%) compared with the low modal dose- category (12.6%).

Malignancies

Due to concerns about potential carcinogenicity of hydrazine, malignancies were evaluated in the foslevodopa/foscarbidopa clinical development program.

Three subjects in M15-741 experienced malignancy events. Basal cell carcinoma in 2 subjects and squamous cell carcinoma of skin in 1 subject. None of these events resulted in study discontinuation or were considered treatment related.

The low number of subjects and the shorter duration of Study M15-737 does not suit the assessment of malignancy risks.

There were no cases of melanoma in the foslevodopa/foscarbidopa clinical development program.

Withdrawal and rebound

Withdrawal or rebound effects with foslevodopa/foscarbidopa have not been studied.

Risk Management Plan (RMP) evaluation

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 12.

The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Table12: Safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infusion site infection	✓*	–	✓	–
	Impulse control disorders†	✓	–	✓	–
	Polyneuropathy†	✓	–	✓	–
Important potential risks	None	–	–	–	–
Missing information	None	–	–	–	–

*Follow-up questionnaire
† Australia-specific safety concern

ASA version 2.0 (June 2022) and existing Core RMP version 1.0 (July 2021; DLP 30 March 2021) were evaluated.

The sponsor proposed 'Infusion site infection' as an important identified risk.

As per the RMP evaluator's recommendation, the sponsor included 'impulse control disorders' (ICD) and 'polyneuropathy' as Australia specific important identified risks.

- The sponsor proposed routine pharmacovigilance activities only which include a targeted follow-up questionnaire. The evaluator considered this acceptable.
- The sponsor proposed a commitment to tighten the PDE limit of uranium from 1.2 µg/day to 0.12 µg/day post approval. The acceptability of which, will be considered by the non-clinical/toxicology evaluator. In the toxicology evaluator's report, kidney damage was stated as the principal effect of uranium toxicity. Prescribers are recommended to conduct periodic evaluation of renal function for patients on extended therapy with Vyalev as per the Product Information. From an RMP perspective, with the recommended patient monitoring and the appropriate controls in place as determined by the tox evaluator, the uranium content is not considered a safety concern in the RMP for Vyalev.
- The risk minimisation plan was considered acceptable.

Outstanding issues

- The sponsor proposed to provide the CMI and Vyalev Instructions for Use (IFU) documents electronically only. The evaluator considered this approach as complex for patients to access, considering the demographics of the target population. This issue was brought to the Delegate's attention to consider the clinical implications associated with the sponsor's approach to provide the consumer information documents via QR code on the outer packaging only. The Delegate sought the ACM's advice on this matter.
- The evaluator noted the following: *the sponsor has been requested to closely monitor for medication error and/or device error and assess the clinical impact in PSUR reporting.* In view of the clinical data, the Delegate agrees with this recommendation and requests the Sponsor to clarify what measures have been taken to address this matter.
- The RMP evaluator supports the Delegate's recommendation for the sponsor to implement appropriate training for healthcare professionals to undertake and complete before prescribing Vyalev. This approach would further mitigate the potential for medication and/or device error. Please note, the risk of medication and/or device error is not a listed safety concern. The training for healthcare professionals is out of scope for the RMP.

RMP evaluator's recommendations regarding condition/s of registration

The Vyalev Core Risk Management Plan (RMP) (version 1.0, dated July 2021, data lock point 30 March 2021), with Australian Specific Annex (version 2.0, dated June 2022), included with submission PM-2021-03724-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

As Vyalev is a new chemical entity, it should be included in the Black Triangle Scheme. The following wording is recommended for the conditions of registration:

> *Vyalev (foslevodopa/foscarbidopa) is to be included in the Black Triangle Scheme. The PI and CMI for Vyalev must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.*

Risk-benefit analysis

Delegate's considerations

In this application, the evidence to suggest a comparable efficacy and safety between foslevodopa/carbidopa (CSIC) and the Duodopa (LCIG) is heavily dependent on the comparability of the PK parameters of these products. The Sponsor is requested to clarify the comparability between the Duodopa used in clinical studies in this application and the Duodopa that has been approved by TGA.

In the BE Study M17-220 in healthy adults, the systemic exposure to LD following administration of foslevodopa/foscarbidopa 700/35 mg over 24 h was comparable to that of LCIG 350/87.5 mg LD/CD over 16 h followed by 2 100/25 mg LD/CD oral doses at 18 and 21 h after the start of infusion. It was noted that a subtherapeutic dose of foslevodopa/foscarbidopa was selected for this study.

The Sponsor's rationale for the lower dose was *to be in a tolerable range for healthy volunteers*. In view of the dose proportionality that has been demonstrated for foslevodopa/foscarbidopa, this approach was considered as acceptable by the clinical evaluator.

The Delegate noted studies M15-738 and M15-739 that were aimed to demonstrate steady state plasma level for LD and dose proportionality in patients with PD.

The toxicology evaluator highlighted hydrazine as an impurity in foslevodopa/foscarbidopa. Based on the module 3 and 4 reports, the Delegate considered that the daily hydrazine exposure level at the maximum dose of foslevodopa/foscarbidopa is lower than the corresponding dose of TGA approved Duodopa (0.5mg vs 8mg). Based on that finding, the quality and nonclinical (toxicology) evaluators concluded this impurity was not a major concern.

The Delegate noted the following in the clinical evaluator's report:

> *Although no increased incidence of malignancies, or specific types of malignancy, were observed in the Duodopa clinical program or post-market setting, or in the interim study results presented from the foslevodopa/foscarbidopa clinical program, an association with increased incidence of malignancies, particularly in the liver and lung (based on non-clinical findings secondary to hydrazine exposure), cannot be ruled out. Notwithstanding there is an approx. 15-foLevodopa greater reduction in hydrazine exposure with foslevodopa/foscarbidopa infusion compared with levodopa/carbidopa intestinal gel*

> *infusion (Duodopa), the risk of development of neoplasms remains, as the maximum hydrazine exposure following foslevodopa/foscarbidopa infusion (525 microgram/day) is still much higher than the maximum FDA-recommended levels of hydrazine in humans (39 microgram/day).*

The toxicology evaluator mentioned hydrazine as a rodent carcinogen and recommended the following statements be included in the proposed PI.

> *VYALEV contains hydrazine, a degradation product of foscarbidopa. Hydrazine has been found to be genotoxic and a rodent carcinogen. It is considered by IARC (International Agency for Research on Cancer) to be a possible human carcinogen and by the US EPA (Environmental Protection Agency) to be a probable human carcinogen. The maximum recommended dose of foscarbidopa could result in a hydrazine dose of approximately 0.5 mg/day which is higher than the recommended dose. The clinical significance of this hydrazine exposure is not known.*

The Delegate noted that the level of hydrazine in Vyalev was lower than in Duodopa. However, the Delegate also noted concerns from a clinical perspective, with the following uncertainties:

- rate and magnitude of absorption of hydrazine from subcutaneous route of administration for Vyalev, compared to enteral route for Duodopa
- cumulative exposure from 24-hour continuous infusion of Vyalev, compared to 16-hour infusion of Duodopa, followed by an 8-hour break, in patients with advanced PD.

The Delegate sought ACM's advice on the above uncertainties.

The Delegate noted uranium, as an impurity, is a critical safety issue of concern. The quality evaluator stated that:

> *foslevodopa and foscarbidopa are made from levodopa and carbidopa using a phosphorylating reagent itself made from phosphate salts. Those salts can contain uranium as an impurity and they are used in the last synthetic step in preparation of the drug substances. Thus, uranium is a risk associated with foslevodopa and foscarbidopa and not Duodopa (or most other drugs).*

The toxicology evaluator recommended a uranium PDE (Permitted Daily Exposure) of 0.12 µg/day. The Delegate noted the Sponsor's commitment to adopt *control strategies* to limit the uranium content <0.12 µg/day. The Delegate has also noted the Sponsor's commitment to develop an analytical method by Q1 2023 that will be capable to demonstrate whether the uranium level is <0.12 µg/day (PDE) and the toxicology evaluator's comment in this regard that the level of uranium until demonstrated by a validated method can only be referred to as an interim limit based on practicality.

The toxicology evaluator also commented that *the issue should be rectified as soon as possible to further minimise the risk.* The Delegate noted that the uncertainty regarding the actual level of uranium and the associated risks remains until it is demonstrated by a suitable analytical method. The Delegate further noted that the critical issue would be the uncertainty regarding the absolute risk and the cumulative risk from the potential exposure of up to 1.1 µg/day, which is around 10 times greater than the toxicology evaluator's recommended PDE for uranium.

The Delegate highlighted that the risks associated with the uranium content in Vyalev need to be evaluated in the context of the use of foslevodopa/foscarbidopa in patients with advanced PD, if approved. The risks due to systemic exposure are potentiated by the radioactive nature of the uranium as an element, the long half-life.

According to the Agency for Toxic Substances and Disease Registry (ATSDR*) the least radioactive isotope is 238U with a half-life of 4.5 billion years and the potential systemic effects from this agent that could remain in the body for a prolonged period of time*.[5] ATSDR states: *Uranium that is absorbed is deposited throughout the body; the highest levels are found in the bones, liver, and kidneys. Sixty-six percent of the uranium in the body is found in your bones. It can remain in the bones for a long time; the half-life of uranium in bones is 70–200 days (this is the amount of time that it takes for half of the uranium to leave the bones). Most of the uranium that is not in bones leaves the body in 1–2 weeks* [4]).

From a clinical perspective, with the background of a serious neurological condition and possibly >1 co-morbidities, it is highly likely to be difficult to identify the onset of any possible adverse effects from the greater (continuous) exposure to uranium from the continuous infusion of foslevodopa/foscarbidopa. In view of the uranium content in Vyalev, the Delegate considered that there is uncertainty about the exposure implications to carers and to the environment from the disposal of the waste (single use vials, infusion set, syringe and vial adapter). In addition, there is also uncertainty about the effects from the uranium that will be excreted by the patients.

In consideration of the above facts and reasons, the Delegate was not convinced that, if approved, use of Vyalev will not put health practitioners, patients with advanced PD, their carers and the environment at risks from exposure to uranium. The Delegate considered that Vyalev should only be registered in the ARTG, once the actual level of uranium has been demonstrated as <0.12 µg/day (0.02 ppm) by a validated test. The Delegate sought ACM's advice on this matter.

Based on the comparability of PK parameters, the efficacy profiles of foslevodopa/foscarbidopa CSCI and Duodopa LGIC are expected to be essentially similar. The exploratory efficacy results from the ongoing phase III studies (*M15-741* and *M15-737*), and the completed phase I study (*M15-739*) suggests a comparable efficacy profile between the foslevodopa/foscarbidopa foslevodopa/foscarbidopa CSCI and Duodopa LGIC.

M15-741 is the only study that included a reasonable number of subjects and provided exploratory efficacy data for a reasonable duration of time. However, the high discontinuation rate in this study (39.9% (n = 89 subjects)) was considered as a limitation that may have implications on the internal validity of the study findings. With due consideration of the exploratory nature of the efficacy endpoints, foslevodopa/foscarbidopa treatment showed clinically meaningful reductions in motor complications and improvements in motor symptom control in subjects with advanced PD, which were generally consistent with Duodopa.

The Delegate noted that data to support long term efficacy was lacking in this submission. The Delegate considered this important, particularly in view of the drug tolerance and reduction of therapeutic effect from continuous levodopa administration. This possibility was the rationale to suspend the Duodopa infusion overnight.

The Delegate noted a mechanistic possibility for foslevodopa/foscarbidopa continuous infusion to result in the above issue. Long term efficacy data is required to conclude that the treatment benefits reported in Study M15-741 are sustained. The Delegate is aware that a (M15-736) Phase 3 randomized, double-blind, double-dummy, active-controlled study that compared the efficacy, safety and tolerability of ABBV-951 (foscarbidopa/foslevodopa) to oral immediate-release CARBIDOPA/LEVODOPA in patients with advanced PD was submitted to FDA but was not submitted to TGA for evaluation.

[5] U.S. Department of Health and Human Services, A.T.S.D.R., *TOXICOLOGICAL PROFILE FOR URANIUM.* https://www.atsdr.cdc.gov/ToxProfiles/tp150.pdf, 2013.

Long term safety data for foslevodopa/foscarbidopa is lacking in this submission. The Delegate has noted that the safety data set has satisfied the minimum requirement for a New Chemical Entity: *144 subjects with advanced PD had been exposed ≥ 12 months.* The study M15-741 provided safety data up to 26 weeks. In Study M15-737, as of the data cut-off date for the interim report (30 March 2021), only 12 subjects had reached Week 24. Safety also has been extrapolated from Duodopa, based on the comparability of PK parameters.

However, the Delegate considers that in view of the frequent interventions to change the infusion site, the infusion site adverse events, the handling of the complex infusion pump (as described below) and more importantly due to the uncertainties related to the uranium content, the foslevodopa/foscarbidopa has a safety profile that is distinct from Duodopa. Hence, long term safety and patient compliance data is required for the assessment of benefit-risk profile for this product, rather than extrapolation of safety data from Duodopa.

Similarly, the Delegate is aware of the potential for motor complications from the high dose of levodopa in Vyalev [[5] [6]]. It is an important safety aspect to consider, in view of the relatively higher daily dose of levodopa in Vyalev (4260 mg), compared to Duodopa (3500 mg). It was noted that such events have not been reported from the available data from the studies included in the dossier. However, the efficacy (interim) data is limited by the short duration and the exploratory nature.

Across studies, administration site conditions were the commonest TEAEs that were reported. These TEAEs were also the commonest reason for treatment discontinuation in Study M15-741. The Delegate has noted the Sponsor's intervention to address this issue by re-retraining subjects and study sites and also the introduction of the Neria™ guard, the primary intended commercial infusion set for delivery of foslevodopa/foscarbidopa. The incidence for these TEAEs were lower in the Study M15-737, compared to study M15-741. However, the safety data from Study M15-737 is limited by the short duration and the low number of subjects. Long term safety data from the ongoing studies is needed to make any conclusions in this regard. Based on the above findings, the Delegate considers that training should be mandated for prescribers prior to administering this medicine. Patient education regarding the handling of the device is equally important to achieve treatment compliance and reduce the likelihood for administration site TEAEs. The Delegate noted that the infusion set (canula) needs to be replaced every 3 days, along with rotation of infusion site, which should be at least 2.5cm from sites used in the previous 12 days. As evidenced in Study M15-741, retraining of study sites and personnel was required to prevent subjects from early discontinuation of the study. Long term patient compliance data from M15-737 will provide greater certainty in this matter.

The sub-cutaneous infusion site, particularly with frequent change of sites once every three days is prone for infection and sepsis, as reported in study M15-741. Each vial delivers 2400 mg of foslevodopa, thus for a patient receiving a dose greater than 2400mg will need to replace the vial manually and those receiving the maximum dose of 5999mg will need to change three vials a day. The Delegate considers that the above issues are highly likely to have a negative impact on patient compliance and increase the risk for infusion-site related events, infection and sepsis.

The lack of head-to-head comparison data between foslevodopa/foscarbidopa and Duodopa limits the ability to make any conclusions regarding comparative treatment benefit for foslevodopa/foscarbidopa, compared to Duodopa.

Proposed action

Bioequivalence between the foslevodopa/foscarbidopa and the Duodopa is adequately demonstrated in healthy adults and not in patients with PD. The risks associated with the cumulative exposure to hydrazine and absolute and cumulative exposure to uranium in patients

with advanced PD is a critical issue. Studies that were aimed to provide comparative efficacy and safety between foslevodopa/foscarbidopa are limited by the lack of internal validity, low number of participants and short duration.

As a new fixed dose combination medicine, containing two new chemical entities, the long-term efficacy and safety data for foslevodopa/foscarbidopa is lacking in this submission.

Independent expert advice

The Delegate received the following independent expert advice.

Advisory Committee on Medicines (ACM) considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice from the ACM to the Delegate

1. ***Please comment on the risks (absolute and cumulative) associated with hydrazine as an impurity in Vyalev and its potential long-term effects in patients with advanced Parkinson's disease, particularly in view of its carcinogenic potential in rodents. Are there any concerns regarding the level and bioavailability of hydrazine from subcutaneous route of administration of Vyalev?***

The ACM noted that hydrazine is a reagent used in the synthesis of carbidopa and is present as a degradation impurity of foscarbidopa in Vyalev. Hydrazine is noted to be genotoxic, a rodent carcinogen and a possible human carcinogen with cumulative exposure. The ACM noted the proposed finished product limits for hydrazine (relative to the foscarbidopa) for clinical in-use are 1740 ppm.

The ACM noted that the risks of hydrazine are cumulative but difficult to clinically quantify given the inconclusive evidence regarding whether hydrazine is mutagenic or non-mutagenic, and the lack of human and subcutaneous toxicity data.

The toxicity assessment was completed based off data from animal modelling and assumed a life-time hydrazine exposure however potential patients receiving Vyalev will not be exposed for 70 years. It is noted that this product will not be used for a lifetime hence the use calculation of cancer risk by the sponsor across 5, 10 and 20 years. The ACM considered that given patients with advanced PD likely have a further 10 years of life, this is a suitable approach.

The ACM also noted lower hydrazine levels in Vyalev than in Duodopa, which is administered enterally not subcutaneously, and there have been no post market safety signals related to hydrazine exposure nor increased cancer incidence from Duodopa to date.

The ACM was of the view that although human exposure to hydrazine in Vyalev likely exceeds permissible daily exposure (PDE) and Acceptable Intake (AI) levels, the risk of patient harm from subcutaneous administration resulting from the potential durations of Vyalev therapy is difficult to quantify. However, the ACM considered the hydrazine levels at the maximum limit to be concerning and advised that hydrazine levels should be kept as low as practicable.

The ACM agreed that this risk should be clearly highlighted in the Product Information.

2. ***Please comment on the risks (absolute and cumulative) associated with uranium as an impurity in Vyalev and its potential long-term effects.***

a. ***At this stage, are there any concerns regarding the uncertainties related to the level of uranium?***

b. ***b. Does the committee consider that the actual level of uranium in Vyalev should be demonstrated by the Sponsor's proposed analytical method prior to registration of this product on the ARTG?***

The ACM noted that uranium was identified as a possible impurity from the phosphorylation steps in the synthesis of foslevodopa and foscarbidopa. The contaminant uranium species has not been identified, and the ACM was of the view that as that toxicity varies with solubility, the associated risk cannot be properly elucidated until this is characterised. It was noted that the low level of uranium was attributed as a challenge to characterise the species of uranium.

Uranium has been shown to be poorly absorbed following inhalation, oral or dermal exposure in rat models, but SC administration resulted in higher uranium bioavailability. Uranium has a long half-life (70-200 days in bones) however the implications of uranium accumulation and potential nephrotoxic effects is unknown following SC administration. Due to the paucity of human data, it is noted that the toxicology assessment is based on animal data.

The maximum uranium exposure following foslevodopa/foscarbidopa infusion (1.1 µg/day) is ten times higher than the maximum recommended levels of uranium in humans (0.12 µg/day) so the risk of development of renal toxicity remains, particularly in view of the continuous infusion. The ACM noted that the Sponsor has confirmed that they have adopted the required control strategy to achieve the level of uranium (0.02 ppm or 0.12 µg/day) as stipulated by the toxicology evaluator, however the ACM note it is likely to take additional time to measure uranium down to a Permitted Daily Exposure level of 0.12 µg/day. The ACM noted different detection limits existed for foslevodopa (< 0.18 ppm) and foscarbidopa (< 0.04 ppm) and advised additional information be provided to substantiate this difference.

The ACM expressed concern regarding potential risks not just to the patient, but to carers and healthcare professionals handling and disposing of the product, device and infusion set, and through urinary excretion.

The ACM noted that the uranium content validated analytical method will be submitted by the end of quarter 1 2023. The ACM advised the TGA to await this data given the multiple uncertainties present at this stage which impact the risk-benefit profile.

3. ***The TGA-approved Duodopa PI states that "Continuous levodopa administration may lead to the development of tolerance and reduction of therapeutic effect". This possibility was one of the rationales to suspend the Duodopa infusion overnight. Does the ACM consider the above issues as a limitation for Vyalev when levodopa will be administered as a continuous infusion? If so, does the ACM consider there is a need for long term efficacy data at this stage?***

The ACM was of the view that continuous dosing is not an issue.

The ACM considered the need in advanced PD to maintain additional dopaminergic stimulation for as much of the 24-hour period as possible, and there are patients who require 24-hour treatment with Duodopa or require oral levodopa/carbidopa doses overnight to maintain mobility and symptom control, to ensure comfortable sleeping positions and reduce falls risk attending the bathroom overnight.

The ACM noted the lack of evidence to support this concern of tolerance with continuous levodopa administration and was of the view that it is unlikely that tolerance is a significant issue, rather it is likely a holdover from historical ideas regarding neuroprotection and levodopa toxicity which have been disproven.

Maintenance of effect and long-term safety data would provide additional reassurance when available.

4. ***In view of the relatively higher dose of levodopa in Vyalev, compared to Duodopa, are there any concerns for motor complications due to levodopa? If so, does the ACM consider there is a need for long term efficacy data at this stage?***

The ACM considered that motor fluctuations and dyskinesia are known dose-related complications of levodopa in the advanced PD patient cohort.

The ACM noted there was an immaturity to the data, however advised that there is long term experience with levodopa via other routes of administration. The ACM noted pharmacokinetic data in healthy adults (M17-220 and M20-141) and the single arm efficacy trial did provide some reassurance, however noted that efficacy data from a controlled trial would enable additional assessment. The ACM advised that longer term efficacy data would be useful when available.

The ACM discussed the toxicity profile of levodopa and was of the view that the idea that levodopa is neurotoxic is likely overstated and historical. The ACM advised that in current practice levodopa dosing is individually monitored and titrated by subspecialist neurologists, who have appropriate expertise and understanding of levodopa's toxicity profile.

5. ***In view of the infusion-related reactions, sepsis and high treatment-related discontinuation rates based on the interim study results, does the ACM consider there is a need for further long-term safety data at this stage?***

The ACM advised that longer term safety data would be needed to further understand the safety profile of Vyalev, given the high treatment-related discontinuation rate and the correlation to delivery device issues and infusion-related reactions. The ACM noted that both exposure numbers and duration of data collection for safety assessment are limitations to interpretability at this stage and this impacts on the ability to make conclusions regarding safety (with the device) at the stage.

The ACM also noted that the infusion device requires separate evaluation via the devices pathway and was informed that at this time a device application has not yet been submitted to the TGA.

6. ***Does the ACM consider that the access to Vyalev should be restricted to those prescribers who have completed training for the use of the infusion device?***

The ACM highlighted that usability of the infusion device is an important safety consideration and expected that education and clinical support on usage would be provided by the sponsor to users and healthcare professionals in line with other products for advanced PD. The ACM also noted that it is reasonable to assume that patients and carers will be able to change the SC catheter and load the medication into the device.

The ACM agreed that prescribing access should mirror other comparable agents within this field.

The ACM noted the 40% patient discontinuation rate within the clinical trial (M15-741) in addition to the 'product complaints' adverse event of interest and discussed, whether discontinuation was due to infusion device issues. The ACM queried whether additional training would improve the usability of the infusion device.

7. ***The Sponsor is proposing to provide the CMI and Vyalev Instructions for Use (IFU) documents electronically only (QR code on the outer packaging). Does the committee consider this approach acceptable in a patient population with advanced Parkinson's Disease and also in consideration of the patient demographics?***

The ACM considered there to be potential benefits to all patients for the CMI and IFU documents to be provided electronically via a QR code, specifically with the capability to increase font and graphic size and the increased contrast on an electronic device, making these documents easier to read, searchable and more durable. The ACM acknowledged that provision of printed CMIs on request from doctors and pharmacists would remain feasible.

The ACM was of the view that to transition from the inclusion of printed patient instructions within a product to electronic availability via a QR code only would require consumer engagement and an educational awareness campaign, as this approach varies from current practice.

The ACM did not consider legislative requirements in making this recommendation.

ACM conclusion

The proposed indication considered by the ACM was:

> *For the treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimised alternative pharmacological treatment.*

The ACM agreed there was currently insufficient safety data to support the proposed use of this product. The main area of uncertainty is the actual level of uranium in Vyalev. The ACM noted that the uranium content validated analytical method will be submitted by the end of quarter 1 2023. The ACM advised the TGA to defer its decision until this data is provided for evaluation.

The ACM also noted the availability of the additional phase III study and recommended that this be provided to the TGA for consideration.

Risk-benefit assessment of new data

In response to the concerns raised by the Delegate and the ACM, the Sponsor submitted:

- additional long-term safety and efficacy data
  - Study M15-736 and its extension study
  - Third interim Clinical Study Report for Study M15-741 and its extension study
- updated control strategy to support tightening of the uranium limit to 0.12 µg/day.

Manufacturing and quality control data

Based on the evaluation of the new data, the quality evaluator stated that *the new control should ensure that the product meets the PDE of 0.12 µg/day,* which was the upper limit for the uranium content that was previously specified by the evaluator.

There were no outstanding quality or manufacturing issues related to these components of the submission.

Efficacy and safety data

The additional phase III study 736 provided comparative efficacy and safety data between Vyalev and oral levodopa/carbidopa.

In terms of long-term data, it appears that the magnitude of treatment benefit (improvement in "On" Time without Troublesome Dyskinesia and "Off" time (around 3 hours each)) in Study 741 at week 26 was sustained until week 54. It was also comparable with the treatment outcomes in Study 736.

The lower magnitude of treatment benefit in Study 737 was noted and the Sponsor was requested to clarify.

The high study discontinuations due to both infusion site reactions and infections was noted. The clinical evaluator highlighted that *While 'infusion site infection' is an Important Identified Risk for Vyalev continuous subcutaneous treatment, the high number of study discontinuations (35-39%) in 2 phase III clinical studies remains an ongoing concern*. Majority of subjects (82%) in study 741 that provided long term safety data for up to 52 weeks reported infusion site reactions. It was also noted that most of these events were mild in severity.

In response to the evaluator's request, the Sponsor provided the following as further explanations, with a focus on the infusion site reactions that led to discontinuation.

> *AEs that led to Vyalev discontinuation were 26% and 21% in each study, respectively. The Sponsor has compared the incidence of infusion site AEs and discontinuation rate observed in the Vyalev phase III clinical studies to other PD products delivered as continuous SC infusions e.g., apomorphine (23% discontinued before 12 weeks). In both apomorphine studies, infusion site reactions were common (59% and 71%, respectively; skin nodules at the infusion site in particular). The Sponsor has also cited the incidence rate of skin events with SC infusion therapies, including insulin administration.*
>
> The Sponsor highlighted that *most of the premature discontinuations in both Vyalev phase III studies occurred during the first 4-6 weeks of treatment, which emphasises the importance of training and education during treatment*.

The Delegate considered that the Sponsor's proposed training and prescriber education may enable to reduce the discontinuation rates. The nature of infusion site AEs and rate of discontinuations were similar to previously submitted data and no new safety concerns were identified.

A nearly five-fold increase in the rate of incidence of hallucination or psychosis was reported in subjects in the Vyalev arm, compared to oral levodopa/carbidopa arm in Study 736 (14.9% vs 3%). A dose-dependent increase (almost twice) in the incidence was noted (20.7% high-dose vs 11.1% low-dose). With due consideration of the limitations of indirect comparison (lack of 54-week data with Duodopa), the incidence rate for these events in the Vyalev arm is much higher (three times) than that reported from studies with Duodopa (5.8%).

Nil new types of adverse events were noted in the long-term safety data.

Vyafuser pump is the device that was utilised to administer Vyalev in the clinical studies included in this submission. The Delegate noted that Vyalev can only be administered with the Vyafuser pump. This device had not yet been evaluated by TGA. The Delegate further noted that US FDA has refused approval of Vyalev and issued a Complete Response Letter (CRL) to the Sponsor to address numerous outstanding issues related to the device. This was considered a critical uncertainty, in view of the fact that safety and quality aspects of Vyafuser pump are integral to achieve the expected treatment benefits for patients with advanced PD.

Proposed action

The Delegate noted the following.

- The revised controls appear to lower the level of uranium below the PDE of 0.12 µg/day.
- The magnitude of treatment benefit appears to be sustained until 52 weeks of treatment with Vyalev.

- Five-fold increase in the incidence of hallucinations and psychosis in Vyalev arm, compared to oral CARBIDOPA/LEVODOPA arm highlights a safety concern. A dose-dependent effect was noted.
- High discontinuations rates that were related to infusion site reactions and infections were noted. Prescriber and user education may mitigate this risk to a certain extent. Post market safety data will enable to assess the impact of these events in a clinical setting.
- The Vyafuser pump has not yet been evaluated by TGA. The outstanding device-related issues listed in the US FDA's CRL is a concern and highlights potential uncertainties related to the safe and effective administration of Vyalev and to achieve the expected treatment benefits.

At this point in time, the Delegate was inclined to reject this application to register Vyalev. However, the Delegate was prepared to consider deferral to making a regulatory decision if the application to include the Vyafuser pump in the ARTG was imminent. This was in consideration of the outstanding device-related issues listed in the US FDA's Complete Response Letter and FDA's refusal to approve Vyalev.

The ACM was requested to provide advice based on the additional data, evaluations and the Delegate's second risk/benefit assessment, to inform the regulatory decision.

Independent expert advice on additional data and questions

The ACM noted that the data considered at the October 2022 meeting demonstrated efficacy. However, it was limited in relation to the number of patients and duration of treatment.

The ACM acknowledged that additional data had been provided since October 2022 including an additional Phase III study (Study M15-736) and follow up data for Study M15-741.

The ACM noted that as of August 2024, foslevodopa and foscarbidopa had been approved within the European Union, Canada and Japan.

Specific advice from the ACM to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice.

1. ***A nearly five-fold increase in the rate of incidence of hallucination or psychosis was reported in subjects in the Vyalev arm, compared to oral levodopa/carbidopa arm in Study 736 (14.9% vs 3%). With due consideration of the limitations of indirect comparison (lack of 54-week data with Duodopa), the incidence rate for these events in the Vyalev arm is higher than that reported from studies with Duodopa (5.8%). Please comment on any potential implications on the safety profile of this observation. Please advise the need for additional risk mitigation strategies.***

The ACM advised that hallucination or psychosis is a known side effect of dopaminergic stimulation therapies. The ACM indicated that hallucination or psychosis may be more common in the context of continuous stimulation due to the likely improved bioavailability of subcutaneously administered therapies. As such, the ACM suggested that dose titration (or discontinuation) may be an option for affected patients.

In providing this advice, the ACM highlighted that hallucination or psychosis are a concerning event and advised that close monitoring of patients with these adverse events is required. The ACM noted that treating neurologists are familiar with these adverse events and the safety profile of dopaminergic stimulation therapies and no additional risk mitigation strategies are indicated.

2. Please comment on the adequacy of long-term efficacy and safety data of Vyalev for the proposed indication

On balance, the ACM was of the view that the long-term efficacy and safety data is adequate to support Vyalev for the treatment of advanced idiopathic Parkinson's Disease with severe motor fluctuations.

The ACM advised that the treatment effect appears similar to existing device assisted therapies. Further noting that the provided efficacy data demonstrates that the treatment effect of Vyalev is sustained up to 52 weeks, with extension studies providing additional data. Additionally, the Phase III study (M15-736) provided comparative data between Vyalev and oral CARBIDOPA/LEVODOPA supporting the use of Vyalev in the proposed population.

The ACM noted that the safety profile for Vyalev appears to align with the real-world experience for these types of medicines. The ACM discussed the high incidence of infusion site reactions and infections within the submitted studies and indicated that within clinical practice these adverse events, if recurrent, may necessitate discontinuation. The ACM also commented on the rates of dyskinesia (11% in M15-736) and advised that dyskinesia often accompanies good motor control within advanced disease and as such is not always troubling for patients. The ACM advised that patients receiving device-assisted pharmacotherapies for PD receive intensive support from nursing services, which are usually funded by the sponsors. The ACM was of the view that this nurse-provided support would assist with the mitigation and management of the risks of infusion site reactions and other adverse effects as well as facilitating pharmacovigilance.

The ACM also noted that Vyalev is less invasive than some other treatment options and having another option is useful for patients and clinicians.

3. Please comment on whether the issues listed in the FDA's Complete Response Letter regarding the device could affect the efficacy and safety of Vyalev

The ACM discussed the issues listed in the FDA's Complete Response Letter and noted that these appear to mainly relate to deficiencies in testing and specifications. However, the ACM also acknowledged that should there be issues with the battery alarms and flow accuracy etc, these could potentially affect the efficacy and safety of the medicine. The ACM advised that with the limited information available it is challenging to provide advice on the extent to which the identified issues with the device could affect the efficacy and safety of the medicine.

The ACM was of the view that it would be unlikely that the medicine will be used without the device, and if the medicine were approved it would be assumed that it (the medicine) would not be marketed until the associated device has been appropriately evaluated.

The ACM also noted that the device is referenced within the medicine PI and the specificity of Vyalev (medicine) only to be administered with the Vyafuser device. In consideration of the regulatory issues and the outstanding issues with the device, the ACM noted that it may be appropriate to consider approval of the registration of the medicine only after the device has been fully considered by the TGA and an appropriate recommendation/decision reached.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *For the treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimised alternative pharmacological treatment.*

The ACM also noted the regulatory challenges due to the associated device not yet being available for evaluation by the TGA, particularly in view of the outstanding issues with the device. They acknowledged that this may impact on the Delegate's ability to make a favourable regulatory decision in terms of the registration of the medicine at this time.

Regulatory decision

Based on the evaluation of additional data for quality, safety and efficacy, and subsequent application to include the Vyafuser pump in the ARTG, the TGA decided to register Vyalev (foslevodopa 2400 mg/10 mL and foscarbidopa 120 mg/10 mL) solution for subcutaneous infusion vial for the following indication.

> *For the treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimised alternative pharmacological treatment.*

Specific conditions of registration applying to these goods

Vyalev (foslevodopa/foscarbidopa) is to be included in the Black Triangle Scheme. The PI and CMI for Vyalev must include the black triangle symbol and mandatory accompanying text for 5 years, which starts from the date that the sponsor notifies the TGA of supply of the product.

The Vyalev EU Risk Management Plan (RMP) (version 1.2, dated May 2022, data lock point 05 November 2021), with Australian Specific Annex (version 4.0, dated April 2023), included with submission PM-2021-03724-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the registration approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of 2 PSURs each covering 6 months. If the sponsor wishes, the six-monthly reports may be submitted separately as they become available.

Reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than 3 years from the date of this approval letter. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within 90 calendar days of the data lock point for that report.

Attachment – Product Information (PI)

The Product Information (PI) approved with the submission for Vyalev is at Attachment 1. It may have been superseded. To view the current PI and Consumer Medicines Information (CMI), please use the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #