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APPLICATION NUMBER:

214869Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW OF SAFETY

Application Type	NDA 505 (b)(2)
Application Number(s)	214869
Priority or Standard	Standard
Receipt Date(s)	10/14/20
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Division/Office	Division of Neurology 1 (DN1)
Reviewer Name(s)	Leonard P. Kapcala, M.D.
Review Completion Date	7/16/21
(Proposed) Trade Name	DHIVY
Applicant	Riverside Pharmaceuticals
Formulation(s)	Tablet
Dosing Regimen	3-8 times daily orally
Applicant Proposed Indication(s)/Population(s)	Treatment of Parkinson's disease
Recommendation on Regulatory Action	Approval

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List of Abbreviations and Definitions of Terms

A	Abnormal
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC0-inf	Area under the concentration-time curve from time zero to infinity (extrapolated)
AUC0-t	Area under the concentration-time curve from time zero to time of last non-zero concentration
BLQ	Below limit of quantitation
BMI	Body mass index
bpm	Beats per minute
CD	Carbidopa
CFR	Code of Federal Regulations
C.I.	Confidence interval
C_{max}	Maximum observed concentration
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organisation
CS	Clinically significant
CV	Coefficient of variation (equivalent to C.V.)
DMP	Data management plan
DF	Degree of freedom
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic (edetic) acid
F	Fisher
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLM	General Linear Model
GLP	Good Laboratory Practice
H	High
HAMD-7	7-Item Hamilton depression rating scale

HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
Inc.	Incorporated
IRB	Institutional review board
IUD	Intra-uterine device
L	Low
LD	Levodopa
Max.	Maximum
MAO	Monoamine oxidase
MDMA	3,4-methylenedioxy-N-methylamphetamine; ecstasy
MedDRA	Medical Dictionary for Regulatory Activities
Min.	Minimum
mmHg	Millimeters of mercury
msec	Millisecond
OT	Oral temperature
OTC	Over-the-counter
PCP	Phencyclidine
PK	Pharmacokinetic
Pr	Probability (equivalent to Pr and p)
PT	Preferred Term
QA	Quality assurance
QI	Qualified investigator
QTcB	Bazett's correction: QT(msec) / RR1/2(sec)
QTcF	Fridericia's correction: QT(msec) / RR1/3 (sec)
R	Reference (for study medication)
rpm	Revolutions per minute
RLD	Reference listed drug
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SAS	Statistical Analysis System

SD	Standard deviation
SOC	System Organ Class
SOP	Standard operating procedure(s)
SS	Sum of squares
SUSARS	Suspected, unexpected, serious adverse reactions
T	Test (for study medication)
$T_{1/2}$	Elimination half-life (equivalent to $t_{1/2}$)
Tel.	Telephone
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
T_{max}	Time of observed C_{max}
USA	United States of America
vs	Versus
WHO DD	World Health Organization Drug Dictionary

1. Executive Summary

1.1. Product Introduction

Riverside Pharmaceuticals Corporation (Riverside Pharmaceuticals; Sponsor) has developed a novel redesign tablet of the Sinemet® (carbidopa/levodopa) 25/100 mg immediate release (IR) tablet which was approved in 1988 under NDA 17555. "Dhivy" (the proposed proprietary name) tablets employ a (b) (4), (b) (4) scored design, illustrated in Figure 1 below. Each tablet is pre-divided by (b) (4) scoring during the manufacturing process to allow for incremental dosing.

Figure 1 Schematic representation of a Dhivy tablet (right: actual tablet)

(b) (4)

During the review of NDA 214869 for Dhivy, this proposed proprietary name was rejected. After submission of the NDA, the applicant submitted a revised proprietary name (DHIVY), which was determined by FDA to be acceptable.

It is also important to recognize that the review of Dhivy was based upon reference to a generic immediate release carbidopa/levodopa tablet (Activas Pharma Inc.; ANDA 074260) because of the sponsor's inability to gain access to immediate release tablets of Sinemet (immediate release carbidopa/levodopa tablet). The Agency was aware of the sponsor's problem in obtaining Sinemet for conducting a bioavailability and bioequivalence study and informed the sponsor that it could use immediate release tablets of an ANDA approved generic product of carbidopa/levodopa to conduct an acceptable bridging study. The following advice from the Agency was communicated to the sponsor in the Study May Proceed letter for IND 135441 for Dhivy.

> *"Generally, if you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug(s), then you should use the specified listed drug(s) approved under an NDA (rather than a bioequivalent ANDA product or a non-U.S. approved version of the product) in your bridging study to justify reliance. In this case, however, we recognize that the listed drug you propose to rely on, Sinemet immediate-release tablets, NDA 17555, is currently in shortage, and may therefore be unavailable in sufficient quantities for your proposed bridging study. If you are unable to obtain Sinemet immediate release tablets to conduct your bridging study,*

your proposal to use an immediate release carbidopa/levodopa oral tablet product approved under an ANDA that is identified in FDA's Orange Book as therapeutically equivalent to Sinemet immediate release tablets is acceptable."

Each whole tablet of Dhivy contains 25 mg of carbidopa (CD) and 100 mg of levodopa (LD); these amounts are identical to those contained in the approved Sinemet® tablet. Each Dhivy tablet is triple-scored for ease of fractionated dosing and may be used whole (25/100 mg CD/LD) or divided into 6.25/25 mg (one segment), 12.5/50 mg (two segments), or 18.75/75 mg (three segments) CD/LD doses.

The proposed indications for Dhivy are identical to those approved for Sinemet®:

- The proposed indication for Dhivy is the treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication

Parkinson's disease (PD) is a common neurodegenerative disorder of the human central nervous system (CNS). It typically presents with three major clinical signs: resting tremor, bradykinesia, and muscular rigidity. In addition, postural instability and various neurobehavioral abnormalities may occur. Parkinsonian signs largely reflect a loss of dopamine (DA)-containing neurons in the basal ganglia. Accordingly, drugs used to relieve symptoms generally act by restoring dopaminergic neurotransmission. They aim to normalize DA-mediated transmission either by directly stimulating postsynaptic DA receptors or by replenishing depleted neuronal stores of the transmitter amine. The latter approach using the DA precursor, LD, has stood since the late 1960s as the "gold standard" of PD therapy. The pharmacologic goal is to reestablish virtually normal motor function, while holding adverse events (AEs) to a minimum. For most early-stage patients, this objective is not too difficult to achieve when LD is co-administered with CD. Compared with other available dopaminergic therapies, LD confers the greatest improvement in motor function. Understandably, it has been the most frequently used treatment for over 40 years, now accounting for up to perhaps 85% of all antiparkinsonian drug prescriptions.

LD is usually administered with CD to inhibit the precursor's peripheral metabolism. A greater proportion of LD thus can enter the CNS for biotransformation into its active moiety, DA. By inhibiting aromatic-L-amino-acid decarboxylase (DOPA decarboxylase) in the periphery, but not within the CNS, CD also diminishes AEs, especially gastrointestinal, due to excessive peripheral DA receptor stimulation. CD reduces the amount of LD required to produce a given response by about 75% and increases both plasma levels and the plasma half-life of LD. The elimination half-life of LD in the presence of CD is about 1.5 hours. Recommended doses of CD range from 75-200 mg/day, usually combined with LD in a ratio of 1:4 or 1:10. Higher CD doses may have the potential of inhibiting brain DOPA decarboxylase and thus potentially reducing clinical efficacy.

1.2. *Conclusions on the Substantial Evidence of Effectiveness*

This is a 505 (b)(2) application based upon a pivotal bioavailability and bioequivalence study to bridge the safety and efficacy of the new (b) (4) formulation to the approved tablet dosage form of carbidopa/levodopa. Efficacy was not assessed in the development program for Dhivy, and the applicant is seeking an indication consistent with that of the listed drug.

The Office of Clinical Pharmacology review team (Primary Reviewer: Srinivas Chennamaneni: Team Leader: Bilal AbuAsal) has reviewed the results of this pivotal bioequivalence study (Study 190051) and recommends approval based upon the bioequivalence between 25 mg carbidopa/100 mg levodopa (Dhivy) and the reference approved generic product of immediate release tablet of carbidopa/levodopa (i.e., generic of Actavis sponsor/owner under ANDA 074260). For details, refer to the Clinical Pharmacology review.

1.3. *Benefit-Risk Assessment*

The overall benefit-risk assessment of the new formulation of carbidopa/levodopa (Dhivy) is unchanged from that of the approved immediate-release carbidopa/levodopa tablets (i.e., generic product of Actavis, and Sinemet). The Actavis product is considered equivalent to Sinemet.

2. Therapeutic Context

2.1. *Analysis of Condition*

Parkinson's disease (PD) is a neurodegenerative disorder which progressively deteriorates over time and may eventually be a cause of death related to the progressive debilitation associated with this disorder. Initially, the main clinical dysfunction consists of motor problems, hypokinesia/akinesia, muscle rigidity, tremor, postural instability. As these motor manifestations can worsen, patients also experience dyskinetic movements particularly after levodopa treatment and the onset of various non-motor complications. These non-motor complications include different manifestations of autonomic dysfunction (e.g., urinary problems, constipation, orthostatic hypotension, etc.). cognitive impairment, sleep disorders, depression, fatigue, pain, hallucinations, and impulse control disorders.

2.2. *Analysis of Current Treatment Options*

There are no medications approved for "curing" Parkinson's disease nor slowing disease progression. All approved treatments are for managing signs or symptoms of Parkinson's disease. Oral immediate release carbidopa/levodopa is considered a mainstay in the treatment of Parkinson's disease and might be the most impactful medication which can be used at all stages of Parkinson's disease once motor abnormalities become evident. Sinemet was initially approved in 1970 and is considered in the category of dopaminergic agonists. The following are the various drugs (with different formulations with different release characteristics such as

immediate release and slower release for longer acting effects and different routes of administration) approved in the U.S. according to the category of the drug:

Dopaminergic Agonists
Carbidopa/Levodopa (Sinemet, Sinemet CR, Rytary, Duopa, Stalevo also contains entacapone)
Ropinirole (Requip. Requip XL)
Pramipexole (Mirapex, Mirapex ER)
Rogitotine (Neupro)
Apomorphine (Apokyn, Inbrija, Kynmobi)

Monoamine Oxidase (MAO) Inhibitors (relatively selective for MAO B)
Selegiline (Eldepryl, Zelapar)
Rasagiline (Azilect)
Safinamide (Xadago)

Catechol O-Methyl Transferase (COMT) Inhibitors
Tolcapone (Tasmar)
Entacapone (Comtan, Stalevo also contains carbidopa/levodopa)
Opicapone (Ongentys)

NMDA Receptor Antagonist
Amantadine (Symmetrel, Gocovri)

Adenosine A2 Receptor Antagonist
Istradefylline (Nourianz)

Deep Brain Stimulation (DBS) is a surgical procedure which can also be used to treat certain patients with Parkinson's disease.

3. Regulatory Background

3.1. *Summary of Presubmission/Submission Regulatory Activity*

The Agency held a Type B Pre-IND written responses only (WRO) meeting with the sponsor on 7/17/17. During that meeting, various responses were given regarding CMC, Clinical Pharmacology, Clinical, and Regulatory questions/issues. Most importantly, the Agency concurred that a potential approval of the Dhivy product might be possible with a bioavailability/bioequivalence study with bridging to a suitable FDA approved product(s).

The sponsor submitted IND 135441 for Dhivy on 6/7/19. The IND was allowed to proceed and a Study May Proceed letter was issued on 8/8/19. That letter noted that the sponsor might be able

to bridge to a generic product approved by an ANDA if the sponsor was not able to obtain immediate release carbidopa/levodopa tablets (i.e., Sinemet) for a bridging study.

On 6/27/20 a Pre-NDA meeting (WRO) was held between the Agency and the sponsor. The meeting minutes reflect the Agency's responses to the sponsor questions related to planning an NDA submission.

3.2. *Foreign Regulatory Actions and Marketing History*

Dhivy is not approved or marketed in any country.

4. Sources of Clinical Data and Review Strategy

4.1. Clinical Studies

Only one clinical study was conducted. This clinical study (190051) was the bioavailability and bioequivalence study which serves as the basis for approval.

Study Objectives

Primary Objectives

The primary objectives of the study were:

- To compare the rate and extent of absorption of the immediate-release CD/LD 25/100 mg Dhivy® tablet (Test) versus the immediate-release CD/LD 25/100 mg tablet (Reference), each administered orally as a single tablet under fasting conditions;
- To evaluate the effect of food on the pharmacokinetics (PK) of the Dhivy® tablet (CD/LD 25/100 mg) when administered as a single tablet (i.e., a single 25/100 mg CD/LD dose).

Secondary Objective

The secondary objective of the study was to evaluate the PK profile of a fraction of the Dhivy® tablet when administered at frequent intervals every 2 hours comparing to whole tablet every 4 hours.

Overall Study Design

This was a single center, open-label, BE and food-effect study conducted in 3 sequential parts (Parts I, II, and III), to evaluate the PK and effect of food on the study medication in healthy subjects under fasting and fed conditions.

- Part I: BE and food-effect, randomized, open-label, single-dose, 3-period, 6-sequence, crossover design;

- Part II: multiple-dose (every 4 hours), open-label, 1-period design;
- Part III: multiple-dose (every 2 hours), open-label, 1-period design.

A total of 48 healthy, male and/or female adult non-smokers were planned to be included in this study. Prior to entering the trial, subjects had a screening visit to establish eligibility within 28 days before study drug administration.

This study is intended for filing under FDA regulations. The study was intended to dose in more than one group; all groups were dosed at the same clinical site and the same protocol requirements and procedures were followed within each group.

Part I (single dose, compared to RLD):

Upon arrival for confinement, all subjects were randomized to receive each of Treatments A, B, and C in a 3-Period, 6-sequence manner in accordance with the block randomization scheme generated by Syneos as follows:

- Treatment A: 1 x Dhivy® tablet (immediate release CD/LD 25/100 mg; Riverside Pharmaceuticals Corporation, USA), administered under fasting conditions;
- Treatment B: 1 x CD/LD 25/100 mg tablet (immediate release CD/LD 25/100mg; FDA approved generic reference), administered under fasting conditions;
- Treatment C: 1 x Dhivy® tablet (immediate release CD/LD 25/100 mg; Riverside Pharmaceuticals Corporation, USA), administered under fed conditions.

Parts II and III (multiple dose, Dhivy only):

A subset of 24 subjects who completed Part I were to be enrolled to complete Part II and III and received Treatments D and E, respectively as follows:

- Study Treatment D: 1 x Dhivy® tablet (immediate release CD/LD 25/100 mg; Riverside Pharmaceuticals Corporation, USA) administered at 0 and 4 hours post-first dose, for a total daily dose of CD/LD 50/200 mg;
- Study Treatment E: ½ x Dhivy® tablet (immediate release CD/LD 12.5/50 mg; Riverside Pharmaceuticals Corporation, USA) administered at 0, 2, 4, and 6 hours post-first dose, for a total daily dose of CD/LD 50/200 mg.

Subjects were confined for at least 10 hours before study drug administration in Period 1 (Day -1) of Part I until approximately 24 hours post-dose in Period 3 (Day 6) of Part I or 24 hours post-first dose of Part III (Day 10).

For Part I, the treatment phases were separated by a washout period of at least 48 hours between each drug administration for Periods 1, 2, and 3. For Part II, there was a washout period of at least 48 hours between drug administration in Period 3 of Part I and first dosing of Part II. For Part III, there was a washout period of at least 40 hours between last drug administration of Part

II and first dosing of Part III. Subjects were asked to come back for a follow-up visit approximately 7±1 days following the last dose administration (at Day 12±1 or Day 16±1).

Study design is described in Table 1 below here.

Table 1: Study Design Schematic

Part I			Part II	Part III
Period 1	Period 2	Period 3		
Reference (Fasting) or Test drug (Fasting or Fed)	Reference (Fasting) or Test drug (Fasting or Fed)	Reference (Fasting) or Test drug (Fasting or Fed)	Test drug (25/100 mg) every 4 hours	Test drug (12.5/50 mg) every 2 hours

4.2. *Review Strategy*

This review only includes the safety review of the new formulation of carbidopa/levodopa (i.e., Dhivy).

5. Review of Relevant Individual Trials Used to Support Efficacy

This section is not applicable because this application is a 505 (b)(2) application based on a bioequivalence study to bridge the safety and efficacy of the new (b) (4) formulation to the approved tablet dosage form. The applicant is relying on efficacy data from the already-approved generic product of immediate release carbidopa/levodopa (Activas; ANDA 064260) The applicant has not conducted any studies of efficacy.

6. Review of Safety

The review of safety evaluated a single study with three parts (Part A-bioavailability/ bioequivalence, Part B-a food effects study, Part C- a study showing fractionation of a Dhivy tablet).

6.1. *Safety Review Approach*

The review attempted to identify any new, significant safety signals from the submitted study that could possibly change the current safety profile of immediate release carbidopa/levodopa

6.2. *Review of the Safety Database*

6.2.1. *Overall Exposure*

For Part I, the safety population consisted of 48 subjects who received at least one dose of the study medication: 46 subjects received Treatments A (Dhivy 25/100, fasting), 47 subjects received Treatment B (RLD 25/100, fasting), and 46 subjects received Treatment C (Dhivy 25/100, fed state). Of these, 45 subjects completed all treatment periods of the study.

For Part II and Part III, the safety population consisted of 22 subjects who received at least one dose of the study medication: 22 subjects received Treatments D and E. All subjects completed the study.

6.2.2. *Adequacy of the Safety Assessments*

The applicant's safety assessments for this 505(b)(2) application appeared to be adequate. The clinical safety assessments included treatment-emergent adverse events (TEAEs), vital signs, and clinical laboratory analyte assessments. Although an ECG was conducted at screening, there was no post-treatment ECG conducted.

6.3. *Safety Results*

6.3.1. *Deaths, Serious Adverse Events, and Significant Adverse Events*

No deaths, serious adverse events, or significant TEAEs were reported during this study.

6.3.2. *Dropouts or Discontinuations Due to Adverse Effects*

No subjects were withdrawn due to TEAEs. Three subjects were withdrawn from the study during Part I due to vomiting within 4 hours after dosing; the withdrawal was not considered due to a TEAE, but due to the risk of impacting the characterization of the PK profile (i.e., a PK reason).

6.3.3. *Treatment Emergent Adverse Events*

Part I (Bioequivalence/Food Effect)

A total of 53 treatment-emergent adverse events (TEAEs) were reported by 21 (43.8%) of the 48 subjects who received at least one dose of the study medication (safety population). Of these, 26 TEAEs were reported by 12 (26.1%) of the 46 subjects who received Treatment A (Dhivy fasting), 19 TEAEs were reported by 11 (23.4%) of the 47 subjects who received Treatment B (Reference fasting), and 8 TEAEs were reported by 6 (13.0%) of the 46 subjects who received Treatment C (Dhivy fed). The majority (45) of TEAEs were of mild severity, with 7 TEAEs being of moderate severity, and 1 TEAE being severe (severe syncope observed in Subject No. (b) (6) 2 hours post-dose with Treatment B, Reference fasting). Most (34 of 53; 64%) of the TEAEs were judged as possibly related to study medication.

A summary of overall TEAE frequencies is presented below in Table 2.

Table 2: Summary of Adverse Events – Part I

	(b) (4) – Fasting (A)	Reference – Fasting (B)	(b) (4) – Fed (C)	Overall
Number of subjects dosed	46	47	46	48
Number of subjects with at least one TEAE, N (%)	12 (26.1)	11 (23.4)	6 (13.0)	21 (43.8)
Number of TEAEs	26	19	8	53
Number of serious TEAEs	0	0	0	0
Number of severe TEAEs	0	1	0	1
Number of related TEAEs[1]	24	16	8	48
Number of subjects who discontinued due to TEAEs	0	0	0	0
Number of deaths	0	0	0	0

Treatment A (Dhivy-fasting): 1 x Dhivy (CD/LD 25/100 mg IR) tablet, administered under fasting conditions; Treatment B (Reference-fasting): 1 x FDA-approved generic Sinemet® (CD/LD 25/100 mg IR) tablet, administered under fasting conditions; Treatment C (Dhivy-fed): 1 x Dhivy (CD/LD 25/100 mg IR) tablet, administered under fed conditions
1 Includes remotely related, possibly relate , and probably related to study medication.
TEAE=treatment-emergent adverse event.

The most commonly reported TEAEs during this study were related to the System Organ Class (SOC) nervous system disorders (17 TEAEs in 11 subjects overall), followed by gastrointestinal disorders (18 TEAEs in 10 subjects overall), and general disorders and administration site conditions (6 TEAEs in 6 subjects overall).

Reviewer Comment

The total number of TEAEs and the incidence of subjects with at least one TEAE was higher for the Dhivy fasting group (26) vs the Reference product fasting group (19) with both groups having a very similar total number of subjects dosed. These differences were relatively small. I would not consider them to be a cause of concern with the experimental product.

Table 3: Treatment-Emergent Adverse Events Reported in 2 or More Subjects – Part I

SOC Preferred Term	Statistic	Treatment			
		(b) (4) – Fasting (A)	Reference – Fasting (B)	(b) (4) – Fed (C)	Overall
Number of subjects dosed	N	46	47	46	48
Number of TEAEs	E	26	19	8	53
Number of subjects with TEAEs	n (%)	12 (26.1)	11 (23.4)	6 (13.0)	21 (43.8)
TEAEs reported in 2 or more subjects					
Nervous system disorders	n (%) E	5 (10.9) 7	5 (10.6) 5	4 (8.7) 5	11 (22.9) 17
Somnolence	n (%) E	1 (2.2) 1	1 (2.1) 1	4 (8.7) 4	5 (10.4) 6
Dizziness	n (%) E	2 (4.3) 2	1 (2.1) 1	1 (2.2) 1	4 (8.3) 4
Headache	n (%) E	3 (6.5) 3	1 (2.1) 1	0	3 (6.3) 4
Gastrointestinal disorders	n (%) E	6 (13.0) 9	5 (10.6) 7	2 (4.3) 2	10 (20.8) 18
Nausea	n (%) E	5 (10.9) 5	2 (4.3) 2	1 (2.2) 1	7 (14.6) 8
Vomiting	n (%) E	2 (4.3) 2	2 (4.3) 2	0	4 (8.3) 4
Constipation	n (%) E	0	2 (4.3) 2	0	2 (4.2) 2
General disorders and administration site conditions	n (%) E	4 (8.7) 4	2 (4.3) 2	0	6 (12.5) 6
Fatigue	n (%) E	2 (4.3) 2	1 (2.1) 1	0	3 (6.3) 3

Treatment A (Dhivy-fasting): 1 x Dhivy (CD/LD 25/100 mg IR) tablet, administered under fasting conditions; Treatment B (Reference-fasting): 1 x FDA-approved generic Sinemet® (CD/LD 25/100 mg IR) tablet, administered under fasting conditions; Treatment C (Dhivy-fed): 1 x Dhivy (CD/LD 25/100 mg IR) tablet, administered under fed conditions.
E: Number of treatment-emergent adverse events; N: Number of subjects dosed; n (%): Number and percent of subjects with TEAEs; SOC: System Organ Class; TEAEs: Treatment-emergent adverse events.

Reviewer Comment

Overall, the profiles for specific preferred term TEAEs for Dhivy and the reference product were relatively similar under fasting conditions. The incidence of TEAEs for Dhivy under fed conditions (associated with a lower Cmax for levodopa) was greater for somnolence but notably less for nausea.

Parts II and III (Effect of Dose Interval on Plasma PK of LD and of CD)

A total of 11 TEAEs were reported by 9 (40.9%) of the 22 subjects in Part II (Dhivy 25/100 q4hr) and a total of 3 TEAEs were reported by 2 (9.1%) of the 22 subjects in Part III (Dhivy 12.5/50 q2hr), who received at least one dose of the study medication (safety population). All the TEAEs reported were mild in severity and most of the TEAEs were deemed as possibly related to study medication.

A summary of overall TEAE frequencies is presented below in Table 4 for Part II and Part III.

Table 4: Summary of Adverse Events – Part II and Part III

	Part II (b) (4) 25/100 q4hr (Treatment D)	Part III (b) (4) 12.5/50 q2hr (Treatment E)
Number of subjects dosed	22	22
Number of subjects with at least one TEAE, N (%)	9 (40.9)	2 (9.1)
Number of TEAEs	11	3
Number of serious TEAEs	0	0
Number of severe TEAEs	0	0
Number of related TEAEs[1]	11	2
Number of subjects who discontinued due to TEAEs	0	0
Number of deaths	0	0

1 Includes remotely related, possibly related, and probably related to study medication.
TEAE=treatment-emergent adverse event

Reviewer Comment

The incidence of TEAEs for part II administering a "higher" dose of carbidopa/levodopa every 4 hours was much higher (~41 %) compared to a dosing regimen of administering half the dose in Part II every 2 hours (~9 %). Thus, the same amount of carbidopa and levodopa was administered over 4 hours but the regimen administering carbidopa and levodopa at half the dose at a more frequent interval (2 hours vs 4 hours) was associated with less TEAEs. This observation supports the rationale for which the product was developed.

The most commonly reported TEAEs were related to the SOC of nervous system disorders (4 events by 4 subjects), and the frequently reported TEAEs by 2 or more subjects were headache and somnolence, reported by 2 (9.1%) subjects each during Part II (Dhivy 25/100 q4hr).

A listing of TEAEs reported in 2 or more subjects is presented below in Table 5.

Table 5: Treatment-Emergent Adverse Events Reported in > 2 Subjects – Parts II and III

SOC Preferred Term	Statistic	Treatment: Part II (b) (4) 25/100 q4hr (Treatment D)	Treatment: Part III (b) (4) 12.5/50 q2hr (Treatment E)
Number of subjects dosed	N	22	22
Number of TEAEs	E	11	3
Number of subjects with TEAEs	n (%)	9 (40.9)	2 (9.1)
TEAEs reported in 2 or more subjects			
Nervous system disorders	n (%) E	4 (18.2) 4	1 (4.5) 1
Headache	n (%) E	2 (9.1) 2	1 (4.5) 1
Somnolence	n (%) E	2 (9.1) 2	0

E: Number of treatment-emergent adverse events; N: Number of subjects dosed; n (%): Number and percent of subjects with TEAEs; SOC: System Organ Class; TEAEs: Treatment-emergent adverse events.

As shown in
Table 5 above, TEAEs were more frequent in subjects who received Dhivy 25/100 every 4 hours than in subjects who received Dhivy 12.5/50 every 2 hours. Notably, this was true for somnolence (9.1% versus 0%) and headache (9.1% versus.4.5%).

Reviewer Comment

The specific preferred terms TEAEs of somnolence and headache were slightly less frequent with the dosing regimen E (Dhivy 12.5/50 mg) at a more frequent interval of 2 hours vs 4 hours for regimen E (25/100 mg).

6.3.4. *Laboratory Findings*

Abnormalities in clinical laboratory results were observed for a number of parameters; however, none of the laboratory findings were considered clinically significant and no TEAEs related to laboratory abnormalities were reported. The abnormalities generally occurred in subjects with low or high baseline values that were not notably different from the post-dose results.

Reviewer Comment

Results for clinical laboratory analytes did not suggest any safety concerns.

6.3.5. *Vital Signs*

The mean values across all time points and all parameters were within normal range. No relevant differences in mean values and changes from baseline were observed for vital signs measurements and orthostatic blood pressure over time; no clinically relevant differences were observed between results of subjects who received Treatments A (Dhivy fasting), B (Reference fasting), C (Dhivy fed), D (Dhivy 25/100 q4hr), and E (Dhivy 12.5/50 q2hr).

Abnormal values for vital signs results were observed for some parameters for some subjects. For 3 subjects, these abnormalities were considered clinically significant by the Investigator and were reported as TEAEs:

- Subject No. (b) (6), 62-year-old female had a TEAE of heart rate increased in Part 1 of the study (118 bpm versus 74 bpm at baseline) after administration of Dhivy fasting, judged as mild and unrelated to study treatment;

- Subject No. (b) (6), 63-year-old male experienced TEAEs of blood pressure orthostatic decreased (supine: 123/81; standing 109/65) after administration of Dhivy 25/100 q4hr in Part II. The TEAE was judged as mild in severity and possibly related to study treatment;

- Subject No. (b) (6), 36-year-old female experienced a TEAE of orthostatic heart rate response increased (supine: 72 bpm; standing: 102 bpm) after administration of Dhivy 25/100 q4hr in Part II. The TEAE was judged as mild and possibly related to study treatment.

Reviewer Comment

One subject in the Dhivy group had a moderate increase in heart rate unrelated to an orthostatic measurement. One subject in the Dhivy group exhibited mild orthostatic diastolic hypotension. One subject in the Dhivy group exhibited a moderate increase in heart rate with an orthostatic maneuver. It is not clear whether or not these mild abnormalities in vital signs were related to Dhivy treatment; however, cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, and hypertension are adverse reactions in the label of the RLD. Overall, these mild abnormalities observed on one occasion each in these 3 patients does not raise any significant safety concern.

6.4. *Safety in the Postmarket Setting*

6.4.1. *Safety Concerns Identified Through Postmarket Experience*

The sponsor did not provide a review of post-market experience but did note in the Clinical Safety document "There is no postmarket experience with Dhivy because Dhivy has not been approved anywhere."

The sponsor did provide a document for a review of the literature. In one section, the sponsor summarized some findings in a few publications about patients on some type of carbidopa/ levodopa treatment. Most commonly, these publications described adverse events in patients treated with carbidopa/levodopa intestinal gel (i.e., Duopa in the U.S) and that many of these patients had a polyneuropathy. Peripheral neuropathy or polyneuropathy are adverse reactions reported with other drugs containing carbidopa/levodopa, including the RLD, as well as in in patients treated with carbidopa/levodopa intestinal gel. No publications reviewed provided any new information about a safety signal from carbidopa/levodopa treatment,

This reviewer reviewed the last Periodic Adverse Drug Experience Report (PADER) for Sinemet (NDA 17555, submitted 6/25/21 for the period 5/3/20-5/20/21. There was no significant information about a new safety signal for carbidopa/levodopa.

This reviewer also reviewed the last Periodic Adverse Drug Experience Report (PADER) for the generic reference immediate release carbidopa/levodopa product (owned by Actavis Pharma Inc.) and did not find anything prompting a new safety concern for the safety profile of the immediate release carbidopa/levodopa product.

7. Labeling Recommendations

7.1. Drug Labeling

The Dhivy label is based upon the label for Sinemet and Rytary which is carbidopa/levodopa with immediate release and also a slower release formulation in Rytary. I reviewed the sponsor's proposed label and did not have any significant revisions. In particular, I did not have any concerns about the description of safety information in the Dhivy label which is identical to the safety information shown in the Sinemet label because an approval of Dhivy would be based upon the safety (and efficacy) of Sinemet.

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