CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209410Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209410
Priority or Standard	Standard
Submit Date(s)	January 18, 2017
Received Date(s)	January 18, 2017
PDUFA Goal Date	February 18, 2018
Division / Office	DNP/OND
Reviewer Name(s)	Susanne R. Goldstein, MD
Review Completion Date	January 12, 2018
Established Name	Amantadine HCl ER
(Proposed) Trade Name	Osmolex ER
Therapeutic Class	
Applicant	Osmotica
Formulation(s)	160mg, 240mg, 320mg
Dosing Regimen	po
Indication(s)	(b) (4) Parkinson's disease, Extrapyramidal Reactions
Intended Population(s)	Adult

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Following the assessment of clinical data, it is the opinion of this reviewer that amantadine ER (OSMOLEX ER) is a safe and effective treatment for patients with Parkinson's disease and drug-induced extrapyramidal reactions. The applicant established a scientific bridge through bioequivalence (BE) to FDA's previous findings of safety and effectiveness for Symmetrel syrup.

1.2 Risk Benefit Assessment

This 505(b)(2) NDA relies on relative bioavailability data from three Phase 1 studies, the FDA's prior findings of safety and efficacy of amantadine HCl syrup, supplemental safety data from two recently conducted Phase 3 studies, and relevant safety and efficacy results from the published literature and information in the public domain.

The clinical safety profile of the RLD is well established. The applicant submitted safety information for amantadine ER from two Phase 3 randomized, placebo controlled trials. However, the safety information includes a large amount of missing patient data. The labeled safety information for immediate release amantadine syrup, adverse reactions reported by patients treated with OSMOLOEX ER were generally the same as the adverse reaction reported in the label for Symmetrel. The most commonly observed adverse drug reactions were hallucinations, dry mouth, nausea and peripheral edema. On the basis of these findings, the risk to benefit assessment supports the safe use of OSMOLEX ER in the treatment of Parkinson's disease and Extrapyramidal Reactions.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No further postmarketing evaluation of mitigation strategy is recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

This review does not recommend any postmarketing requirements or commitments for clinical studies.

2 Introduction and Regulatory Background

Osmotica Pharmaceutical US LLC has submitted a New Drug Application (NDA) for OSMOLEX™ ER (Amantadine Hydrochloride Extended Release Tablets) for once daily oral administration for the treatment of Parkinson's disease. This is a 505(b)(2) application and relies on FDA's previous finding of safety and effectiveness for SYMMETREL® Syrup, the reference listed drug (amantadine HCl 50 mg/5 mL, NDA 016023).

2.1 Product Information

OSMOLEX™ ER (Amantadine extended release) is available in three dose strengths: 129 mg, 193 mg, or 258 mg of amantadine which correspond to 160 mg, 240 mg, or 320 mg of amantadine hydrochloride. The strengths are expressed in the base to conform with the United States Pharmacopeia's Salt Policy that uses the name of the active moiety instead of the salt for drug products.

OSMOLEX ER has an extended release core and an immediate release outer layer. Drug release from the extended release core is controlled by an osmotic pump system. The reference listed drug (RLD), SYMMETREL® Syrup, is approved with a twice daily regimen, whereas OSMOLEX™ ER is recommended in a once daily regimen.

2.2 Tables of Currently Available Treatments for Proposed Indications

Dopamine Agonists	**Levodopa**	**COMT Inhibitors**	**MAO Inhibitors**	**Unknown**
ropinirole	Carbidopa levodopa	entacapone	rasagiline	Amantadine IR
pramipexole	Carbidopa levodopa ER	tolcapone	selegiline	Amantadine ER
rotigotine	Carbidopa levodopa entacapone			
safinamide	Carbidopa levodopa intestinal solution			
Bromocriptine				

2.3 Availability of Proposed Active Ingredient in the United States

Amantadine, has been approved for use an marketed in the US since 1966. The originator, Symmetrel (Endo Pharmaceuticals NDA 16020, NDA 16023 and NDA 18101 has been discontinued for reasons other than safety by the sponsor according to the listing in the FDA's Orange Book.

The reference listed drug for this application is (NDA 016023), Symmetrel Syrup. However, since Symmetrel syrup is no longer available, the sponsor used amantadine HCl syrup, 50mg/5mL (Wockhardt ANDA 075060) as the reference standard.

2.4 Important Safety Issues with Consideration to Related Drugs

Adverse events of special interest associated with amantadine include psychiatric side effects, sleep disorders, orthostatic hypotension, hallucinations, suicidal ideation or behavior and impulse control disorders.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

pIND meeting January 12, 2009

1.0 BACKGROUND

In a letter dated September 12, 2008, Osmotica Pharmaceutical requested a pre-IND meeting for IND 103,538 to discuss the requirements for submission and approval of an NDA submitted pursuant to section 505(b)(2) of the Federal, Food, Drug and Cosmetic Act for the proposed product. The Division's preliminary responses to the questions posed in the background package were electronically mailed to the Sponsor on January 9, 2009.

Key advice from the FDA to the sponsor is summarized below:

CMC

- The stability protocol should include, at the minimum, three batches each of the highest and lowest strengths per container type/container size.
- The 30- count and 90-count containers may be used to bracket intermediate sizes.

CLINICAL

Indication

- (b) (4)

Trial and Design

- (b) (4)

Efficacy Endpoints

- (b) (4)
-

CLINICAL PHARMACOLOGY

- We recommend that you conduct a single dose food effect study on the highest strength of the proposed extended release tablet (320 mg).
- We recommend a steady state study with the highest strength of the extended release formulation compared to an approved immediate release reference.
- You need to provide dose adjustment recommendations in patients with renal impairment based on the new extended release formulation(s).

- Dose dumping with alcohol should be evaluated. First, in vitro dissolution studies in various concentrations of alcohol (e.g. 5, 10, 20 and 40%) should be conducted. Once results are available, you should discuss this with the Office of Clinical Pharmacology for assessing the need for an in vivo study.

SPA No Agreement - July 2, 2009

SPA No Agreement – August 24, 2010

SPA No Agreement – February 3, 2011

EOP2 Meeting January 15, 2014

1.0 BACKGROUND

This is a 505(b)(2) application for Amantadine HCl Extended Release Tablets for Treatment of Levodopa-Induced Dyskinesias in Patients with Parkinson's disease. On September 17, 2013, Osmotica Pharmaceutical Corp. requested a Type B EOP2 meeting to discuss the overall development program that includes two Phase 3 studies. The meeting package was submitted on December 17, 2013. The preliminary responses were sent to the sponsor on January 13, 2014.The sponsor provided pre meeting responses on January 14, 2014 and those responses have been incorporated into this document.

Key advice from the FDA to the sponsor is summarized below:

CLINICAL:

Dosing:

- (b) (4)
- A waiver of in vivo studies for the different strengths may be granted if the drug product meets the biowaiver criteria. The sponsor needs to refer to the FDA guidance for how to determine whether the different strengths are proportionally similar. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U CM070124.pdf

- The Agency accepted the sponsor's proposal to conduct a dedicated study in patients with severe renal impairment and use simulations to support dosing in patients with moderate renal impairment. The sponsor will study patients with mild renal impairment in the phase 3 trial.

- The Division asked the sponsor to submit the protocol for review and propose dosing adjustments in patients with renal impairment, similar to those in the Symmetrel label using the ER tablet strengths (160 mg, 240 mg, 320 mg).

Trial Design:

- (b) (4)

STATISTICS

- (b) (4)

- (b) (4)

preNDA Meeting November 2, 2016

BACKGROUND

Osmotica Pharmaceutical US LLC (Osmotica), has developed a new extended release dosage form, Amantadine HCl Extended Release (ER) Tablets (Osmolex ER), for once daily oral administration for treatment of Parkinson's disease. Osmotica has been in discussion with the Division regarding this product since the January 2009, Pre-IND Meeting. Osmotica and the Division have also held a December 2009, SPA discussion meeting, a January 2014, End-of-Phase 2 meeting (EoP2), and a July 2014, EoP2 CMC meeting.

All of these discussions centered on the use of Osmolex ER for the treatment of Levodopa- Induced Dyskinesia (LID). Two phase 3 studies in LID were completed; however, (b) (4) Osmotica desires to seek approval of Osmolex ER for the treatment of Parkinson's disease. In support of this 505(b)(2) application, Osmotica intends to rely on the FDA's previous finding of safety and/or effectiveness for amantadine HCl capsules (discontinued Endo NDA 016020, Symmetrel Capsules). Osmotica Pharmaceutical US LLC is targeting the submission of an NDA for Osmolex ER (Amantadine HCl ER Tablets) in 4th quarter 2016.

FDA sent Preliminary Comments to Osmotica on October 31, 2016.

Key advice from the FDA to the sponsor is summarized below:

CMC:

Drug Substance

- The current specification includes testing for Heavy Metals per USP <231>. We recommend that you transition to testing for Elemental Impurities consistent with ICH Q3D and USP <232>/<233>.

- We recommend that you revise the limit for individual unknown impurities from not more than (NMT) (b) (4)% to NMT (b) (4)% consistent with the recommendation in ICH

Q3A (R2) Impurities in New Drug Substances.

- Currently, assay is determined by titration per USP. Provide justification that the GC related compounds methods is specific for process impurities and potential degradants.

Drug Product

- We do not agree with your proposed dissolution acceptance criteria at this time. As we conveyed to you at the EoP2 CMC meeting (July 9, 2014), (b) (4) Acceptability of the proposed dissolution acceptance criteria will be a review issue and determined at the NDA stage based on the totality of the data. Please investigate the root cause for the variability associated with the dissolution method.

- We agree that the in-vitro dissolution profiles you have generated for up to 2 hours seem to indicate a lack of alcohol-induced dose-dumping of the proposed ER drug product. However, submit the complete dissolution profiles (i.e., up to 8 hours) within the NDA.

- We note the increased drug release rate as a function of alcohol content in the dissolution media. In the NDA submission, discuss the potential clinical consequences (including labeling implications) of increased drug release with alcohol consumption.

- FDA is concerned about a potential for increased drug release at 2 hours post dose. FDA also recommended that the Sponsor provide supporting information with the NDA submission to address any clinical concern and labeling implications of increased drug release from the proposed ER drug product with alcohol consumption.

CLINICAL PHARMACOLOGY:

- As presented in your briefing packet, the Cmax and AUC for amantadine HCl ER and amantadine HCl oral syrup (RLD) appear within bioequivalence (BE) limits. However, there is a significant difference in Tmax between Amantadine HCl ER and the RLD (mean 7.5 hours for amantadine HCl ER vs. 2-3 hours for amantadine HCl oral syrup). You will need to address the possible pharmacodynamic effect and clinical implications of a delayed Tmax.

- In addition to the BE analyses for Cmax, AUC and Cmin, you should provide a point-by-point comparison for the PK profiles of the amantadine ER product and immediate release product, to further assess the similarities between the profiles.

- FDA had concerns about the potential clinical implications of having a delayed

Tmax with Osmolex versus amantadine IR. The Sponsor opined that the clinical effect of amantadine is better described by AUC rather than the time to dose response.

- In order to use BA/BE pathway, the Sponsor would need to rely on the similarity between the pharmacokinetic (PK) profiles of Osmolex and amantadine IR. This would require comparing the Osmolex PK parameters at multiple time points (partial AUC measurements) and to amantadine IR. Although the two drug products may not match on every time point, a justification should be provided for the time points at which Osmolex is disparate from amantadine IR.

- You need to conduct in-vitro studies to evaluate whether amantadine is a substrate/inhibitor of major drug transporters. Please refer to the FDA guidance for drug interaction for additional details. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm 292362.pdf

CLINICAL:

Indication:

- If you provide an adequate PK bridge to amantadine immediate-release oral capsules, your application may support a similar indication to that of Symmetrel for the treatment of Parkinson's disease.

- The RLD for comparison with Osmolex is amantadine IR syrup. However, this product has been withdrawn. The Sponsor has submitted a petition to have an FR notification placed stating that the withdrawal was not for safety or lack of efficacy. The sponsor is unsure that the FR notification posting will occur prior to filing of their NDA and is concerned this will lead to a refusal to file.

- The Division stated they would have to consult with the (b)(2) committee and include a post-meeting response in this document.

- Post Meeting Note:
  A product does not have to be listed in the Federal Register as "not withdrawn for reasons of safety or efficacy" to be used as the RLD.

Safety:

- If you provide an adequate PK bridge to amantadine immediate-release oral capsules, it is unclear whether data from studies OS320-3005 and OS320-3006 would provide additional useful safety information that needs to be described in labeling. This will be a matter for review.

- Yes, we agree with your plan to include CRFs of subjects who died, reported a

serious adverse event (SAE) or discontinued due to adverse event.

- You should also include narratives for all subject deaths, nonfatal SAEs, adverse events leading to withdrawal, dose reduction, or institution of concomitant therapy in your submission.

- In addition, you should include a tabular summary of all subjects who discontinued. Provide a tabular and written summary of all patients who reported an adverse event any time before discontinuing from the study, regardless of the reason given for discontinuation (e.g., lost to follow-up or consent withdrawn).

- The division's clinical reviewers noted that a high proportion of patients in the amantadine ER group (approximately 30-40%) discontinued study participation early. The Division requested the Sponsor provide a summary and discussion of the temporal relationship between adverse events and patient discontinuation from the studies submitted in the NDA.

- The Division requests the sponsor analyze the potential relationship between the study drug and adverse events, such as the type of event and the time from adverse event to patients discontinuation, regardless of whether the event was classified as causing the patients to withdraw.

- The Division requests the Sponsor include written and tabular summaries of these analyses, but there is no need to create additional individual case narratives.

Regulatory:

- You have identified NDA 16020 for Symmetrel (amantadine) immediate-release oral capsules, which is no longer marketed, as the listed drug upon which you intend to rely to support approval of your proposed product, an extended-release tablet formulation of amantadine. However, your scientific bridge is a comparison of the relative bioavailability (BA) of your proposed product to
- an ANDA product for a different dosage form of amantadine, i.e., ANDA 75060 (Wockhardt) amantadine oral syrup, a marketed listed drug identified in the Orange Book as a reference standard. Please explain how the results of a comparison of your proposed product to ANDA 75060 support reliance on our finding of safety and effectiveness for Symmetrel oral capsules.

- A satisfactory finding from your relative BA study and scientific explanation bridging NDA 16023 for Symmetrel to the amantadine oral syrup product may provide justification for reliance on our finding of safety and effectiveness of NDA 16023 for Symmetrel.

- Note also that reliance on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on FDA's finding that the drug was not

discontinued for reasons of safety or effectiveness.

Review Extension – Major Amendment, Facility

On October 10, 2017, the sponsor submitted a major amendment. Therefore, the PDUFA goal date was extended by three months to provide time for a full review of the submission. The extended user fee goal data is February 18, 2018.

IR Issued: 08/18/2017 Response
Received: 10/10/2017

Review for process related IRs and response

1. [redacted] (b) (4)

Sponsor's Response:
Osmolex ER (Amantadine ER Tablets) uses an [redacted] (b) (6)

2.6 Other Relevant Background Information

NA

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The clinical sections of the application were provided in full at the time of the original submission. All appropriate information needed to adequately review the data and insure its traceability to source documents was provided. Data submitted electronically adhered

to CDISC SDTM and ADaM data standards. MedDRA 17.1 was used to code adverse events.

3.2 Compliance with Good Clinical Practices

All studies in the development program for amantadine HCl ER, with the exception of ***Pilot Study OS320-PKP3,*** were conducted under IND 103538. The sponsor provided attestation that the clinical studies in the development program were conducted in accordance with 21CFR part 50, 21CFR part 56, and 21 CFR312.50-312.70 in accordance with GCP. No persons debarred under 21 CFR 306 were associated with this application.

3.3 Financial Disclosures

The sponsor has disclosed financial interests with clinical investigators for all clinical and PK studies; however, the applicant's CROs submitted their proprietary financial disclosure forms instead of Form FDA 3455.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Drug Product

The proposed product is an extended-release (ER) tablet that contains either 129 mg, 193 mg, or 258 mg of amantadine (as 160 mg, 240 mg, or 320 mg of amantadine hydrochloride).

The tablets are intended to be taken once daily in the morning and provide for controlled release of the drug over an 8 to 12-hour interval.

Note: The applicant originally proposed to label the product based on content of amantadine hydrochloride. Consistent with USP Salt Policy for "Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations" the product will be labeled based on the active moiety. In some sections of the clinical review, the product and dosage strengths are identified based on the hydrochloride salt.

The drug product manufacturing process involves (b) (4) to produce the finished tablets

The drug substance (DS) manufacturer of amantadine HCL is supplied to the applicant by (b) (4) (b) (4) Drug Master File (DMF (b) (4)) for amantadine

was reviewed by Govindaraj Kumaran (FDA) on May 6, 2015. The applicant cross-referenced the (b) (4) DMF in the application.

The drug product (DP) contains an amantadine extended-release tablet core with an outer immediate-release layer. Drug release from the extended-release core is controlled by an osmotic pump system. Osmotic pump systems consist of a drug core inside of a semipermeable polymer membrane that is permeable to water molecules but not to the drug. The semipermeable polymer membrane has a laser drilled orifice for drug delivery. Drug release is driven by the osmotic pressure generated within the drug core upon exposure to water.

Based on the sponsor's risk assessment and data provided in the original NDA, acceptable risk mitigation strategies were demonstrated for most unit operations; however, some gaps were identified by the quality review team. In response to information requests, the sponsor has clarified how critical process parameters (e.g., (b) (4)

The proposed regulatory specification for Amantadine ER Tablets includes test parameters that are typical for an extended-release product. In general, the analytical procedures are straightforward and supported by adequate method validation studies. The proposed acceptance criteria for most test parameters are considered suitable. At the Agency's request, the sponsor revised the dissolution method (b) (4) with acceptance criteria of not more than (NMT) % of drug released from the 129 mg tablets, and NMT (b) (4)% released from 193 mg and 258 mg tablets. The applicant also (b) (4) the acceptance criteria for the (b) (4)-hour time points.

(b) (4) The CMC reviewer found the sponsor's dissolution testing acceptable and it met the criteria for an ER product.

These studies demonstrated that the dissolution method for Amantadine HCl ER Tablets is discriminating with regards to:

- The critical material attribute (b) (4)
- The critical material attribute (b) (4)
- The critical process parameters (b) (4) and,
- The critical process parameters (b) (4)

Overall, the proposed dissolution method is suitable for batch release and stability testing of Osmolex® ER (Amantadine Hydrochloride Extended Release) Tablets 160 mg, 240 mg and 320 mg.

A summary of the facilities inspection and final recommendation is provided in Table 1

Table 1 Facilities Inspection

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
Osmotica Pharmaceutical US LLC 895 Sawyer Road Marietta, GA 30062	3009078927	TTR • DP manufacturing, release and stability testing; • Packaging and labeling in HDPE bottles	Medium process risk (b) (4)	Approve

(b) (4)	Medium risk for facility component	Approve
	Low	Approve

Source CMC Reviewer

4.2 Clinical Microbiology

NA

4.3 Preclinical Pharmacology/Toxicology

The applicant did not include results from new nonclinical studies in the NDA and no new studies were required during the IND stage of development. The application was submitted as a 505(b)(2) NDA relying on the FDA's finding of safety and effectiveness, information included in labeling for the reference product (Symmetrel syrup) and published medical literature.

The proposed labeling and information supporting reproductive and developmental toxicology from publications was reviewed by the non clinical reviewer. The reproductive toxicology studies were published in 1969 and 1970, before implementation of GLP regulations.

4.4 Clinical Pharmacology

The clinical data to support Amantadine HCl ER Tablets and the 505(b)(2) application includes the following three bioavailability studies in healthy volunteers, a PK study in patients with renal impairment and one non-IND bioavailability study:

A brief description of the five Phase 1 studies is provided below:

- **Study OS320-PKP04** was an open-label, randomized, two-period, two-sequence, single dose, bioavailability study under fasting and fed conditions of Amantadine HCl ER 320 mg tablets in normal, healthy, adult human subjects. This study assessed the potential effect of food on the bioavailability of Amantadine HCl ER Tablets.
- **Study OS320-PKP05** was a single center, randomized, laboratory-blinded, 4-

treatment, 4-period, 4-sequence, single oral dose crossover design study in healthy male and female volunteers. This study assessed the relative bioavailability of Amantadine HCl ER Tablets compared to the equivalent dose administered in syrup form and evaluated the dose proportionality of Amantadine HCl ER Tablets across three doses (160 mg, 240 mg, and 320 mg).

- **Study OS320-PKP06** was a single center, laboratory-blinded, randomized, 2-treatment, 2-period, 2-sequence, multiple oral dose crossover design study with a 2-day titration period. The primary objective of the study was to compare the steady-state relative bioavailability after multiple dosing (i.e., for 7 consecutive days) of Amantadine HCl ER Tablets, 320 mg once a day compared to an equivalent daily dose of 320 mg Amantadine HCl Oral Syrup (50 mg/5mL) divided into two equal doses (i.e., for 7 consecutive days), in healthy male and female volunteers under fasting conditions.

Study OS320-PKP07 was a Phase 1, open-label, adaptive, single dose pharmacokinetic study of orally administered Amantadine HCl ER Tablets in patients with renal impairment and subjects with normal renal function under fasting conditions. This study assessed the pharmacokinetics of Amantadine HCl Tablets when administered to subjects with severe renal impairment. **Of note, the clinical pharmacology reviewer did not rely on this study to develop dosing in patients with renal impairment, but rather used PK modeling (Section 4.4.3 Renal Dosing.)**

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4.4.1 Mechanism of Action

The mechanism of action of amantadine hydrochloride in the treatment of Parkinson's disease is not known. It is suggested that amantadine hydrochloride is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and it is believed to act on the dopaminergic system.

Absorption
After oral administration of 320 mg OSMOLEX™ ER tablet once daily for 7 days, the mean ± SD C_{max} was 1.3 ± 0.03 mcg/mL. The median time to C_{max} (T_{max}) was about 7.5 hours (range: 5 to 12 hours). Presence of food did not affect the absorption of amantadine from OSMOLEX™ ER tablets.
Results from Study OS320-PKP05 demonstrated that PK of amantadine from OSMOLEX™ ER tablets are dose proportional. Plasma amantadine exposure (Cmax, AUCinf) after single oral doses (160 mg, 240 mg, 320 mg amantadine HCl) of OSMOLEX™ ER increased proportionally with increasing dose.

Distribution
Amantadine is 67% bound to plasma proteins. The volume of distribution from after intravenous administration was 3-8 L/Kg.

Elimination:
Amantadine is mainly eliminated renally and about 85% of the administered dose is excreted unchanged in urine. After the oral administration of a single 160 mg OSMOLEX™ ER tablet, the apparent oral clearance was approximately 11 L/h . The elimination half-life was about 18 hrs.

Metabolism:
Metabolism accounts for only 5-15% of the total clearance for amantadine. Eight metabolites of amantadine have been identified in human urine. One metabolite, an N-acetylated compound, was quantified in human urine.

Excretion:
Amantadine is primarily excreted unchanged in the urine by glomerular filtration and tubular secretion. The pH of the urine has been reported to influence the excretion rate of amantadine. Since the excretion rate of amantadine increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body.

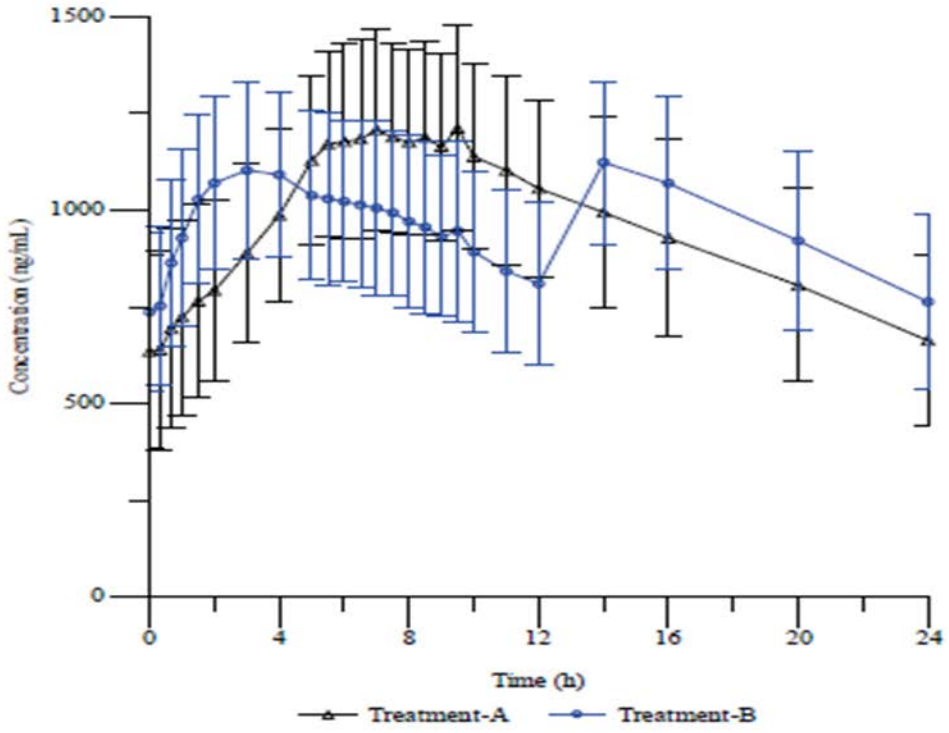
4.4.2 Pharmacodynamics

NA

4.4.3 Pharmacokinetics

This is a 505(b)(2) NDA based on PK bridging of the proposed ER product to the justify the applicant's reliance on FDA's finding of safety and effectiveness for SYMMETREL® Syrup. The sponsor conducted a relative bioavailability study (Study OS320-PKP06) to bridge the PK of OSMOLEX ER to the RS (Amantadine syrup (Wockhart). This was a single center, randomized, 2-treatment, 2-period, 2-sequence, multiple dose, crossover study with a 2-day titration period. The relative bioavailability at steady state was compared after 7 consecutive days of dosing with 320 mg OSMOLEX ER in a once a day regimen and 320 mg amantadine Syrup (50 mg/5mL) divided into two equal doses (i.e., 160 mg twice daily), in healthy subjects under fasting conditions. The results of this study are shown in Figure 1 and Figure 2. OSMOLEX ER was found to be bioequivalent to the RLD in terms of AUC_{inf} and C_{max} at steady state.

Figure 1 Mean plasma concentration-time profiles following oral administration of 320-mg OSMOLEX ER tablets once daily (Treatment-A: 320 mg amantadine HCl ER tablets) or SYMMETREL syrup twice daily (Treatment-B: 160 mg amantadine HCl) for 7 days in healthy volunteers, Study OS320-PKP06

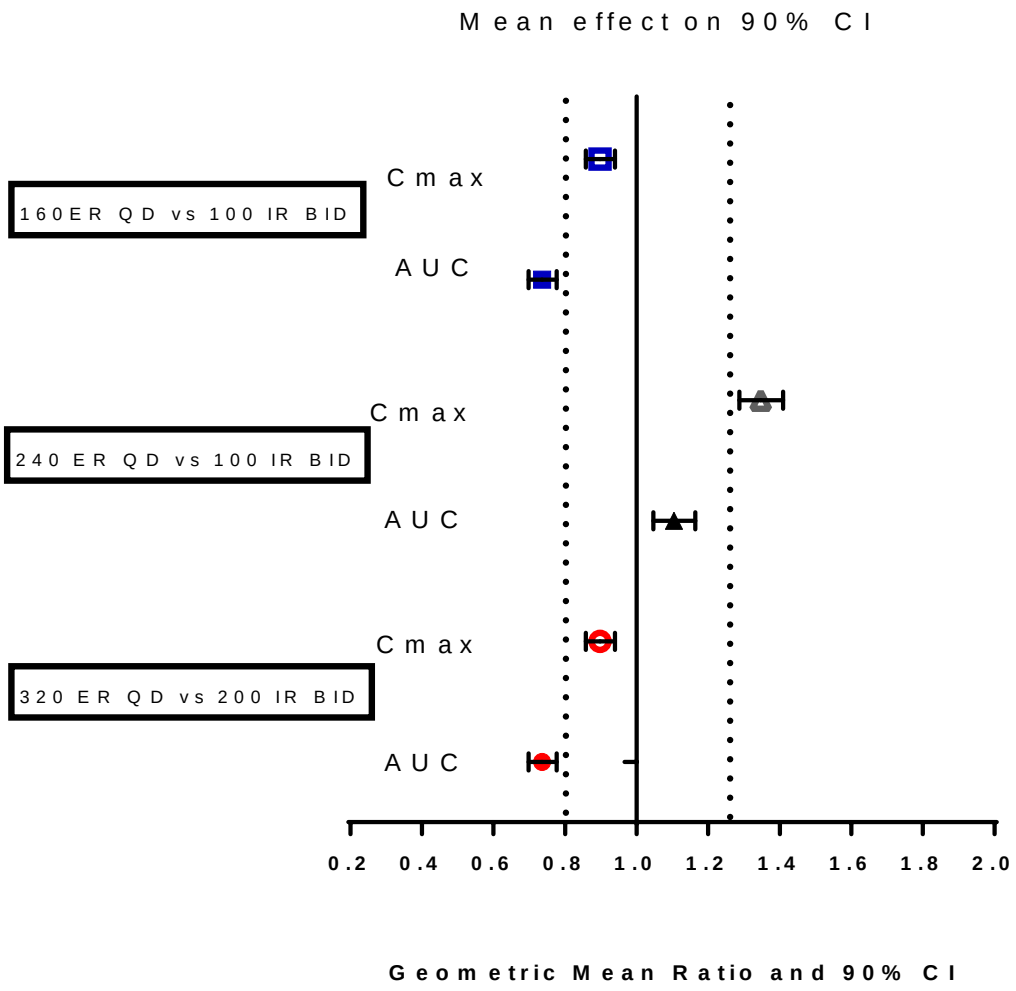


Source Clinical Pharmacology Reviewer

The sponsor also conducted a dose proportionality study to confirm PK linearity across the proposed dose strengths of 160, 240 and 320 mg OSMOLEX ER tablets (Study OS320-PKP05). Plasma amantadine exposure (Cmax, AUCinf) after single oral doses increased proportionally with increasing dose.

Even though OSMOLEX ER tablets administered once daily is shown to be bioequivalent to SYMMETREL syrup administered twice daily on a mg to mg basis, this study was not conducted at any of the approved dose levels of the RLD. Note that the approved usual dose of the RLD is 200 mg per day and the maximum daily dose is 400 mg for the treatment of Parkinson's disease. Therefore, the clinical pharmacology reviewer conducted PK simulation studies and repeated the BE analysis. Results of this analysis are presented in Figure 3.

Figure 2 BE evaluation of OSMOLEX ER with the approved doses for SYMMETREL Syrup



Source Clinical Pharmacology Reviewer

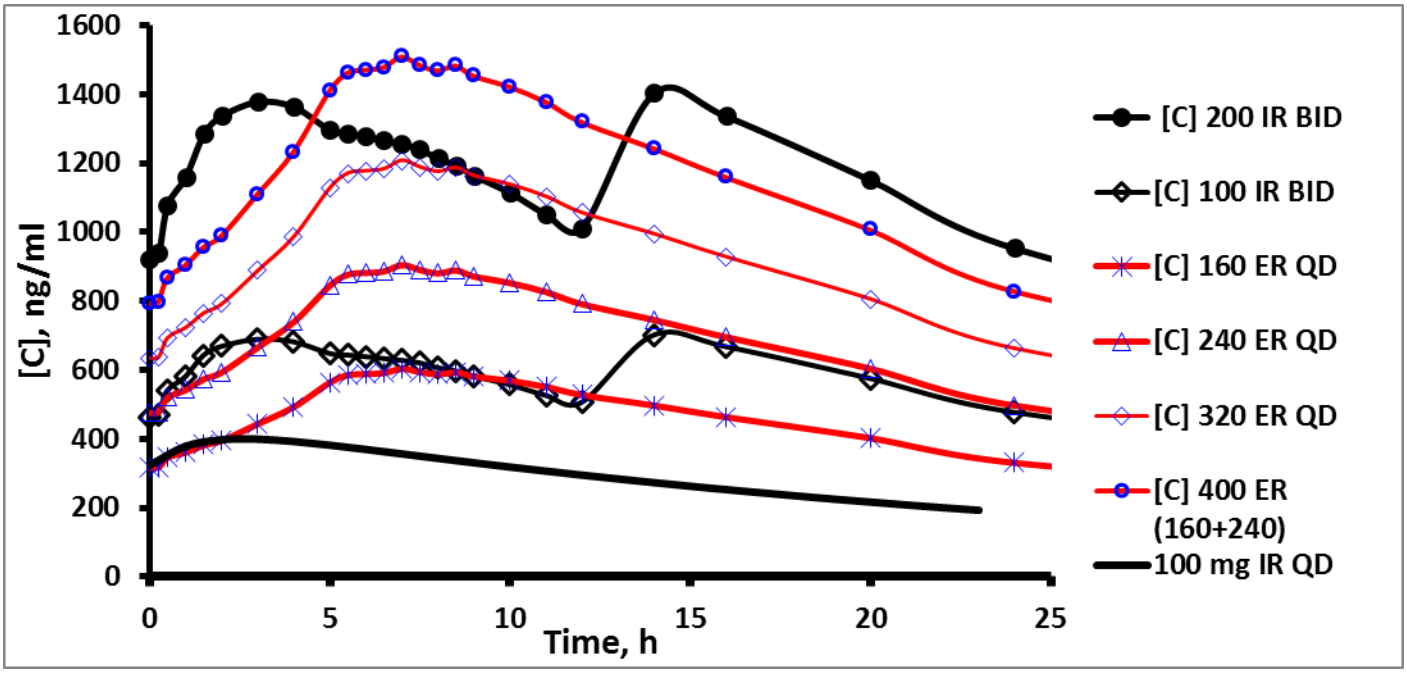
When the lowest dose strength of OSMOLEX ER (i.e., 160 mg) was compared with the closest total daily dose of the RLD (i.e., 200 mg per day as 100 mg twice daily) the geometric mean ratio for AUC was lower and out of the BE limit (less than 80 %). On the other hand, the C_{max} ratio for 240-mg dose of OSMOLEX ER, the next available dose strength, was higher and outside the BE limit (greater than 125%) when compared with the 200-mg total daily dose of the RLD.

The clinical pharmacology reviewer also compared the PK profiles of different dose strengths of OSMOLEX ER with the lowest and highest dose of the approved daily dosing regimens of the RLD (See Figure 4). Based on this comparison it was found that the PK profiles for all the doses of OSMOLEX ER, except for the 160 mg daily dose fall within the PK profiles for the highest (200 mg twice daily) and the usual dose of the RLD (100 mg twice daily). Therefore, the 160 mg dose of OSMOLEX ER is considered as the starting dose to initiate therapy.
It should be noted that the 160 mg dose of OSMOLEX ER is higher than the lowest initial dose of the RLD recommended for some patients (i.e. 100 mg per day). This

limits the use of OSMOLEX ER in such patients who may require a starting dose of 100 mg amantadine hydrochloride per day.

The maximum daily dose of the RLD can be achieved by using a combination of 160 mg and 240 mg tablets of OSMOLEX ER. This approach of combining two ER tablets to obtain a maximum daily dose of 400 mg was suggested to the applicant during the review and was accepted by the applicant.

Figure 3 Comparison of the steady state PK profiles of amantadine from the proposed OSMOLEX ER doses (160 mg, 240 mg, 320 mg and 160+240 mg) with the approved doses for the RLD, SYMMETREL Syrup. The lowest dose of 100 mg once daily(QD), usual dose of 100 mg twice daily (BID) and maximum dose of 200 mg BID are shown for the RLD. SYMMETREL Syrup is marked as IR and OSMOLEX ER tablets as ER respectively.



Source: Clinical Pharmacology Reviewer

As observed in Figure 4 there are differences in the shape of the PK profiles of amantadine between OSMOLEX ER and the RLD. Following multiple-dose oral administration of 160-mg amantadine syrup twice daily, plasma concentrations increased rapidly with a median Tmax value of 2 to 3hours post-dose and thereafter declined with a terminal half-life of 13.7 hours. By comparison, following multiple-dose oral administration of OSMOLEX ER 320-mg tablets once daily, amantadine plasma concentration increased slowly with a median Tmax of 7.5 hours and declined with a similar terminal phase half-life of 13.3 hours. Longer Tmax values confirmed slower rate of amantadine absorption from OSMOLEX ER tablets. Because of this delayed T_{max}, OSMOLEX ER tablets should be administered in the morning and not at bed time. If administered at bed time, amantadine peak levels will be reached during the night and is not considered desirable.

The clinical pharmacology review team considered the following, in addition to the steady state BE study conducted at 320 mg dose level for OSMOLEX ER, for evaluating the PK bridging strategy that supports this application.

- The pharmacokinetics of amantadine is dose proportional over the proposed dosing range.
- The exposure to amantadine from once daily dosing with the available dose strengths of OSMOLEX™ ER tablets (i.e., 240 mg and 320 mg of amantadine HCl) is bracketed by the exposures obtained from the approved usual dose (i.e., 200 mg daily) and the highest dose (i.e., 400 mg daily) of SYMMETREL® Syrup, the reference listed drug. A combination of 160 mg and 240 mg strengths of OSMOLEX™ ER can match exposures of the maximum daily dose of the RLD.
- Amantadine is generally dosed using a titration strategy to optimal and tolerated dose levels for each patient. Therefore, 160 mg strength OSMOLEX™ ER, although not bioequivalent to the approved usual dose of the RLD (i.e., 200 mg daily), can be considered as the initial or starting dose.
- Amantadine is a chronically administered drug and the reported onset of action as per the USPI of the RLD is about 48 hours. Therefore, the difference in time to peak plasma concentration between OSMOLEX ER and the RLD (7.5 hours vs. 2-3 hours) may not be clinically relevant.

Renal Impairment

The sponsor conducted a single dose study in subjects with renal impairment and normal renal function, (Study OS320-PKP07) for OSMOLEX ER. However, the clinical pharmacology did not rely on the sponsor's findings in the study, but rather through modeling independently developed dosing recommendations in patients with renal insufficiency. Dosing recommendations for patients with renal impairment were derived using PK simulations and are presented in 2.

It should be noted that the time required to reach PK steady state with OSMOLEX ER ranges from one week for patients with normal renal function and mild renal function impairment (CrCL >60 mL/min) to one month in patients with severe renal impairment (CrCL 15-29 mL/min).

Table 2. Dosing in Patients with RI

Renal Function/Estimated GFR (mL/min/1.73 m2)		OSMOLEX ER Dosing Regimen
Normal & Mild impairment	≥60	Once every 24 hours
Moderate	30 to 59	Once every 48 hours
Severe	15 to 29	Once every 96 hours

Source Clinical Pharmacology Reviewer

Food Effect

In a food-effect study (OS320-PKP04), ingestion of high-fat, high-calorie meal did not affect the plasma PK of amantadine and therefore, the food-drug interaction is not considered clinically relevant. OSMOLEX ER can be taken with or without food.

Alcohol Effect

In vitro alcohol dose dumping: The results from the in vitro alcohol- induced dose dumping studies showed an increase in drug release at earlier time points in the presence of 40 % alcohol (e.g., approximately 20-25% increases at 2-2.5 hours).

Table 3: Summary of comparison of Amantadine HCl dissolution profiles (up to 2 hours) for 160 mg, 240 mg, 320- mg Amantadine HCl ER tablets in acidic (0.1 N HCl) or QC (water) media containing 0%, 5%, 20% and 40% ethanol

	160 mg		240 mg		360 mg	
Dissolution Media	*f*2 value	Amount dissolved	*f*2 value	Amount dissolved	*f*2 value	Amount dissolved
0% EtOH /0.1 N	NA	43%	NA	29%	NA	39%
5% EtOH /0.1 N	90	44%	86	33%	82	42%
20% EtOH /0.1 N	65	52%	59	42%	61	47%
40% EtOH /0.1 N	46	63%	43	52%	49	52%
0% EtOH /water	NA	43%	NA	32%	NA	42%
5% EtOH /water	77	48%	78	37%	68	48%
20% EtOH /water	57	56%	56	46%	54	52%
40% EtOH /water	42	66%	42	55%	50	54%
	160 mg		240 mg		360 mg	
Dissolution Media	Amount dissolved		Amount dissolved		Amount dissolved	
0% EtOH /0.1 N	69 mg		70 mg		125 mg	
5% EtOH /0.1 N	70 mg		79 mg		134 mg	
20% EtOH /0.1 N	83 mg		101 mg		150 mg	
40% EtOH /0.1 N	101 mg		125 mg		166 mg	
0% EtOH /water	69 mg		70 mg		134 mg	
5% EtOH /water	77 mg		89 mg		154 mg	
20% EtOH /water	90 mg		110 mg		166 mg	
40% EtOH /water	106 mg		132 mg		173 mg	

Source Biopharmaceutics Reviewer

Results presented in Table 3 above show that there is an approximately noticeable 20-25% increases in amantadine dissolution from Amantadine HCl ER Tablets at 2-2.5 hours in presence of 40% ethanol.

In summary, the Biopharmaceutics Reviewer agrees with the sponsor in the conclusion that Amantadine HCl ER Tablets do not dose dump in ethanol solutions containing up to 20% ethanol (*f*2>50 for the dissolution profile comparison with 0% alcohol).

Extended-Release (ER) claim: The proposed drug product meet the "Extended Release" claim based on the totality of the data/information, according to the criteria cited in 21 CFR 325.25(f), mainly:

- Similar pharmacokinetic steady-state performance between the proposed drug product and amantadine HCl oral syrup in humans, with established bioavailability profiles and ruling out the occurrence of dose-dumping.
- Extended-release characteristics in humans provides dosing benefit.

5 Sources of Clinical Data

This NDA relies on relative bioavailability data from three Phase 1 studies, the FDA's prior findings of safety and efficacy of amantadine HCl syrup, supplemental safety data from two recently conducted Phase 3 studies, and relevant safety and efficacy results from the published literature and the public domain.

Phase I studies

Study OS320-PKP06 compared the steady-state bioavailability of amantadine from one Amantadine HCl ER 320 mg Tablet administered orally once daily to 160 mg amantadine HCl syrup, 50 mg/5 mL administered orally twice daily for 7 days;

Study OS320-PKP05 compared the single-dose bioavailability and pharmacokinetics of Amantadine HCl ER Tablets, at 160 mg, 240 mg, and 320 mg to a single oral 160 mg dose of amantadine HCl syrup, 50 mg/5 mL; and

Study OS320-PKP04 evaluated the effect of a high-fat meal on amantadine bioavailability for Amantadine HCl ER Tablets, at 320 mg.

PK- Bridging Study

Osmotica is relying on the data from the steady-state comparative bioavailability **Study OS320-PKP06** to provide a bridge to amantadine HCl syrup. Note that amantadine HCl syrup, 50 mg/5 mL (Wockhardt ANDA 075060, a reference listed drug [RLD]) was used as the reference product in the comparative bioavailability studies, since Symmetrel syrup is no longer available.

Phase 3 Studies

Additional clinical safety data of Amantadine HCl ER Tablet in PD patients was provided by two randomized, double-blind, placebo-controlled Phase 3 studies

(**Study OS320-3005 and Study OS320-3006**) that evaluated the efficacy and safety of Amantadine HCl ER Tablets at 240 mg/day and 320 mg/day for the treatment of PD patients with levodopa-induced dyskinesia (LID).

5.1 Tables of Studies/Clinical Trials

Study Type	**Protocol No. (eCTD section)**	**Study Objective(s)**	**Study Design and Type of Control**	**Test Product; Dosage Regimen; Route of administration**	**Number enrolled** **Healthy Volunteers or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
BA	OS320-PKP3	To characterize the relative bioavailability and dose proportionality of Amantadine HCl ER tablets after a single dose	Randomized, open label, single center, single dose, 4-treatment, 4-period crossover Phase 1	160 mg, 240 mg, 320 mg Amantadine HCl ER tablets, Amantadine HCl syrup, 50 mg/5 mL Single dose Oral	25 Healthy male & female volunteers	Single Dose	Complete; abbreviated
BA	OS320-PKP04	To characterize the effect of food on amantadine bioavailability from Amantadine HCl ER tablets	Randomized, open-label, single center, single dose, 2-treatment, 2-period crossover Phase 1	320 mg Amantadine HCl ER tablets Single dose Oral	24 Healthy male & female volunteers	Single Dose	Complete; Full

BA	OS320-PKP06	To characterize the relative bioavailability of Amantadine HCl ER tablets at steady state	Randomized, open abel, single center, multiple-dose, 2-treatment, 2-period crossover Phase 1	320 mg Amantadine HCl ER tablets, Amantadine HCl Oral Solution Titration for both Treatments: Amantadine HCl Oral Solution 160 mg x 2 days Amantadine HCl ER tablet: q24h x 7 days Amantadine HCl oral solution q12h x 7 days Oral	24 Healthy male & female volunteers	18 days	Complete ; Full
BA	OS320-PKP05	To characterize the relative bioavailabilit y and dose proportionali ty of Amantadine HCl ER tablets after single dose	Randomized, open abel, single center, single dose, 4-treatment, 4-period crossover Phase 1	160 mg, 240 mg, 320 mg Amantadine HCl ER tablets, Amantadine HCl oral solution Single dose Oral	24 Healthy male & female volunteers	Single Dose	Complete ; Full
PK	OS320-PKP07	To characterize amantadine PK in subjects with severe or moderate renal mpairment compared to healthy volunteers	Open label, single center, single dose, parallel group Phase 1	160 mg Amantadine HCl ER tablets Single dose Oral	24 Male and female severe and moderate renal impaired patients and healthy volunteers	Single Dose	Complete ; Full

Efficacy and safety	OS320-3005	To demonstrate efficacy and safety of Amantadine HCl ER tablets in patients with Parkinson's disease and Levodopa Induced Dyskinesia	Randomized, multi-center, placebo-controlled, double-blind, parallel group Phase 3	160 mg Amantadine HCl ER Tablets (titration dose) 240 mg Amantadine HCl ER Tablets, 320 mg Amantadine HCl ER Tablets, or Placebo Tablets 1 tablet twice daily for 16 weeks (2 weeks titration+12 weeks fixed dose+ 2 weeks taper) Oral	87 Parkinson's Disease Patients with Levodopa-Induced Dyskinesias	16 weeks	Complete; Full

Study Type	**Protocol No. (eCTD section)**	**Study Objective(s)**	**Study Design and Type of Control**	**Test Product; Dosage Regimen; Route of administration**	**Number enrolled** **Healthy Volunteers**	**Duration of Treatment**	**Study Status; Type of Report**
Efficacy and safety	OS320-3006	To demonstrate efficacy and safety of Amantadine HCl ER tablets in patients with Parkinson's disease and Levodopa Induced Dyskinesia	Randomized, multi-center, placebo-controlled, double blind, parallel group Phase 3	160 mg (titration dose) Amantadine HCl ER Tablets, 240 mg Amantadine HCl ER Tablets, 320 mg Amantadine HCl ER Tablets, or Placebo Tablets 1 tablet twice daily for 26 weeks (2 weeks titration+22 weeks fixed dose+ 2 weeks taper) Oral	135 Parkinson's Disease Patients with Levodopa-Induced Dyskinesias	26 weeks	Complete; Full

Source Sponsor

5.2 Review Strategy

Two Phase III studies were conducted by the sponsor. The primary endpoint of these studies was the change from baseline in Unified Dyskinesia Rating Scale (UDysRS) total score in patients with Parkinson's disease. The sponsor is seeking approval for OSMOLEX ER for the treatment of PD, (b) (4) and drug-induced extrapyramidal reactions by referencing FDA's finding of safety and effectiveness for Symmetrel in a 505(b)(2) NDA. The applicant's bridge to Symmetrel consists of demonstrating amantadine ER is bioequivalent to the reference standard amantadine product. In my review of the the results of the Phase III studies Itis the opinion of the reviewer that the studies do not support a finding of efficacy because of design flaws, limitations in

the methods of analysis and a large amount of missing data in this application. A brief summary of the studies is presented in Section 6.0.

The safety results from the Phase 3 studies are summarized in Section 7.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Amantadine hydrochloride is currently approved for treatment of idiopathic Parkinson's disease (Paralysis Agitans) and Parkinson's Syndrome that include the following conditions: postencephalitic parkinsonism, symptomatic parkinsonism due to carbon monoxide intoxication, and parkinsonism associated with cerebral arteriosclerosis. The efficacy of amantadine HCl for treatment of Parkinson's disease is established by the approved product label and is further supported from clinical studies described in the published literature.

Two Phase 3 studies (Study OS320-3005 and Study OS320-3006) were conducted in support of the Amantadine HCl ER Tablet clinical development program in PD patients with levodopa induced dyskinesias (LID) and therefore, are not supportive of efficacy for the proposed indication of Parkinson's disease and extrapyramidal reactions.

The Phase 3 studies were randomized, double-blind, placebo-controlled trials that enrolled male and female subjects 30 to 85 years of age who had been diagnosed with idiopathic Parkinson's disease with levodopa-induced predictable peak-effect dyskinesia considered by the subject to be problematic and/or disabling. From the two Phase 3 studies, a total of 222 subjects were randomized including 75 subjects to Amantadine HCl ER 320 mg, 75 subjects to Amantadine HCl ER 240 mg, and 72 subjects to placebo.

Tabular Summary of Phase 3 Clinical Studies

Study Type	Protocol No. (eCTD section)	Study Objective(s)	Study Design and Type of Control	Test Product; Dosage Regimen; Route of administration	Number enrolled Healthy Volunteers or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and safety	OS320-3005 5.3.5.1	To demonstrate efficacy and safety of Amantadine HCl ER Tablets in patients with Parkinson's disease and Levodopa Induced Dyskinesia	Randomized, multi-center, placebo-controlled, double-blind, parallel group Phase 3	160 mg Amantadine HCl ER Tablets (titration dose) 240 mg Amantadine HCl ER Tablets, 320 mg Amantadine HCl ER Tablets, or Placebo tablets 1 tablet twice daily for 16 weeks (2 weeks titration + 12 weeks fixed dose + 2 weeks taper) Oral	87 Parkinson's Disease Patients with Levodopa-Induced Dyskinesias	16 weeks	Complete; Full
Efficacy and safety	OS320-3006 5.3.5.1	To demonstrate efficacy and safety of Amantadine HCl ER Tablets in patients with Parkinson's disease and Levodopa Induced Dyskinesia	Randomized, multi-center, placebo-controlled, double blind, parallel group Phase 3	160 mg (titration dose) Amantadine HCl ER Tablets, 240 mg Amantadine HCl ER Tablets, 320 mg Amantadine HCl ER Tablets, or Placebo tablets 1 tablet twice daily for 26 weeks (2 weeks titration + 22 weeks fixed dose + 2 weeks taper)	135 Parkinson's Disease Patients with Levodopa-Induced Dyskinesias	26 weeks	Complete; Full

Source Sponsor

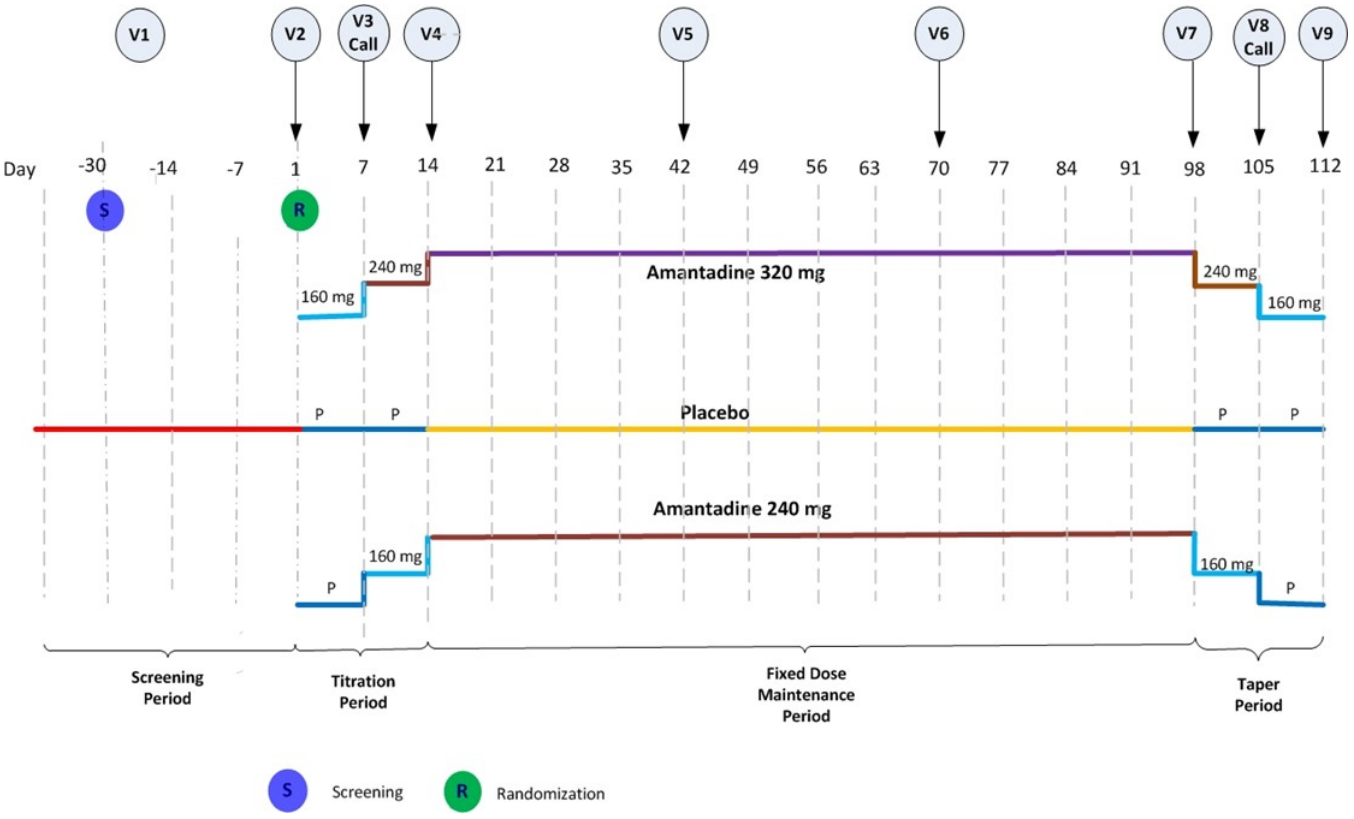
6.1.1 Methods

STUDY OS320-3005

Study **OS320-3005** was a randomized, double-blind, placebo-controlled parallel-group, 3-arm, Phase 3, multicenter study. This was a fixed-dose trial (after a Titration Period) that compared the efficacy and safety of Amantadine HCl ER tablets with placebo in subjects30 to 85 years of age with PD who had LID. Each subject was to participate in the study for up to 16 weeks and have a total of 7 outpatient clinic visits during the following study periods:

- Screening: Day -30 to 0;
- Randomization: Day 1, Visit 2; start study medication;

- Titration (Titration Period): Day 1 to Day 14 Visit 4;
- Dose maintenance (Maintenance Period): 12 weeks, (Days 15-98), Visits 5, 6 and 7; and
- Dose controlled taper (Taper Period): Day 99 to Day 112, Visit 9.

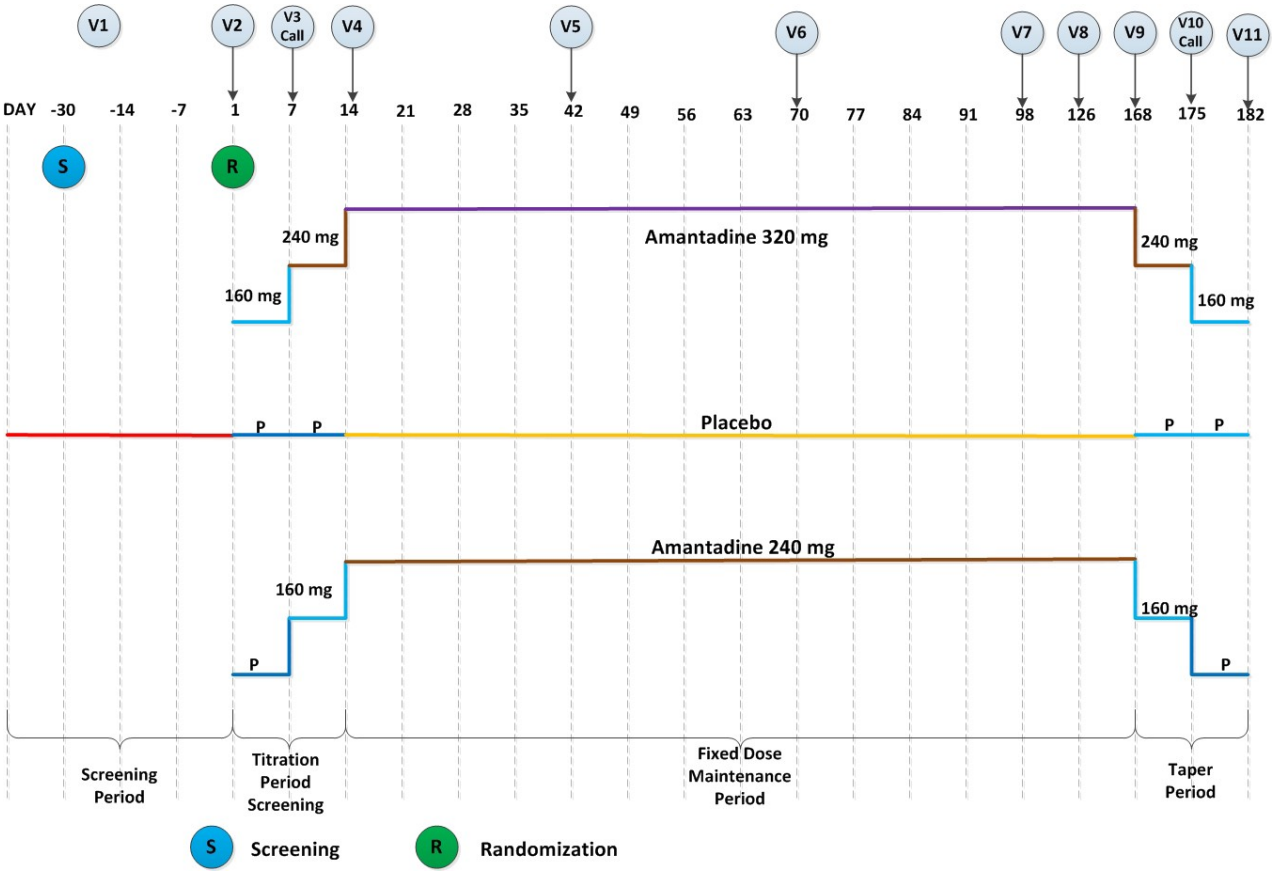


Study OS320-3006

Study **OS320-3006** was a randomized, double-blind, placebo-controlled parallel-group, 3-arm, Phase 3, multicenter study. This was a fixed-dose trial (after a Titration Period) that compared the efficacy and safety of Amantadine HCl ER tablets with placebo in subjects 30 to 85 years of age with PD who had LID. Each subject was to participate in the study for up to 26 weeks and have a total of 9 outpatient clinic visits during the following study periods:

- Screening: Day -30 to 0;
- Randomization: Day 1, Visit 2; start study medication;
- Titration (Titration Period): Day 1 to Day 14 Visit 4;
- Dose maintenance (Maintenance Period): 22 weeks, (Days 15-168), Visits 5, 6, 7, 8, and 9; and
- Dose controlled taper (Taper Period): Day 169 to Day 182, Visit 11.

Study Schematic, Study OS320-3006



Primary Efficacy Endpoint

Studies OS320-3005 and OS320-3006

The primary efficacy endpoint was the change in UDysRS from baseline to end of study, Day 98:

OS320-3005

The primary endpoint of this study was the change from baseline to Day 98 (Visit 7) of treatment in the sum of the items comprising the UDysRS. The analysis visit window for Day 98 (Visit 7) for the primary endpoint used stable dose last observation carried forward (last data point collected after Day 39). The value closest to Day 98 was used for the primary efficacy endpoint.

OS320-3006

The primary endpoint of this study was the change from baseline to Day 98 (Visit 7) of treatment in the sum of the items comprising the UDysRS. The analysis visit window for Day 98 (Visit 7) for the primary endpoint used stable dose last observation carried forward (last data point collected after Day 39 and before Day

102). The value closest to Day 98 was used for the primary efficacy endpoint.

The **UDysRS** provides an assessment of dyskinesia in PD. The UDysRS has a four-part scale that assesses:

Part I: Historical Disability (subject perceptions) of On-Dyskinesia impact (11 items: 1 item with involvement of the rater to assist in obtaining the portion of the day the subject has dyskinesia and 10 items answered by the subject/caregiver in the form of a questionnaire. Score range was from 0 to 44).

Part II: Historical Disability (subject perceptions) of Off-Dystonia impact (4 items:1 with involvement of the rater to determine the hours per day with Off-dystonia and 3 answered by the subject/caregiver in the form of a questionnaire. Score range was from 0 to 16).

Part III: Objective Impairment (dyskinesia severity and anatomical distribution based on observation of four activities). Seven anatomical areas are rated for severity of dyskinesia or dystonia on each task with the highest score for the four tasks recorded as the final score for each body region. Score range was from 0 to 28.

Part IV: Objective Disability (four items with ratings based on the same four activities in Part III). Score range was from 0 to 16.

The Total Historical sub-score, the Total Objective sub-score, and the Total UDysRS score were derived.

- The Total Historical sub-score was calculated as the sum of the individual scores for Part I and II (score range is from 0 to 60).
- The Total Objective sub-score was calculated as the sum of the individual scores for Part III and IV (score range was from 0 to 44).
- The Total UDysRS score was calculated as the sum of the Total Historical sub-score and the Total Objective sub-score (score range was from 0 to 104).

Secondary Efficacy Endpoint

Studies OS320-3005 and OS320-3006

The secondary efficacy endpoint was the following:

- The change from baseline to Day 98 (Visit 7) in the number of awake “ON” hours without troublesome dyskinesia (without dyskinesia and with non-troublesome dyskinesia).

Definition of Secondary Efficacy Endpoint

The secondary efficacy endpoint was defined as the change from baseline in the number of awake "ON" hours without troublesome dyskinesia (without dyskinesia and with non-troublesome dyskinesia endpoints). The analysis of this endpoint was based on the ITT Population.

The analysis visit window for Day 98 (Visit 7) for the secondary endpoint used stable dose last observation carried forward (last data point collected after Day 39). The value closest to Day 98 was used for the secondary efficacy endpoint.

Exploratory Efficacy Endpoints OS320-3005

The exploratory efficacy endpoints were the following:

- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), and Day 98 (Visit 7) of treatment in the sum of the items comprising the UDysRS;
- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), and Day 98 (Visit 7) of treatment in the number of waking hours that subjects report being "OFF" in the Mobility State Self-Assessment (Subject Diaries);
- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), and Day 98 (Visit 7) of treatment in the number of waking hours that subjects report being "ON" having without dyskinesia, non-troublesome dyskinesia, and troublesome dyskinesia in the Mobility State Self-Assessment (Subject Diaries);
- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), and Day 98 (Visit 7) of treatment in the sum of Parts II, and III of the MDS-UPDRS; and
- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), and Day 98 (Visit 7) in the FSS.

Exploratory Efficacy Endpoints OS320-3006

The exploratory efficacy endpoints were the following:

- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), Day 98 (Visit 7), Day 126 (Visit 8), and Day 168 (Visit 9) of treatment in the sum of the items comprising the UDysRS;
- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), Day 98 (Visit 7), Day 126 (Visit 8), and Day 168 (Visit 9) of treatment in the number of waking hours that subjects report being "OFF" in the Mobility State Self-Assessment (Subject Diaries);
- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), Day 98 (Visit 7), Day 126 (Visit 8), and Day 168 (Visit 9) of treatment in the number of waking hours that subjects report being "ON" having without dyskinesia, non-troublesome dyskinesia, and troublesome dyskinesia in the

Mobility State Self-Assessment (Subject Diaries);

- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), Day 98 (Visit 7), Day 126 (Visit 8), and Day 168 (Visit 9) of treatment in the sum of Parts II, and III of the MDS-UPDRS; and
- The change from baseline to Day 14 (Visit 4), Day 42 (Visit 5), Day 70 (Visit 6), Day 98 (Visit 7), Day 126 (Visit 8), and Day 168 (Visit 9) in the FSS.

Analysis of the Primary Efficacy Endpoint Study OS320-3005

(b) (4)

Analysis of the Primary Efficacy Endpoint Study OS320-3006

(b) (4)

(b) (4)

Analysis of the Primary Efficacy Endpoint

(b) (4)

6.1.2 Demographics

The demographic and baseline characteristics for Study OS320-3005 are presented in Table 4

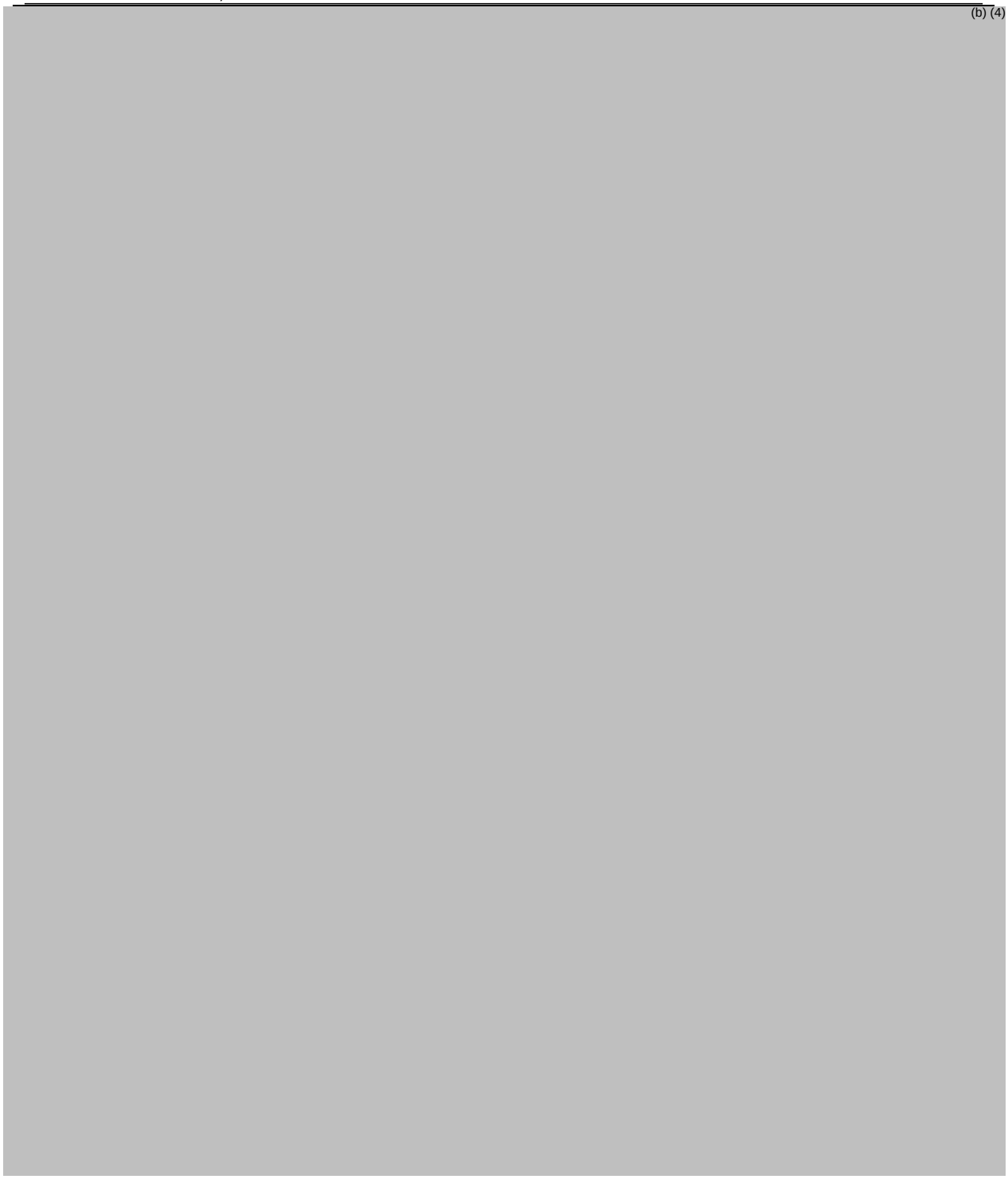
Table 4 Demographic and Baseline Characteristics – Safety Population, Study OS320-3005

Category Statistics	Amantadine HCl ER 320 mg (N=29)	Amantadine HCl ER 240 mg (N=30)	Placebo (N=28)	All Subjects Combined
Age (years)				
n	29	30	28	87
Mean (SD)	63.3 (9.17)	68.6 (8.02)	66.1 (8.04)	66.1 (8.61)
Minimum - Maximum	43 - 76	46 - 81	43 - 79	43 - 81
Gender n (%)				
Male	19 (65.5)	14 (46.7)	16 (57.1)	49 (56.3)
Female	10 (34.5)	16 (53.3)	12 (42.9)	38 (43.7)
Race n (%)				
White	28 (96.6)	26 (86.7)	28 (100.0)	82 (94.3)
Black or African American	1 (3.4)	0 (0.0)	0 (0.0)	1 (1.1)
Other	0 (0.0)	3 (10.0)	0 (0.0)	3 (3.4)
Missing	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.1)
Ethnicity n (%)				
Hispanic or Latino	3 (10.3)	3 (10.0)	8 (28.6)	14 (16.1)
Not Hispanic or Latino	26 (89.7)	26 (86.7)	20 (71.4)	72 (82.8)
Missing	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.1)
Height (cm)				
n	29	29	28	86
Mean (SD)	174.4 (10.12)	166.6 (10.68)	166.5 (10.46)	169.2 (10.95)
Weight (kg)				
n	29	29	28	86
Mean (SD)	77.2 (16.32)	73.5 (18.26)	73.4 (20.93)	74.7 (18.44)
Body mass index (kg/m^2)				
n	29	28	28	85
Mean (SD)	25.2 (3.41)	26.9 (5.18)	26.2 (5.93)	26.1 (4.93)

ER = extended-release; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SD = standard deviation; UDysRS = Unified Dyskinesia Rating Scale.

(b) (4)

(b) (4)



Source Sponsor

REVIEWER COMMENT:

In study OS320-3005, the Amantadine HCl ER 320mg cohort were slightly younger on average than the amantadine HCL ER 240mg or placebo cohorts (63

versus 69 or 66 years old respectively.) In addition, there were a greater proportion of males (65%) in the amantadine HCl ER 320mg cohort compared to the other two cohorts (47%, 57%). (b) (4)

[redacted]

The demographic and baseline characteristics for Study OS320-3006 are presented in Table 5

Table 5 Demographic and Baseline Characteristics – Safety Population, Study OS320-3006

Parameter Statistics	Amantadine HCl ER 320 mg (N=46)	Amantadine HCl ER 240 mg (N=45)	Placebo (N=44)	All Subjects Combined
Age (years)				
n	46	45	44	135
Mean (SD)	63.0 (8.98)	63.9 (8.88)	63.5 (10.36)	63.5 (9.36)
Minimum - Maximum	42 - 82	46 - 81	37 - 82	37 - 82
Gender n (%)				
Male	25 (54.3)	29 (64.4)	26 (59.1)	80 (59.3)
Female	21 (45.7)	16 (35.6)	18 (40.9)	55 (40.7)
Race n (%)				
White	41 (89.1)	43 (95.6)	40 (90.9)	124 (91.9)
Black or African American	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.7)
Asian	3 (6.5)	0 (0.0)	1 (2.3)	4 (3.0)
Other	0 (0.0)	2 (4.4)	2 (4.5)	4 (3.0)
Missing	2 (4.3)	0 (0.0)	0 (0.0)	2 (1.5)
Ethnicity n (%)				
Hispanic or Latino	8 (17.4)	7 (15.6)	3 (6.8)	18 (13.3)
Not Hispanic or Latino	37 (80.4)	38 (84.4)	41 (93.2)	116 (85.9)
Missing	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Height (cm)				
n	46	45	44	135
Mean (SD)	169.4 (10.85)	169.7 (8.57)	170.9 (9.11)	170.0 (9.52)
Weight (kg)				
n	46	45	44	135
Mean (SD)	75.4 (14.90)	77.7 (15.13)	76.4 (13.43)	76.5 (14.44)
Body mass index (kg/m^2)				
n	46	45	44	135
Mean (SD)	26.2 (4.22)	26.9 (4.42)	26.2 (4.52)	26.4 (4.36)

ER = extended-release; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SD = standard deviation; UDysRS = Unified Dyskinesia Rating Scale.

(b) (4)

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(b) (4)

Source Sponsor

REVIEWER COMMENT:

In study OS320-3006, the average age, gender distribution and disease duration were similar across treatment cohorts. (b) (4)

6.1.3 Subject Disposition

The disposition for Study Population in Study OS320-3005 is presented in Table 6 below.

Table 6 Subject Disposition by Treatment Group – Study Population, Study OS320-3005

	Amantadine HCl ER 320 mg (N=29)	Amantadine HCl ER 240 mg (N=30)	Placebo (N=28) n (%)	All Subjects Combined (N=87) n (%)
Screened				140
Enrolled				87
Randomized Population	29	30	28	87
Safety Population	29 (100.0)	30 (100.0)	28 (100.0)	87 (100.0)
ITT Population	29 (100.0)	30 (100.0)	28 (100.0)	87 (100.0)
Per-Protocol Population	16 (55.2)	18 (60.0)	16 (57.1)	50 (57.5)
Completed Study by Period	19 (65.5)	17 (56.7)	18 (64.3)	54 (62.1)
Up to Visit 4 (Titration Period)	29 (100.0)	30 (100.0)	28 (100.0)	87 (100.0)

Up to Visit 7 (Maintenance Period)	28 (96.6)	28 (93.3)	26 (92.9)	82 (94.3)
Up to Visit 9 (Taper Period)	19 (65.5)	18 (60.0)	18 (64.3)	55 (63.2)
Discontinued Study by Period	10 (34.5)	13 (43.3)	10 (35.7)	33 (37.9)
Titration	1 (3.4)	2 (6.7)	2 (7.1)	5 (5.7)
Maintenance	9 (31.0)	10 (33.3)	8 (28.6)	27 (31.0)
Taper Period	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.1)
Discontinued Study by Reason	10 (34.5)	13 (43.3)	10 (35.7)	33 (37.9)
Adverse Event	5 (17.2)	3 (10.0)	3 (10.7)	11 (12.6)
Protocol Violation	0 (0.0)	2 (6.7)	0 (0.0)	2 (2.3)
Trial Screen Failure	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.1)
Study Terminated by Sponsor	3 (10.3)	4 (13.3)	3 (10.7)	10 (11.5)
Withdrawal by Subject	2 (6.9)	4 (13.3)	2 (7.1)	8 (9.2)
Other	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.1)
The denominator for calculating percentages is the number of subjects in the Randomized Population. ER = extended-release; ITT = Intention-to-Treat.				

Source: Sponsor

Of note, if a subject withdrew prematurely at a visit, a Premature Termination Visit was completed, not the scheduled visit.

The analysis windows for Premature Termination Visit Study OS320-3005 are outlined in the table below.

Visit	**Visit Window**
Baseline (Day 1), date of first study drug administration	1 day (no window)
Visit 4 (Day 14)	2 to 17 days
Visit 5 (Day 42)	18 to 45 days
Visit 6 (Day 70)	46 to 73 days
Visit 7 (Day 98)	>= 74 days
Stable Dose LOCF*	>= 39 days

* Stable Dose LOCF used the last observation captured after Day 39.

REVIEWER COMMENT:

Overall only 62% of the subjects completed the study (Table X), with the lowest completion rate in the amantadine 240mg cohort. Most of the subjects who discontinued did so during the maintenance period (approximately 30%.) The most common reasons for study discontinuation were adverse event (amatandine 320mg 17.2%, amantadine 240mg 10.0% and placebo 10.7%) followed by early termination of the study by the sponsor and withdrawal by subject.

Study OS320-3006

The disposition for Study Population in Study OS320-3006 is presented in Table 7 below.

Table 7 Subject Disposition by Treatment Group – Study Population, Study OS320-3006

	Amantadine HCl ER 320	**Amantadine HCl ER 240**	**Placebo (N=44) n (%)**	**All Subjects Combined (N=135)**
Screened				208
Enrolled				135
Randomized Population	46	45	44	135
Safety Population	46 (100.0)	45 (100.0)	44 (100.0)	135 (100.0)
ITT Population	46 (100.0)	45 (100.0)	44 (100.0)	135 (100.0)
Per-Protocol Population	25 (54.3)	14 (31.1)	26 (59.1)	65 (48.1)
Completed Study by Period	27 (58.7)	27 (60.0)	25 (56.8)	79 (58.5)
Up to Visit 4 (Titration Period)	45 (97.8)	44 (97.8)	39 (88.6)	128 (94.8)
Up to Visit 7 (Maintenance Period)	31 (67.4)	33 (73.3)	27 (61.4)	91 (67.4)
Up to Visit 9 (Maintenance Period)	28 (60.9)	29 (64.4)	26 (59.1)	83 (61.5)
Up to Visit 11 (Taper Period)	27 (58.7)	27 (60.0)	25 (56.8)	79 (58.5)
Discontinued Study by	19 (41.3)	18 (40.0)	19 (43.2)	56 (41.5)
Titration Period	1 (2.2)	1 (2.2)	5 (11.4)	7 (5.2)
Maintenance Period (Up to Visit 7)	14 (30.4)	11 (24.4)	12 (27.3)	37 (27.4)
Maintenance Period (Up to Visit 9)	3 (6.5)	4 (8.9)	1 (2.3)	8 (5.9)
Taper Period	1 (2.2)	2 (4.4)	1 (2.3)	4 (3.0)

Discontinued Study by	19 (41.3)	18 (40.0)	19 (43.2)	56 (41.5)
Adverse Event	8 (17.4)	5 (11.1)	3 (6.8)	16 (11.9)
Lack of Efficacy	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.7)
Lost to Follow-up	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.7)
Non-Compliance with Study Drug	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.7)
Physician Decision	0 (0.0)	2 (4.4)	1 (2.3)	3 (2.2)
Protocol Violation	1 (2.2)	0 (0.0)	1 (2.3)	2 (1.5)
Study Terminated by Sponsor	5 (10.9)	7 (15.6)	5 (11.4)	17 (12.6)
Withdrawal by Subject	4 (8.7)	4 (8.9)	6 (13.6)	14 (10.4)
Other	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
The denominator for calculating percentages is the number of subjects in the Randomized Population. ER = extended-release; ITT = Intention-to-Treat.				

Source: Sponsor

Of note, if a subject withdrew prematurely at a visit, a Premature Termination Visit was completed, not the scheduled visit.

The analysis windows for Premature Termination Visit Study OS320-3006 are outlined in the table below.

Visit	**Visit Window**
Baseline (Day 1), date of first study drug administration	1 day (no window)
Visit 4 (Day 14)	2 to 17 days
Visit 5 (Day 42)	18 to 45 days
Visit 6 (Day 70)	46 to 73 days
Visit 7 (Day 98)	74 to 101 days
Stable Dose LOCF*	39 to 101 days
Visit 8 (Day 126)	102 to 129 days
Visit 9 (Day 168)	≥ 130 days

Source: Sponsor

REVIEWER COMMENT:

Overall only 58.5% of the subjects completed the study (Table 7), with the lowest completion rate in the placebo cohort. Most of the subjects who discontinued did so during the maintenance period (approximately 25-30%.) The most common reasons for study discontinuation were adverse event (amatandine 320mg 17.4%, amantadine 240mg 11.1% and placebo 6.8%) followed by early termination of the study by the sponsor and withdrawal by subject.

These results were independently verified by the clinical review team.

	Actual Treatment for Period 01					
	Amantadine 240 mg		Amantadine 320 mg		Placebo	
	Study Identifier		Study Identifier		Study Identifier	
	OS320-3005	OS320-3006	OS320-3005	OS320-3006	OS320-3005	OS320-3006
Randomized Population Flag	30	45	29	46	28	44
Safety Population Flag	30	45	29	46	28	44
Intent-To-Treat Population Flag	30	45	29	46	28	44
Completers Population Flag	17	27	19	27	18	25
Per-Protocol Population Flag	18	14	16	25	16	26

Source: Clinical Review Team

6.1.4 Analysis of Primary Endpoint(s)

Stable Dose LOCF

STUDY OS320-005

(b) (4)

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(b) (4)

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Efficacy Conclusions

The sponsor is seeking approval based on bioequivalence to Symmetrel, amantadine IR. Amantadine IR is approved for Parkinson's disease and extrapyramidal reactions. The two phase 3 studies conducted by the sponsor were designed to assess the efficacy of OSMOLEX ER to treat LIDS in patients with idiopathic Parkinson's disease, using change in UDysRS score from baseline to week 7, primary endpoint. Therefore, these studies do not support the efficacy claim being sought by the sponsor.

(b) (4)

[redacted]

(b) (4)

7 Review of Safety

Safety Summary

The sponsor is relying on the FDA's prior findings of safety of amantadine HCl (NDA 016020) to support the safety of Amantadine HCl ER Tablets. This 505(b)(2) application contains the results of comparative bioavailability trials that provide a bridge between Amantadine HCl ER Tablets and the approved amantadine HCl reference listed product. Based on the bioequivalence between Amantadine HCl ER Tablets and the reference listed drug at steady state, Osmotica is relying on the FDA's previous findings of safety for amantadine HCl for the treatment of Parkinson's Disease, various forms of parkinsonism and Extrapyramidal Reactions.

In addition, the sponsor conducted two Phase 3 studies (Study OS320-3005 and Study OS320-3006) with Amantadine HCl ER Tablets in PD patients with LID. The safety results from these two Phase 3 studies are applicable to the population of Parkinson's disease and provide additional support to the safety of Amantadine HCl ER Tablets at the 240 mg, and 320 mg dose strengths. These design and key safety results for these studies are shown in the table below.

Summary of Phase 3 Clinical Studies – Design and Key Safety Results

Study No. (No. of	Study Design (Study	Treatments Study	No. and Type of Subjects Randomized (Completed)	Demographics			Key Safety Results
				Mean	Gender	Race	
OS320-3005 (22 in US/ 27 outside the US including 2 in Canada, 6 in Germany, 9 in Spain, and 10 in France)	Randomized, double-blind, placebo-controlled, parallel (16 Week)	Treatments Amantadine HCl ER 320 mg* Amantadine HCl ER 240 mg† Placebo Objective(s) To demonstrate efficacy and safety of Amantadine HCl ER Tablets in patients with Parkinson's disease and Levodopa Induced Dyskinesia	Adult subjects 30 to 85 years of age diagnosed with diopathic PD who had LID 87 (54)	66.1 years	56.3% M 43.7% F	94.3% W 1.1% B 0.0% A 3.4% O 1.1% N/A	Subjects with SAEs, n (%): Amantadine HCl ER 320 mg: 1 (3.4%) Amantadine HCl ER 240 mg: 3 (10.0%) Placebo: 2 (7.1%) Study drug discontinuations due to AEs, n (%): Amantadine HCl ER 320 mg: 5 (17.2%) Amantadine HCl ER 240 mg: 4 (13.3%) Placebo: 3 (10.7%)

OS320-3006 (36 in US/ 31 outside the US including 2 in Canada, 9 in Germany, 9 in Spain, and 11 in France)	Randomized, double-blind, placebo-controlled, parallel (26 Week)	Treatments Amantadine HCl ER 320 mg* Amantadine HCl ER 240 mg† Placebo Objective(s) To demonstrate efficacy and safety of Amantadine HCl ER Tablets in patients with Parkinson's disease and Levodopa Induced Dyskinesia	Adult subjects 30 to 85 years of age diagnosed with diopathic PD who had LID 135 (79)	63.5 years	59.3% M 40.7% F	91.9% W 0.7% B 3.0% A 3.0% O 1.5% N/A	Subjects with SAEs, n (%): Amantadine HCl ER 320 mg: 4 (8.7%) Amantadine HCl ER 240 mg: 1 (2.2%) Placebo: 6 (13.6%) Study drug discontinuations due to AEs, n (%): Amantadine HCl ER 320 mg: 9 (19.6%) Amantadine HCl ER 240 mg: 6 (13.3%) Placebo: 5 (11.4%)

* The Amantadine HCl ER 320 group received the 160 mg QD dose and the 240 mg QD dose during the Titration and Taper Periods.
† The Amantadine HCl ER 240 group received placebo and the 160 mg QD dose during the Titration and Taper Periods.
A = Asian; AE = adverse event; B = Black/African American; ER = extended release; F = female; LID = levodopa-induced dyskinesia; M = male; N/A = not available; O = Other; PD = Parkinson's disease; QD = once daily; SAE

7.1 Methods

The pooled Phase 3 Safety Population included all 222 randomized subjects from both studies who received at least one dose of double-blind study drug.

The sponsor excluded Phase 1 studies from pooling in the integrated safety dataset because they were conducted in healthy volunteers (not PD patients), were not blinded, and were for a very short duration.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, 150 subjects were exposed to Amantadine HCl ER in the Phase 3 trials. Table16 summarizes extent of exposure to study drug for the Phase 3 Safety Population.

Table 16. Extent of Exposure to Study Drug – Study OS320-3005 and Study OS320- 3006 – Phase 3 Safety Population

Duration of Exposure to Study Drug	Amantadine HCl ER 320 mg (N=75)	Amantadine HCl ER 240 mg (N=75)	Placebo (N=72)	All Subjects Combined (N=222)
Overall				
n	75	75	70	220
Mean (SD)	117.9 (57.49)	123.5 (59.24)	118.4 (59.16)	120.0 (58.41)
Min	1.0	13.0	7.0	1.0
Median	113.0	115.0	113.0	113.0
Max	204.0	209.0	215.0	215.0
ER = extended release; SD = standard deviation. Source: ISS Post-text Table 5.1				

Source Sponsor

Overall median exposure to study drug was 113.0 days. The treatment groups were comparable with respect to study drug exposure.

The exposure by days is presented in Table 17

Table 17 Exposure (in days) to Amantadine ER by Dose and Study- Safety Population

	Actual Treatment for Period 01									
	Amantadine 240 mg			Amantadine 320 mg			Placebo			All
	Study			Study			Study			
Study Duration (days) Binned	OS320-3005 (N)	OS320-3006 (N)	All N	OS320-3005 (N)	OS320-3006 (N)	All N	OS320-3005 (N)	OS320-300 (N)6	All N	N
0 — 14	1	1	2	1	1	2	1	0	1	5
15 — 29	1	1	2	1	2	3	1	4	5	10
30 — 44	4	2	6	1	3	4	1	3	4	14
45 — 59	1	2	3	3	3	6	1	1	2	11
60 — 74	2	2	4	2	2	4	1	2	3	11
75 — 89	3	2	5	1	3	4	3	3	6	15
90 — 104	1	1	2	4	0	4	0	4	4	10
105 — 119	13	1	14	15	2	17	14	0	14	45
120 — 134	2	1	3	1	3	4	2	1	3	10
135 — 149	2	0	2	0	0	0	2	0	2	4
150 — 164	0	2	2	0	0	0	2	0	2	4
165 — 179	0	3	3	0	2	2	0	3	3	8
180 — 194	0	22	22	0	24	24	0	20	20	66
195 — 209	0	4	4	0	1	1	0	1	1	6
210 — 224	0	1	1	0	0	0	0	1	1	2
225 — 239	0	0	0	0	0	0	0	1	1	1
All	30	45	75	29	46	75	28	44	72	222

Source: Clinical Review Team

REVIEWER COMMENT:

Overall, 33 of 59 (56%) subjects in the amantadine HCl ER 240mg cohort completed between 105-119 days of treatment while 77 of 91 (85%) subjects in the amantadine HCl ER 320mg completed ≥ 105-119 days of treatment. The highlighted bins include the window for last day of taper and the end of study visit. The window for the end of study visit can extend to the end of the trial.

7.3 Major Safety Results

7.3.1 Deaths

One subject in the Phase 3 Safety Population died during Study OS320-3005. Subject (b) (6) from the Amantadine HCl ER 240 mg group died as a result of an SAE of multi-organ failure that was not considered related to study medication.

Treatment Group: Amantadine HCl ER 240 mg Country: France
Subject (b) (6): megacolon/multiple organ failure
Subject (b) (6), a 70-year-old male (Subject's race reported as Other) with a history of Parkinson's disease with levodopa-induced dyskinesia, signed informed consent on (b) (6) and was randomized to the Amantadine HCl ER 240 mg group on (b) (6) Study medication was discontinued on Study Day 28 (b) (6) and the subject was removed from the study on Study Day 31 (b) (6) due to adverse events of hallucination and somnolence. On Study Day 45 (b) (6), the subject was hospitalized for abdominal pain that he had experienced for several days along with problems with bowel movements. Upon examination at the emergency department, the subject's abdomen was distended and painful and the abdominal X-ray revealed numerous air/fluid accumulations and significant fecal stasis. The computerized tomography scan showed large and distended colon compatible with megacolon with no obstructions.
On the morning of Study Day 47 (b) (6), the subject experienced hemodynamic instability along with respiratory distress. The subject was intubated, blood volume was restored and noradrenaline was administered. Multiple samples were collected for culture and antibiotic treatment (Tazocillin and Amiklin) was initiated. The subject had metabolic acidosis with pH=7.19 and lactates of 4 (units not provided), and kidney failure was noted with urea at 186 and elevated creatinine. While sedated and on noradrenaline, the subject continued to deteriorate quickly with lactates increasing from 7.5 to 10 (units not provided). The subject was transferred for surgery and a total colectomy was performed along with ileostomy. The subject's spleen and gallbladder were also removed. During the surgery, the subject had significant blood loss which required a transfusion with packed red blood cells and fresh frozen plasma. Furthermore, the subject experienced significant hemodynamic instability with cardiac arrest which required internal chest compressions. The subject was returned to the ICU where he had another cardiac arrest. The subject's sinus rhythm was restored with a blood pressure of only 4 to 5 mmHg. Dialysis was initiated along with treatments for the acidosis. On Study Day 47 (b) (6), the subject experienced cardiac arrest and

passed away upon his return to the surgical department. The subject's medical history included hypertension, orthostatic hypotension, restless legs syndrome, osteoarthritis, atrial fibrillation, and prostate adenocarcinoma (curettage and radiotherapy on (b) (6) . Concomitant medications included rasagilin mesylate, dafalgan codeine, fludrocortisone, midorine hydrochloride, isradipine, modopar, pramipexole dihydrochloride, and Sinemet.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events for combined Phase 3 studies are summarized in Table 18 below.

Table 18 Listing of Subjects with Serious Adverse Events During the Study – Study OS320-3005 and Study OS320-3006 – Phase 3 Safety Population

Treatment Subject No.	Adverse Event Preferred Term	Resulted in Discontinuation
Amantadine HCl ER 320 mg		
(b) (6)	syncope	no
	osteoarthritis	no
	constipation	no
	haemorrhoid	no
	vestibular neuronitis	no
	cranial nerve palsies multiple	no
Amantadine HCl ER 240 mg		
(b) (6)	hypertension	no
	traumatic hemothorax	no
	megacolon	yes
	multi-organ failure	yes (death)
	arthralgia	no
	osteonecrosi	no
Placebo		
(b) (6)	transient ischaemic attack	no
	lumbar spinal stenosis	yes
	intervertebral disc protrusion	no
	brain abscess	yes
	constipation	no
	diabetes mellitus inadequate	no
	thoracic vertebral fracture	no
	impulse-control disorder	yes
	arrhythmia supraventricular	no

Source Sponsor

Brief narratives for all SAEs in subjects treated with amantadine HCl ER are presented below.

Treatment Group: ***Amantadine HCl ER 240 mg*** *Country: Spain*
Subject (b) (6) : Arthralgia
Subject (b) (6) , an 81-year-old White female with a history of Parkinson's disease with levodopa-induced dyskinesia, signed informed consent on (b) (6) and was randomized to the Amantadine HCl ER 240 mg group on (b) (6) . On Study Day

85 (b) (6), the subject experienced event of moderate left coxalgia due to weight overload and was hospitalized. Drugs to treat the event included paracetamol, quetiapine, and ibuprofen. The subject was discharged on the same day as admission (b) (6). The subject's medical history included cholecystectomy, worsening of right knee gonarthrosis, osteonecrosis of right knee joint, exostosis (right foot heel spur), right shoulder tendon rupture, hiatus hernia, hysterosalpingo-oophorectomy, dyslipidemia, tachyarrhythmia, hypertension, and diabetes mellitus. The investigator confirmed that the subject had no similar condition (i.e., arthralgia) prior to study participation. Concomitant medications included metformina (metformin), vildagliptim, glimepiride, azilect (rasagiline), pramipexol (pramipexole dihydrochloride), omeprazole, paracetamol, tramadol, diclofenac, enoxaparin, ibuprofen, and madopar (benserazide hydrochloride, levodopa). It is unknown when the subject stopped study medication because the subject was lost to follow-up.

Treatment Group: ***Amantadine HCl ER 240 mg*** *Country: Spain*
Subject (b) (6): Osteonecrosis
Subject (b) (6), an 81-year-old White female with a history of Parkinson's disease with levodopa-induced dyskinesia, signed informed consent on (b) (6) and was randomized to the Amantadine HCl ER 240 mg group on (b) (6). On Study Day 56 (b) (6) the subject was hospitalized for a total right knee replacement due to osteonecrosis. The scheduled surgery was performed with regional anesthesia and no complications were reported. Medications provided during and after the surgery included Paracetamol, Dextoprophen, Metamizol, Bemiparin, and Cephazolin. The subject's medical history included cholecystectomy, worsening of right knee arthritis, osteonecrosis of right knee joint, exostosis (right foot heel spur), right shoulder tendon rupture, hiatus hernia, hysterosalpingo- oophorectomy, dyslipidemia, tachyarrhythmia, hypertension, and diabetes mellitus. Concomitant medications included metformina (metformin), vildagliptim, glimepiride, azilect (rasagiline), pramipexol (pramipexole dihydrochloride), omeprazole, paracetamol, tramadol, diclofenac, enoxaparin, ibuprofen, and madopar (benserazide hydrochloride, levodopa). The subject did not complete the study and was lost to follow up.

Treatment Group: ***Amantadine HCl ER 240 mg*** *Country: France*
Subject (b) (6): Hypertension
Subject (b) (6) a 75-year-old White female with a history of Parkinson's disease with levodopa-induced dyskinesia, signed informed consent on (b) (6) and was randomized to the Amantadine HCl ER 240 mg group on (b) (6). On Study Day 185 (b) (6), the subject was hospitalized with a high blood pressure. Blood pressure at the hospital was 205/125 mmHg in the supine position; 187/123 mmHg after standing 1 minute; and 192/127 mmHg after standing 3 minutes. The cardiovascular examination found regular heart sounds with an aortic systolic murmur and no signs of cardiac insufficiency. The ECG, taken upon admission, revealed an incomplete right bundle branch block with regular sinus rhythm and no repolarization disorder. The laboratory workup showed normal renal function with creatinine of 56 µmol/L and creatinine clearance of 87 mL/min. Electrolytes and blood cell counts were normal and there were no signs of inflammatory syndrome. An echocardiogram was performed on Study Day 185 (b) (6) and with the following findings reported: normal left ventricle size with normal systolic function (LVEF=69%), dilated left aorta

with indexed volume of 54 ml/m, minimal mitral leak, no aortic valve disease, normal right cavities, systolic pulmonary artery pressure = 43 mmHg, and normal sized abdominal and thoracic aorta. In light of this asymptomatic hypertensive episode, the subject's antihypertensive treatment was changed by introducing diuretic treatment with a combination of Amlor/Fludex (natrixam). Improvements in blood pressure control were noted during hospitalization, thus the subject was discharged on Study Day 186 (b) (6) with the following treatment: Natrixam, Azilect, Lansoprazole, Mantadix, Seroplex, Stalevo, Vesciare and Neupro. The subject's medical history includes high blood pressure, depression, upper limb fracture, rib fracture, hiatus hernia, osteoporosis, and urinary tract infection. The subject's concomitant medications included: loxen (nicardipine hydrochloride), omeprazole (omeprazole), paracetamol (paracetamol), vesicare (solifenacin succinate), mantadix (amantadine hydrochloride), neupro (rotigotine), stalevo (carbidopa, entacapone, levodopa), seroplex (escitalopram oxalate), azilect (rasagiline mesylate), and pantopraxole (pantoprazole sodium sesquihydrate). The subject continued taking the study medication and completed the study.

Treatment Group: ***Amantadine HCl ER 320 mg*** *Country: Germany*
Subject (b) (6): Osteoarthritis
Subject (b) (6), a 55-year-old White female with a history of Parkinson's disease with levodopa-induced dyskinesia, signed informed consent on (b) (6) and was randomized to the Amantadine HCl ER 320 mg group on (b) (6). On Study Day 76 (b) (6) the subject experienced worsening of arthritis (rizarthrosis) of her left thumb. The subject was hospitalized on Study Day 76 (b) (6) and surgery was performed on Study Day 77 (b) (6). Medications to treat the event were Voltaren resinat, Pantozol, and Clexane. The left thumb was placed in a cast following surgery through Study Day 120 (b) (6). The subject was discharged from the hospital on Study Day 80 (b) (6). Occupational therapy was started on Study Day 127 (b) (6) and continued through Study Day 133 (b) (6). The subject's laboratory and other diagnostic test results were not provided. The subject's medical history included anemia, menopausal symptoms, thyroid disorder, tendon operation, trigger finger, allergy to wasp sting, allergic rhinitis, benign prostatic hyperplasia, hypercholesterolemia, hyperkeratosis, hypertension, microcytic anemia, osteoporosis, and arthritis (rizarthrosis) of the left thumb. Concomitant medications included amoxicillin, cefuroxin, piribedil, enoxaparin sodium, ergotherapy, fenseven, ibuprofen, levothyroxine, Madopar, pantoprazole sodium sesquihydrate, flucloxacillin, tolcapone, and diclofenac resinate. The study product was not changed as a result of this event and the subject completed the study.

Treatment Group: ***Amantadine HCl ER 320 mg*** *Country: Germany*
Subject (b) (6): Constipation
Subject (b) (6) a 67-year-old White female with a history of Parkinson's disease with levodopa-induced dyskinesia, signed informed consent on (b) (6) and was randomized to the Amantadine HCl ER 320 mg group on (b) (6). On Study Day 98 (b) (6), the subject experienced worsening constipation and stomach ache. The subject was hospitalized on Study Day 98 (b) (6). A bowel irrigation procedure was performed and Resolor (prucalopride succinate) was given to treat the event. The subject's laboratory test results were normal. A chest X-ray was performed

on Study Day 99 (b) (6) with the finding of emphysema, apical pleural thickening with discrete alterations possibly related to previous infection/scarring. A colonoscopy was performed on Study Day 100 (b) (6) with normal findings except for posterior prolapse and hemorrhoids. Magnetic resonance imaging (MRI) of the abdomen performed on Study Day 101 (b) (6) with the finding of an unspecific tumor within or behind the pancreas and a possible cyst of the pancreas tail. The hospital report suggested a re-evaluation (MRI of abdomen) in 6 months. The subject was discharged from the hospital on Study Day 102 (b) (6). The subject's medical history included chronic constipation with fluctuating severity, muscle spasms, postmenopause, and hypertension. Concomitant medications for the subject included magnesium oxide, ropinirole hydrochloride, tolcapone, and acetylsalicylic acid. There was no interruption of study medication as a result of this event and the subject completed the study.

Treatment Group: ***Amantadine HCl ER 320 mg*** *Country: Germany*
Subject (b) (6) Hemorrhoids
Subject (b) (6), a 67-year-old White female with a history of Parkinson's disease with levodopa-induced dyskinesia, signed informed consent on (b) (6) and was randomized to the Amantadine HCl ER 320 mg group on (b) (6). On Study Day 104 (b) (6), the subject experienced moderate anorectal bleeding and was admitted to the hospital. Upon examination by a physician, it was determined that the bleeding was caused by hemorrhoids. The subject's diagnostic test results included a colonoscopy performed on Study Day 105 (b) (6) with the findings of a small ulceration of the left colonic flexure with no signs of malignancy. Resolor (prucaloprid) was administered to treat the event. The subject was discharged from the hospital on (b) (6). The subject's medical history included chronic constipation with fluctuating severity, muscle spasms, postmenopause, and hypertension. Concomitant medications included magnesium oxide, ropinrole hydrochloride, and tolcapone. There was no interruption of study medication as a result of this event and the subject completed the study.

Treatment Group: ***Amantadine HCl ER 320 mg*** *Country: France*
Subject (b) (6): Vestibular neuronitis
Subject (b) (6), a 64-year-old female (race not provided) with a history of Parkinson's disease with levodopa-induced dyskinesia, signed informed consent on (b) (6) and was randomized to the Amantadine HCl ER 320 mg group on (b) (6). On Study Day 149 (b) (6)), the subject experienced rotatory vertigo with phonophobia and without photophobia. The subject was hospitalized from Study Day 149 (b) (6) to Study Day 153 (b) (6). Prior to admission, the subject experienced 48 hours of rotatory vertigo with increasing intensity and intractable vomiting along with neck pain radiating to the vertex, and no fever. At admission, subject's temperature was 36.2°C, blood pressure was 145/70 mmHg, and heart rate was 70 beats/min. The subject had nausea, tinnitus, left ear hearing loss, and a right-beating nystagmus. There were no focal neurological signs. The subject did not experience signs of facial paralysis. The pupils were reactive and symmetrical. The subject's laboratory test results were normal. The results from the electrocardiogram included: irregular sinus rhythm with a heart rate of 66 beats/min, a

normal axis, normal QRS complexes, and no significant repolarization disorder. A brain scan did not show any signs of acute ischemia or hemorrhagic lesions. Medications to treat the event included: Tanganil and Primperan. Concomitant medications included: azilect (rasagiline mesylate), sinemet lp (carbidopa, levodopa), stalevo (carbidopa, entacapone, levodopa), requip lt (ropinirole hydrochloride), requip (ropinirole hydrochloride), xanax (alprazolam), domperidone (domperidone), alprazolam (alprazolam), bisoprolol (bisoprolol), dafalgan (paracetamol), gutron (midodrine hydrochloride), and sinemet (carbidopa, levodopa). The subject's medical history included anxiety, vertigo positional, gastritis, hypertension, epistaxis, vomiting, menopause, and cervicobrachial syndrome. Study medication was not interrupted and the subject completed the study.

Treatment Group: ***Amantadine HCl ER 320 mg*** *Country: Canada*
Subject (b) (6)*: Cranial nerve palsies multiple*
Subject (b) (6)*, a 69-year-old White female with a history of Parkinson's disease with levodopa-induced dyskinesia, signed informed consent on* (b) (6) *and was randomized to the Amantadine HCl ER 320 mg group on* (b) (6)*. On Study Day 83* (b) (6)*, the subject experienced severe 6th and 7th nerve palsy. The subject was hospitalized on Study Day 84* (b) (6) *because she developed double vision for a few days. After developing double vision, the subject went to see a neuro-ophthalmologist; in addition to the double vision, the physician reported the subject had right facial weakness and drooping. The diagnostic test included magnetic resonance imaging (MRI) of the head with contrast on Study Day 90* (b) (6)*. The MRI report included: an increased enhancement of facial nerve labyrinthine segment and intra-canalicular components which were more pronounced on the left than the right side. There was also a finding of left middle cerebral artery (MCA) bifurcation aneurysm (8 X 5 mm). A spinal tap was performed on Study Day 92* (b) (6) *and the findings were: normal glucose, elevated protein (652 units not provided), normal cell count; cerebrospinal fluid culture was negative for herpes simplex virus, and varicella-zoster virus, and polymerase chain reaction (PCR) was negative. The subject was diagnosed with 6th and 7th nerve palsy and was treated with prednisone and underwent occupational therapy. The subject was released from the hospital on Study Day 94* (b) (6) *The subject's medical history included hypertension, depression, and arthritis.*
Concomitant medications included amlodipine, levodopa, pregabalin, quetiapine, sinemet, and stalevo. Study medication was not interrupted and the subject completed the study.

REVIEWER COMMENT:

None of the SAEs discussed above appear to be drug related.

7.3.3 Dropouts and/or Discontinuations

A listing of subjects with adverse events that led to dropout/discontinuation for combined Phase 3 studies is presented in Table 19, below.

Table 19 Listing of Subjects With Adverse Events That Led to Study Drug Discontinuation – Study OS320-3005 and Study OS320-3006 – Phase 3 Safety Population

Treatment Subject No.	Adverse Event Preferred Term	Serious Adverse Event
Amantadine HCl ER 320		
(b) (6)	hallucination, visual vision	no no
	dysuria	no
	anxiety balance disorder diplopia dizziness dry eye hallucination remor	no no no no no no no
	depression	no
	hallucination orthostatic	no no
	hallucination	no
	reezing phenomenon	no
	edema peripheral	no
	hallucinations, mixed	no
	confusional state	no no
	hallucination edema peripheral	no no
	hallucination, visual	no
	hroat tightness	no
	edema peripheral	no

Treatment Subject No.	Adverse Event Preferred Term	Serious Adverse Event
Amantadine HCl ER 240		
(b) (6)	dizziness dyspnea orthostatic hypotension	no no no
	hallucination, visual nightmare	no no
	akinesia muscle rigidity	no no
	hallucination, visual megacolon somnolence	no yes no
	dyskinesia (increased)	no
	confusional state	no
	hallucination, visual	no
	hypotension	no
	Parkinson's disease (deterioration)	no
	confusional state	no
Placebo		
(b) (6)	hallucination tachycardia	no no
	dyskinesia (increased)	no
	umbar spinal stenosis	yes

(b) (6)	hypersexuality	no
	impulse-control disorder	yes
	brain abscess	yes
	dyskinesia (increased)	no
	edema peripheral	no
	gait disturbance	no
	general physical health deterioration	no
	mobility decreased	no
	tension headache	no

Source Sponsor

REVIEWER COMMENT:

The majority of subjects who discontinued in drug treatment groups experienced hallucinations/confusional state. Adverse event of hallucinations/confusional state are known to occur with the use of amantadine products and are included in the label for the RLD. Subjects who discontinued in the placebo group experienced a variety of adverse events including worsening PD and/or dyskinesias.

7.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest were identified based on known amantadine side effects. The adverse events of special interest included hallucinations, sleep disorders, orthostatic hypotension, impulse control disorders, and livedo reticularis.

A summary of TEAEs of special interest by preferred term in Phase 3 studies is presented in Table 20, below.

Table 20 Summary of Treatment-Emergent Adverse Events of Special Interest by Preferred Term – Study OS320-3005 and Study OS320-3006 – Phase 3 Safety Population

System Organ	Amantadine HCl ER 320 mg (N=75) n (%)	Amantadine HCl ER 240 mg (N=75) n (%)	Placebo (N=72) n (%)	All Subjects Combined (N=222)
Psychiatric disorders	23 (30.7)	18 (24.0)	13 (18.1)	54 (24.3)
Abnormal dreams	1 (1.3)	1 (1.3)	0 (0.0)	2 (0.9)
Hallucination (combined terms)*	10 (13.3)	5 (6.7)	3 (4.2)	18 (8.1)
Hallucination	6 (8.0)	1 (1.3)	2 (2.8)	9 (4.1)
Hallucination, auditory	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Hallucination, visual	3 (4.0)	4 (5.3)	1 (1.4)	8 (3.6)
Impulse-control disorder	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.5)
Impulsive behavior	1 (1.3)	0 (0.0)	1 (1.4)	2 (0.9)
Insomnia	2 (2.7)	2 (2.7)	2 (2.8)	6 (2.7)
Middle insomnia	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Nightmare	1 (1.3)	2 (2.7)	0 (0.0)	3 (1.4)

Obsessive-compulsive disorder	1 (1.3)	2 (2.7)	0 (0.0)	3 (1.4)
Rapid eye movements sleep	1 (1.3)	0 (0.0)	1 (1.4)	2 (0.9)
Sleep attacks	1 (1.3)	0 (0.0)	1 (1.4)	2 (0.9)
Sleep disorder	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Skin and subcutaneous disorders	1 (1.3)	3 (4.0)	3 (4.2)	7 (3.2)
Livedo reticularis	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Vascular disorders	9 (12.0)	9 (12.0)	5 (6.9)	23 (10.4)
Orthostatic hypotension	3 (4.0)	2 (2.7)	3 (4.2)	8 (3.6)

* Includes hallucination of all types by combining the preferred terms 'hallucination', 'hallucination, auditory', 'hallucination, visual'. Treatment-emergent adverse events were defined as adverse events that occurred on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing. N = the denominator for calculating percentages, defined as the number of subjects in the Phase 3 Safety Population. n = number of subjects in each treatment group who reported a TEAE; specific although a subject may have had the same TEAE more than once, the specific TEAE was counted once for each subject.

Source Sponsor

REVIEWER COMMENT:

Hallucination (combined term) during the Phase 3 studies was reported by a total of 18 subjects (8.1%): 10 subjects in the Amantadine HCl ER 320 mg group, 5 subjects in the Amantadine HCl ER 240 mg group, and 3 subjects in the Placebo group. Insomnia was reported by a total of 6 (2.7%) subjects: 2 subjects in the Amantadine HCl ER 320 mg group, 2 subjects in the Amantadine HCl ER 240 mg group, and 2 subjects in the Placebo group. A total of 8 (3.6%) subjects had orthostatic hypotension: 3 subjects in the Amantadine HCl ER 320 mg group, 2 subjects in the Amantadine HCl ER 240 mg group, and 3 subjects in the Placebo group. One subject in the Amantadine HCl ER 320 mg group had livedo reticularis.

A total of 3 (1.4%) subjects had obsessive-compulsive disorder: 1 subject in the Amantadine HCl ER 320 mg group and 2 subjects in the Amantadine HCl ER 240 mg group. One subject in the Amantadine HCl ER 320 mg group and 1 subject in the Placebo group had impulsive behavior. In addition, 1 subject in the Placebo group had impulse-control disorder.

Each of these adverse event categories are listed in the Symmetrel label as well as other amantadine products (Gocovri.)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

TEAEs in >2%of subjects in any treatment group is summarized in the sponsor's table below.

Table 21 Summary of Treatment-Emergent Adverse Events (>2% of Subjects in Any Treatment Group) by System Organ Class and Preferred Term – Study OS320-3005 and Study OS320-3006 – Phase 3 Safety Population

System Organ Class Preferred Term	Amantadine HCl ER 320 mg (N=75) n (%)	Amantadine HCl ER 240 mg (N=75) n (%)	Placebo (N=72) n (%)	All Subjects Combined (N=222) n (%)
Gastrointestinal disorders	**17 (22.7)**	**13 (17.3)**	**9 (12.5)**	**39 (17.6)**
Abdominal pain	0 (0.0)	2 (2.7)	0 (0.0)	2 (0.9)
Abdominal pain upper	0 (0.0)	2 (2.7)	0 (0.0)	2 (0.9)
Constipation	4 (5.3)	3 (4.0)	2 (2.8)	9 (4.1)
Dry mouth	7 (9.3)	5 (6.7)	0 (0.0)	12 (5.4)
Nausea	7 (9.3)	6 (8.0)	3 (4.2)	16 (7.2)
Vomiting	2 (2.7)	1 (1.3)	0 (0.0)	3 (1.4)
General disorders and administration site conditions	**14 (18.7)**	**9 (12.0)**	**8 (11.1)**	**31 (14.0)**
Fatigue	4 (5.3)	1 (1.3)	4 (5.6)	9 (4.1)
Gait disturbance	1 (1.3)	1 (1.3)	2 (2.8)	4 (1.8)
edema peripheral	8 (10.7)	2 (2.7)	1 (1.4)	11 (5.0)
Infections and infestations	14 (18.7)	13 (17.3)	8 (11.1)	35 (15.8)
Bronchitis	2 (2.7)	0 (0.0)	1 (1.4)	3 (1.4)
Nasopharyngitis	4 (5.3)	2 (2.7)	0 (0.0)	6 (2.7)
Sinusitis	1 (1.3)	0 (0.0)	2 (2.8)	3 (1.4)
Urinary tract infection	4 (5.3)	4 (5.3)	3 (4.2)	11 (5.0)
Injury, poisoning and procedural complications	**5 (6.7)**	**6 (8.0)**	**7 (9.7)**	**18 (8.1)**
Fall	5 (6.7)	5 (6.7)	6 (8.3)	16 (7.2)
Investigations	4 (5.3)	8 (10.7)	6 (8.3)	18 (8.1)
Bacterial test positive	0 (0.0)	2 (2.7)	1 (1.4)	3 (1.4)
Blood cholesterol increased	1 (1.3)	2 (2.7)	0 (0.0)	3 (1.4)
Hemoglobin urine present	2 (2.7)	1 (1.3)	1 (1.4)	4 (1.8)
Neutrophil count increased	0 (0.0)	2 (2.7)	0 (0.0)	2 (0.9)
Metabolism and nutrition disorders	**3 (4.0)**	**1 (1.3)**	**3 (4.2)**	**7 (3.2)**
Decreased appetite	2 (2.7)	1 (1.3)	0 (0.0)	3 (1.4)

* Preferred term included in this table without meeting the ≥2.0% threshold (i.e., for most common TEAEs) based on a full presentation of all terms for hallucination.
Treatment-emergent adverse events were defined as adverse events that occurred on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing. N = the denominator for calculating percentages, defined as the number of subjects in the Phase 3 Safety Population. n = number of subjects in each treatment group who reported a TEAE; specific although a subject may have

System Organ	Amantadine HCl ER 320 mg (N=75) n (%)	Amantadine HCl ER 240 mg (N=75) n (%)	Placebo (N=72) n (%)	All Subjects Combined (N=222)
Musculoskeletal and connective	**16 (21.3)**	**15 (20.0)**	**6 (8.3)**	**37 (16.7)**
Arthralgia	3 (4.0)	4 (5.3)	0 (0.0)	7 (3.2)
Back pain	2 (2.7)	2 (2.7)	0 (0.0)	4 (1.8)
Muscle spasms	3 (4.0)	3 (4.0)	1 (1.4)	7 (3.2)
Osteoarthritis	2 (2.7)	1 (1.3)	0 (0.0)	3 (1.4)
Pain in extremity	2 (2.7)	1 (1.3)	2 (2.8)	5 (2.3)
Nervous system disorders	**17 (22.7)**	**27 (36.0)**	**18 (25.0)**	**62 (27.9)**
Akinesia	0 (0.0)	2 (2.7)	1 (1.4)	3 (1.4)
Dizziness	5 (6.7)	4 (5.3)	0 (0.0)	9 (4.1)
Dyskinesia	4 (5.3)	8 (10.7)	6 (8.3)	18 (8.1)
Dystonia	2 (2.7)	0 (0.0)	0 (0.0)	2 (0.9)
Headache	3 (4.0)	3 (4.0)	1 (1.4)	7 (3.2)

Parkinson's disease	0 (0.0)	3 (4.0)	1 (1.4)	4 (1.8)
Sciatica	1 (1.3)	0 (0.0)	2 (2.8)	3 (1.4)
Somnolence	0 (0.0)	5 (6.7)	6 (8.3)	11 (5.0)
Psychiatric disorders	**23 (30.7)**	**18 (24.0)**	**13 (18.1)**	**54 (24.3)**
Anxiety	3 (4.0)	2 (2.7)	2 (2.8)	7 (3.2)
Confusional state	2 (2.7)	4 (5.3)	1 (1.4)	7 (3.2)
Depression	1 (1.3)	2 (2.7)	2 (2.8)	5 (2.3)
Hallucination	6 (8.0)	1 (1.3)	2 (2.8)	9 (4.1)
Hallucination, auditory*	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Hallucination, visual	3 (4.0)	4 (5.3)	1 (1.4)	8 (3.6)
Illusion	0 (0.0)	2 (2.7)	0 (0.0)	2 (0.9)
Insomnia	2 (2.7)	2 (2.7)	2 (2.8)	6 (2.7)
Nightmare	1 (1.3)	2 (2.7)	0 (0.0)	3 (1.4)
Obsessive-compulsive disorder	1 (1.3)	2 (2.7)	0 (0.0)	3 (1.4)

* Preferred term included in this table without meeting the ≥2.0% threshold (i.e., for most common TEAEs) based on a full presentation of all terms for hallucination.
Treatment-emergent adverse events were defined as adverse events that occurred on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing. N = the denominator for calculating percentages, defined as the number of subjects in the Phase 3 Safety Population. n = number of subjects in each treatment group who reported

System Organ	Amantadine HCl ER 320 mg (N=75) n (%)	Amantadine HCl ER 240 mg (N=75)	Placebo (N=72) n (%)	All Subjects Combined (N=222)
Renal and urinary disorders	**4 (5.3)**	**5 (6.7)**	**1 (1.4)**	**10 (4.5)**
Dysuria	2 (2.7)	1 (1.3)	0 (0.0)	3 (1.4)
Vascular disorders	**9 (12.0)**	**9 (12.0)**	**5 (6.9)**	**23 (10.4)**
Hypertension	5 (6.7)	2 (2.7)	0 (0.0)	7 (3.2)
Hypotension	1 (1.3)	3 (4.0)	1 (1.4)	5 (2.3)
Orthostatic hypotension	3 (4.0)	2 (2.7)	3 (4.2)	8 (3.6)

* Preferred term included in this table without meeting the ≥2.0% threshold (i.e., for most common TEAEs) based on a full presentation of all terms for hallucination.
Treatment-emergent adverse events were defined as adverse events that occurred on or after the first dose of study drug administration or any pre-existing event which worsened in severity after dosing. N = the denominator for calculating percentages, defined as the number of subjects in the Phase 3 Safety Population. n = number of subjects in each treatment group who reported

Source Sponsor

The same analysis was performed by the clinical review team and is presented in Table 22.

Table 22 Studies 3005 and 3006 Treatment Emergent Adverse Reaction ≥2% All Amantadine ER

Body System or Organ Class	Dictionary-Derived Term	**240 mg N=75 %**	**320 mg N=75 %**	**Placebo N=72 %**	**ALL Amantadine ER N=150 %**
Gastrointestinal disorders	Nausea	8	9	4	9
Gastrointestinal disorders	Dry mouth	7	9	0	8
Nervous system disorders	Dyskinesia	11	5	8	8
General disorders and administration site conditions	Oedema peripheral	3	11	1	7

Injury, poisoning and procedural complications	Fall	7	7	8	7
Nervous system disorders	Dizziness	5	7	0	6
Psychiatric disorders	Hallucination[1]	9	13	4	17
Vascular disorders	Hypertension	3	7	0	5
Gastrointestinal disorders	Constipation	4	5	3	5
Infections and infestations	Urinary tract infection	5	5	4	5
Musculoskeletal and connective tissue disorders	Arthralgia	5	4	0	5
Infections and infestations	Nasopharyngitis	3	5	0	4
Nervous system disorders	Headache	4	4	1	4
Musculoskeletal and connective tissue disorders	Muscle spasms	4	4	1	4
Psychiatric disorders	Confusional state	5	3	1	4
General disorders and administration site conditions	Fatigue	1	5	6	3
Psychiatric disorders	Anxiety	3	4	3	3
Vascular disorders	Orthostatic hypotension	3	4	4	3
Psychiatric disorders	Insomnia	3	3	3	3
Musculoskeletal and connective tissue disorders	Back pain	3	3	0	3
Vascular disorders	Hypotension	4	1	1	3
Nervous system disorders	Somnolence	7	0	8	3
Gastrointestinal disorders	Vomiting	1	3	0	2
Musculoskeletal and connective tissue disorders	Pain in extremity	1	3	3	2
Musculoskeletal and connective tissue disorders	Osteoarthritis	1	3	0	2
Investigations	Haemoglobin urine present	1	3	1	2

Renal and urinary disorders	Dysuria	1	3	0	2
Metabolism and nutrition disorders	Decreased appetite	1	3	0	2
Psychiatric disorders	Depression	3	1	3	2
Psychiatric disorders	Nightmare	3	1	0	2
Psychiatric disorders	Impulse control disorder[2]	3	1	3	3
Investigations	Blood cholesterol increased	3	1	0	2
Nervous system disorders	Parkinson's disease	4	0	1	2

1=Hallucinations, Hallucinations visual, hallucinations auditory and Illusions
2=Obsessive-compulsive disorder, Hypersexuality, Libido increased, Impulse control disorder
Source: Clinical Review Team

REVIEWER COMMENT:

In both the sponsor's and clinical review team's analysis, the most common adverse events were related to psychiatric, nervous system, GI system and musculoskeletal disorders. There does not appear to be a dose response for any of the adverse events by SOC or PT. The adverse events experienced by subjects in the Phase 3 studies are included in the label for Symmetrel.

7.4.2 Laboratory Findings

Mean changes in all laboratory parameters were evaluated from baseline to Day 14 (Visit 4), Day 98 (Visit 7), and Day 168 (Visit 9), and the Taper Period. Mean changes in safety laboratory parameters were not clinically meaningful for any of the treatment groups. There were no consistent treatment-related or dose-related trends in mean changes in safety laboratory parameters were noted for the Phase 3 Safety Population.

7.4.3 Vital Signs

Mean changes in temperature, respiration, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate from baseline to Day 42 (Visit 5), Day 70 (Visit 6), Day 98 (Visit 7), Day 168 (Visit 9), and the Taper Period were evaluated for the Phase 3 Safety Population. All treatment groups had small mean changes in vital

signs over time.

In addition, the numbers and percentages of subjects with abnormal DBP or SBP at any time point during the Phase 3 studies were also summarized (Tables 23 and 24.)

Table 23

Osmotica Pharmaceutical Corp.
Summary of Safety
Analysis: Final

Table 8.2
Abnormal Vital Signs by Visit and Treatment Group
(Phase 3 Safety Population)

Category (SI Unit)	Visit	Amantadine HCl ER Tablets 320 mg/day Group (N=75)	Amantadine HCl ER Tablets 240 mg/day Group (N=75)	Placebo (N=72)	All Patients Combined (N=222)
Diastolic Blood Pressure(mmHg) (N=4)	Visit 1 (Screening)	0	1 (1.3)	0	1 (0.5)
	Visit 2 (Baseline)	0	1 (1.3)	0	1 (0.5)
	Visit 4 (Titration)	0	1 (1.3)	1 (1.4)	2 (0.9)
	Visit 5 (Maintenance)	0	0	0	0
	Visit 6 (Maintenance)	0	0	0	0
	Visit 7 (Maintenance)	0	0	1 (1.4)	1 (0.5)
	Visit 8 (Maintenance)	0	0	0	0
	Visit 9 (Maintenance)	0	0	0	0
	Taper Period	0	1 (1.3)	1 (1.4)	2 (0.9)

The denominator for calculating percentages is the number of patients in the OS320-3005 and OS320-3006 Safety Populations.
Note: only measurements of supine vital signs were summarized.
Visit 8 (Maintenance) and Visit 9 (Maintenance) are for study OS320-3006 only.
Taper Period includes Visit 9 for study OS320-3005 and Visit 11 for study OS320-3006.

Table 24

Osmotica Pharmaceutical Corp.
Summary of Safety
Analysis: Final

Table 8.2
Abnormal Vital Signs by Visit and Treatment Group
(Phase 3 Safety Population)

Category (SI Unit)	Visit	Amantadine HCl ER Tablets 320 mg/day Group (N=75)	Amantadine HCl ER Tablets 240 mg/day Group (N=75)	Placebo (N=72)	All Patients Combined (N=222)
Systolic Blood Pressure(mmHg) (N=4)	Visit 1 (Screening)	0	1 (1.3)	0	1 (0.5)
	Visit 2 (Baseline)	0	1 (1.3)	0	1 (0.5)
	Visit 4 (Titration)	0	1 (1.3)	1 (1.4)	2 (0.9)
	Visit 5 (Maintenance)	0	0	0	0
	Visit 6 (Maintenance)	0	0	0	0
	Visit 7 (Maintenance)	0	0	1 (1.4)	1 (0.5)
	Visit 8 (Maintenance)	0	0	0	0
	Visit 9 (Maintenance)	0	0	0	0
	Taper Period	0	1 (1.3)	1 (1.4)	2 (0.9)

The denominator for calculating percentages is the number of patients in the OS320-3005 and OS320-3006 Safety Populations.
Note: only measurements of supine vital signs were summarized.
Visit 8 (Maintenance) and Visit 9 (Maintenance) are for study OS320-3006 only.
Taper Period includes Visit 9 for study OS320-3005 and Visit 11 for study OS320-3006.

Few subjects had abnormal vital signs and there were no meaningful differences among the treatment groups in the numbers of subjects with abnormal vital signs.

7.4.4

Electrocardiograms (ECGs)Six patients had a normal QT interval at screening but developed an abnormal QT during the study (QT ≥ 450 msec) included one patient in the amantadine ER 320 mg group, three in the amantadine 240 mg group and two in the placebo group. None of abnormalities were clinically significant in the opinion of the investigator/applicant. Four patients had an QTcF (Fridericia) that was normal at screening but was abnormal (≥ 60 msec) during the study, three were in the placebo group and one was in the amantadine ER 240 mg group.

The QT interval abnormalities did not suggest that amantadine ER was associated with an increased incidence of QT or QTcF prolongation. Higher doses of amantadine ER 320 mg/day was not associated with an increased frequency of prolonged QT interval. Only two-third of patients treated with amantadine ER had an ECG by Visit 7. Less than half of the patients randomized in study 3006 (N=133) had an ECG at Visit 9 (End of Study).

Creatinine Clearance

The subgroup with baseline CrCl <90 mL/min had a larger percentage of subjects with

TEAEs in the renal and urinary disorders system organ class compared to the subgroup with baseline CrCl ≥90 mL/min (8.4% vs 0.9%). Subjects with CrCl <90 mL/min also had a greater incidence of fatigue (6 [5.6%] vs 3 [2.6%] subjects), peripheral edema (8 [7.5%] vs 3 [2.6%] subjects), dizziness (6 [5.6%] vs 3 [2.6%] subjects), anxiety (6 [5.6%] vs 1 [0.9%] subjects), and hypertension (5 [4.7%] vs 2 [1.8%] subjects) relative to subjects with CrCl ≥90 mL/min.

Age

Subjects greater than 65 years of age had more adverse events of dizziness (7 [5.6%] vs 2 [2.1%] subjects), accidental fall (12 [9.5%] vs 4 [4.2%] subjects), and hypertension (6 [4.8%] vs 1 [1.0%] subject) compared with subjects 30 to 64 years of age. All 11 cases of peripheral edema occurred in the subgroup of subjects 65 to 85 years of age with the majority of these cases occurring in subjects treated with Amantadine HCl ER 320 mg (8 subjects).

The higher frequency of hallucination and other adverse events experienced by subjects >65 years and those with mild renal impairment may have been due to the comparatively higher amantadine plasma concentrations in these subjects. Safety information from the pooled Phase 3 safety database for Amantadine HCl ER therefore supports recommendations in the current prescribing information for elderly patients and those with impaired renal function (Upsher-Smith Laboratories, Inc.; 2014).

7.7 Additional Submissions / Safety Issues

Summary of Adverse Events in the Amantadine Package Insert

The adverse reactions for the amantadine HCl tablet are reported in the approved amantadine package insert (Upsher-Smith Laboratories, Inc.). Adverse events most commonly (5-10%) associated with use of amantadine include nausea, dizziness, and insomnia. Other known adverse events that are reported less frequently (1-5%) include depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea, and fatigue. Infrequent (0.1-1%) adverse reactions include congestive heart failure, psychosis, urinary retention, dyspnea, skin rash, vomiting, weakness, slurred speech, euphoria, thinking abnormality, amnesia, hyperkinesia, 2 hypertension, decreased libido, and visual disturbance, including punctate subepithelial or other corneal opacity, corneal edema, decreased visual acuity, sensitivity to light, and optic nerve palsy. Those adverse reactions designated as rare (<0.1%) include convulsion, leukopenia, neutropenia, eczematoid dermatitis, oculogyric episodes, suicidal attempt, suicide, and suicidal ideation.

Safety of Amantadine from the Published Literature

A Phase 2/3 study on a different extended release formulation of amantadine HCl was recently reported (Pahwa, 2015). This was an 8-week randomized, double-blind, placebo- controlled trial in PD patients with LID. A total of 83 patients were randomized evenly to treatment with 260 mg, 340 mg, 420 mg ER amantadine and placebo. During the study, adverse events were experienced by 80% of patients in the 260 mg group, 95% in the 340 mg group, 90% in the 420 mg group, and 82% in the placebo group. Adverse events that occurred in >10% or in more than two patients are presented in the table below.

Adverse Events (>10% or >2 patients in any treatment group)

		amantadine extended-release capsule (ADS-5102)		
Adverse Events n (%)	**Placebo (n=22)**	**260 mg (n=20)**	**340 mg (n=21)**	**420 mg (n=20)**
Constipation	2 (9.1)	7 (35.0)	5 (23.8)	3 (15.0)
Dizziness	1 (4.5)	3 (15.0)	6 (28.6)	3 (15.0)
Hallucination	0 (0.0)	4 (20.0)	5 (23.8)	4 (20.0)
Dry mouth	0 (0.0)	3 (15.0)	4 (19.0)	2 (10.0)
Fall	3 (13.6)	1 (5.0)	3 (14.3)	3 (15.0)
Confusion	1 (4.5)	1 (5.0)	3 (14.3)	2 (10.0)
Headache	1 (4.5)	1 (5.0)	3 (14.3)	1 (5.0)
Nausea	1 (4.5)	1 (5.0)	3 (14.3)	1 (5.0)
Asthenia	1 (4.5)	0 (0.0)	3 (14.3)	1 (5.0)
Source: Pahwa et al 2015				

There were no unexpected adverse events reported during the study. Hallucinations (mostly visual) were reported in a total of 13 patients treated with amantadine ER including (20.0%) in the 260 mg group, 5 (23.8%) in the 340 mg group, and 4 (20.0%) in the 420 mg group; no patients in the placebo group had hallucination. Seven SAEs were reported in patients. One patient in the 260 mg group had lobar pneumonia and mental status changes, and 4 patients in the 420 mg group had skin hypersensitivity and psychotic disorder, urinary tract infection, lower extremity cellulitis, and subdural hematoma. Laboratory results and vital signs were not different across treatment groups.

A review of the published literature identified eight additional randomized, double-blind, placebo-controlled studies that evaluated amantadine in a population of PD patients (Ory-Magne 2014; Wolf 2010; da Silva-Junior 2005; Snow 2000; Luginger 2000; Metman 1998; Metman 1999; Thomas; 2004). The primary focus of these studies was the efficacy of amantadine. Published articles for two of the eight studies provided detailed safety results, which are presented below (Ory-Magne 2014; Wolf 2010). Articles for two of the studies reported that no adverse events occurred during the conduct of the trials (da Silva-Junior 2005; Snow 2000), and the remaining four studies did not report safety information within the respective published articles (Luginger 2000; Metman 1998; Metman 1999; Thomas; 2004).

The study conducted by Ory-Magne et al (2014) was a multi-center, randomized, double- blind, placebo controlled study to assess the effects of withdrawing

amantadine in dyskinetic patients with PD over a 3-month period. In total, 56 patients who had been receiving amantadine treatment for ≥ 6 months at doses ≥200 mg/day prior to entering the study were randomized evenly to amantadine or placebo and assessed for safety. Patients randomized to the amantadine group continued with their amantadine treatment while patients randomized to the placebo group were switched to treatment with placebo (down-titrated by 100 mg every two days). A total of 138 adverse events were reported during the 3-month study with the most frequent adverse events presented in the table below. A total of 4 SAEs were reported: 3 patients in the placebo group and 1 patient in the amantadine group.

Adverse events reported by at least 5% of patients

Adverse Events n (%)	**Discontinuing group (Placebo, n= 29)**	**Continuing group (Amantadine, n=27)**
Worsening of dyskinesia	19 (34)	7 (12)
Worsening of parkinsonism	8 (14)	7 (12)
Pain	4 (7)	3 (5)
Fatigue	2 (4)	3 (5)
Sweat, flushing	1 (2)	2 (4)
Asthenia	2 (4)	2 (4)
Nausea, vomiting	2 (4)	2 (4)
Drowsiness	2 (4)	2 (4)
Cephalgia	1 (2)	2 (4)
Fall	0 (0)	3 (5)
Cough	2 (4)	1 (2)
Source: Ory-Magne et al 2014		

Overall Conclusions

The adverse events reported for the Phase 3 studies were consistent with the expected adverse events for amantadine, based on the approved amantadine HCl oral syrup label and published literature. There was no new or unexpected safety issues relative to the once daily administration of Amantadine HCl ER Tablets. However, as noted in 6.1.3, Subject Disposition, there were a significant number of drop outs and discontinuations in both Phase 3 studies, leading to a large amount of missing data, which could affect the interpretability of the safety results. Therefore, the approval of the drug will rely on the safety data from the RLD as well as the literature review conducted by the sponsor ,which showed that once daily treatment with Amantadine HCl ER Tablets at 240 mg, and 320 mg dose was safe and well tolerated by PD subjects.

The adverse events reported were consistent with the expected adverse events for amantadine, based on the approved amantadine HCl oral syrup label and published literature. There was no new or unexpected safety issues relative to the once daily administration of Amantadine HCl ER Tablets.

9 Appendices

9.1 Labeling Recommendations

Recommended labeling for Sections 5 and 6 are outlined below:

5 WARNINGS AND PRECAUTIONS

5.1 Falling Asleep During Activities of Daily Living and Somnolence

Patients treated with amantadine have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes has resulted in accidents. Patients may not perceive warning signs, such as excessive drowsiness, or they may report feeling alert immediately prior to the event.

Before initiating treatment with OSMOLEX ER, advise patients of the potential to develop drowsiness and specifically ask about factors that may increase the risk for somnolence with OSMOLEX ER, such as concomitant sedating medications, alcohol, or the presence of a sleep disorder. If a patient develops daytime sleepiness or episodes of falling asleep during activities that require full attention (e.g., driving a motor vehicle, conversations, eating), OSMOLEX ER should be ordinarily be discontinued.

If a decision is made to continue OSMOLEX ER, advise patients not to drive and to avoid other potentially dangerous activities that might result in harm if they become somnolent. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living or daytime somnolence.

5.2 Suicidality and Depression

Suicide, suicide attempts, and suicidal ideation have been reported in patients with and without prior history of psychiatric illness while treated with amantadine. Amantadine can exacerbate psychiatric symptoms in patients with a history of psychiatric disorders or substance abuse.

Monitor patients for depression, including suicidal ideation or behavior. Prescribers should consider whether the benefits outweigh the risks of treatment with OSMOLEX ER in patients with a history of suicidality or depression.

5.3 Hallucination/Psychotic Behavior

Patients with a major psychotic disorder should ordinarily not be treated with OSMOLEX ER because of the risk of exacerbating psychosis. Treatment with amantadine or abrupt withdrawal can cause confusion, psychosis, personality changes, agitation, aggressive behavior, hallucinations, paranoia, other psychotic or paranoia reactions *[see Warnings and Precautions (5.5)]*.

Monitor patients for hallucinations throughout treatment but especially after initiation and after the dose of OSMOLEX ER is increased or decreased.

5.4 Dizziness and Orthostatic Hypotension

Dizziness and orthostatic hypotension can occur with OSMOLEX ER. Patients should be monitored for these adverse reactions, especially after starting OSMOLEX ER or increasing the dose. Concomitant use of alcohol when using OSMOLEX ER is not recommended *[see Drug Interactions (7.4)]*.

5.5 Withdrawal-Emergent Hyperpyrexia and Confusion

A symptom complex resembling neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in drugs that increase central dopaminergic tone.

Abrupt discontinuation of OSMOLEX ER may cause an increase in the symptoms of Parkinson's disease or cause delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression, or slurred speech. It is recommended to avoid sudden discontinuation of OSMOLEX ER *[see Dosage and Administration (2.4)]*.

5.6 Impulse Control/Compulsive Behaviors

Patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone, including OSMOLEX ER. In some cases, these urges were reported to have stopped when the dose was reduced or the medication was stopped. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, or other urges while being treated with OSMOLEX ER. Consider dose reduction or stopping the medication if a patient develops such urges while taking OSMOLEX ER.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Falling Asleep During Activities of Daily Living and Somnolence *[see Warnings and Precautions (5.1)]*
- Suicidality and Depression *[see Warnings and Precautions (5.2)]*
- Hallucinations/Psychotic Behavior *[see Warnings and Precautions (5.3)]*
- Dizziness and Orthostatic Hypotension *[see Warnings and Precautions (5.4)]*
- Withdrawal-Emergent Hyperpyrexia and Confusion *[see Warnings and Precautions (5.5)]*
- Impulse Control/Compulsive Behaviors *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Immediate-Release Amantadine

The adverse reactions listed in Table 2 were identified in clinical studies of immediate-release amantadine. The most common adverse reactions reported in ≥5% of patients at the recommended dosage of immediate-release amantadine were nausea, dizziness/lightheadedness, and insomnia.

Table 2: The Incidence of Adverse Reactions from Pooled Studies of Immediate-Release Amantadine

5 to 10%	1 to 5%	0.1 to 1%	Less than 0.1%
Nausea	Depression	Congestive heart failure	Convulsion
Dizziness/ lightheadedness	Anxiety and irritability	Psychosis	Leukopenia
Insomnia	Hallucinations	Urinary retention	Neutropenia
	Confusion	Dyspnea	Eczematoid dermatitis
	Anorexia	Skin rash	Oculogyric episodes
	Dry mouth	Vomiting	Suicidal attempt
	Constipation	Weakness	Suicide
	Ataxia	Slurred speech	Suicidal ideation
	Livedo reticularis	Euphoria	
	Peripheral edema	Thinking abnormality	
	Orthostatic hypotension	Amnesia	
	Headache	Hyperkinesia	
	Somnolence	Hypertension	
	Nervousness	Decreased libido	
	Dream abnormality	Visual disturbance	
	Agitation	Punctate subepithelial or other corneal opacity	
	Dry nose	Corneal edema	
	Diarrhea	Decreased visual acuity	
	fatigue	Sensitivity to light	
		Optic nerve palsy	

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/s/

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