CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208944Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	208944
Link to EDR	\\CDSESUB1\evsprod\NDA208944\0001
Submission Date	October 24, 2016
Submission Type	505(b)(2), Standard Review
Brand Name	Gocovri®
Generic Name	Amantadine Hydrochloride
Dosage Form and Strength	68.5, 137 mg Extended Release Capsules
Route of Administration	Oral
Proposed Indication	Treatment of Levodopa Induced Dyskinesia in patients with Parkinosn's Disease
Sponsor	Adamas Pharma, LLC.
Associated IND	78671
OCP Review Team	Gopichand Gottipati, Ph.D., Kevin Krudys, Ph.D., Sabarinath Sreedharan, Ph.D.

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1. EXECUTIVE SUMMARY

This is an original NDA submitted by Adamas Pharma LLC., on October 24, 2016 via 505(b)(2) regulatory pathway for an extended release (ER) formulation of amantadine hydrochloride, GOCOVRI®. Amantadine is a weak uncompetitive antagonist of the N-methyl-D-aspartate receptor (NMDA) and is currently approved for the treatment and prophylaxis of influenza A, and for the treatment of Parkinson's Disease and drug induced extrapyramidal symptoms. The reference listed drug (RLD) for this submission is SYMMETREL® tablets (immediate release amantadine HCl). Since SYMMETREL® tablets are no longer marketed in the US, the agency agreed to use a generic version (tablet) of it as a reference for this submission. The sponsor is seeking approval for the treatment of levadopa-induced dyskinesia in patients with Parkinson's Disease. Currently, there is no FDA approved treatment for this indication and the agency granted Amantadine ER an orphan drug designation in April 2015.

The clinical package in support of this NDA includes five Phase 1 pharmacokinetic studies (relative bioavailability, bioequivalence, food effect, single ascending dose, multiple ascending dose studies), one phase 2/3 dose-finding study and two phase 3 efficacy/safety studies. In addition, PK simulations were performed to optimize dosing in patients with renal function impairment.

Main focus of this review are:

(a) assessing the PK bridging between the proposed ER formulation and a generic version of the reference listed drug (immediate release formulation), and

(b) providing appropriate dosing recommendations in patients with renal impairment.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information included in NDA 208944. This NDA can be approved from a clinical pharmacology perspective for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications.

Additionally, based on the key secondary endpoint analyses from pivotal efficacy/safety studies as well as the results from the bioequivalence study between the proposed ER product and a generic version of RLD, we believe this product can also be used for the treatment of Parkinson's Disease.

Key review issues with specific recommendations and comments are summarized below:

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Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Evidence of effectiveness for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications was demonstrated in two registration trials and one phase 2/3 dose-finding study. There was a significant reduction in the total score of the Unified Dyskinesia Rating Scale (UDysRS) relative to the baseline compared to placebo in these studies. Additionally, there was a significant reduction in the daily OFF time and increase in the daily ON time without troublesome dyskinesia, which supports the use of GOCOVRI for the treatment of Parkinson's Disease. *Please refer to Clinical and Statistical Reviews for detailed information.* In addition, a PK bridging study demosntrated that exposures at steady state ($C_{max,ss}$, $AUC_{0-24,ss}$) for the proposed ER product and a generic version of RLD tablets are within acceptable bioequivalence limits.
General dosing instructions	**<u>Treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications:</u>** The proposed dosing recommendation for this indication is the same as that tested in Phase 3 studies and is acceptable. • The starting daily dose is 137 mg at bedtime for one week administered orally, and daily maintanenace dose is 274 mg at bedtime thereafter. **<u>Treatment of Parkinson's Disease:</u>** The proposed dosing recommendation for the treatment of Parkinson's Disease is consistent with the label of RLD: • 137 mg once daily when used alone. • The initial dose of GOCOVRI is 68.5 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 68.5 mg once daily, the dose may be increased to 137 mg once daily, if necessary.

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- Occassionally, patients whose responses are not optimal with GOCOVRI at 137 mg once daily may benefit from an increase upto 274 mg once daily. However, such patients should be supervised closely by their physicians.

</td></tr>
<tr><td>

Dosing in patient subgroups (extrinsic and intrinsic factors)

</td><td>

- Avoid concomitant use with alcohol
- GOCOVRI® can be administered with/without food. The contents of the capsule can be sprinkled on small amounts (teaspoonful) soft food, such as applesauce and the drug/food mixture should be swallowed immediately without chewing.
- No dose adjustment in patients with hepatic impairment
- Dose adjustment is needed in patients with renal disease (creatinine clearance estimated by Modification of Diet in Renal Disease (MDRD) method) as described below:

Treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications:

<table>
<tr><th>Creatinine Clearance</th><th>Initial Dosage
(Days 1-7)</th><th>Recommended Dosage
(Days 8 and thereafter)</th></tr>
<tr><td>30 to 59 mL/min/1.73 m^2</td><td>68.5 mg once daily at bedtime</td><td>137 mg once daily at bedtime</td></tr>
<tr><td>15 to 29 ml/min/1.73 m^2</td><td>68.5 mg once daily at bedtime</td><td>68.5 mg once daily at bedtime</td></tr>
<tr><td>below 15 mL/min/1.73 m^2</td><td colspan="2">Contraindicated</td></tr>
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Treatment of Parkinson's Disease:

<table>
<tr><th>Creatinine Clearance</th><th>Based on usual daily dose of 137mg</th><th>Based on maximum recommended daily dose of 274 mg</th></tr>
<tr><td>30 to 59 mL/min/1.73 m^2</td><td>68.5 mg once daily at bedtime</td><td>137 mg once daily at bedtime</td></tr>
<tr><td>15 to 29 ml/min/1.73 m^2</td><td>68.5 mg on alternate days at bedtime</td><td>68.5 mg once daily at bedtime</td></tr>
<tr><td>below 15 mL/min/1.73 m^2</td><td colspan="2">Contraindicated</td></tr>
</table>

</td></tr>
<tr><td>Bridge between the to-be-marketed and clinical trial formulations</td><td>The clinical trial formulation is reported to be the same as the to-be-marketed product, except for the color and imprint on capsule shell.</td></tr>
<tr><td>Bioequivalence Study
(ER Vs. IR-reference listed drug)</td><td>The steady state exposures ($C_{max,ss}$, $AUC_{0-24,ss}$) following the administration of GOCOVRI (ER formulation) and a generic version of the reference listed drug (IR formulation), as per their recommended dosing regimen met acceptable bioequivalence (BE) criteria (i.e., once daily ER formulation provided exposures comparable to twice daily IR formulation).

The ER formulation used in this BE study belong to the same batch (Lot # 14JM-070) as those used in both the pivotal efficacy studies supporting the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications indication and were manufactured by the same manufacturer (Catalent Pharma Solutions, Somerset, NJ).</td></tr>
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1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Amantadine is a weak uncompetitive antagonist of the NMDA receptor and received initial approval in the US in 1968. Though Symmetrel®, the immediate-release (IR) innovator formulation of amantadine HCl, is no longer marketed in the US, generic versions of the IR formulations are still currently marketed for prophylaxis and treatment of influenza A, and for the treatment of Parksinson's disease and drug-induced extrapyramidal reactions. Therefore, a generic version of the RLD was agreed upon by the agency. The exact mechanism by which amantadine shows efficacy in the the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications is unknown. Amantadine may have direct and indirect effects on dopaminergic neurons; and exerts dopaminergic-like side effects such as hallucinations and dizziness in humans.

The clinical pharmacology of amantadine is relatively well characterized[1] and is summarized below:

Absorption: Following oral administration of the ER formulation, the median Tmax for plasma amantadine was around 12 hours and the steady-state concentrations were achieved four days after the dose initiation. The steady-state exposures (AUC_{0-24}) were 20-30% higher than after single dosing (accumulation ratio ~1.2-1.3-fold). The relative biovailability of the ER formulation with respect to the IR formulation was reported to be 93% after a single-dose (based on dose-normalized $AUC_{0-t,}$ and AUC_{0-inf}). Additionally, the ER formulation was found to be bioequivalent to the IR formulation (a generic version of Symmetrel® tablet, reference listed drug) based on steady-state exposures ($C_{max,\ ss}$, $AUC_{0-24,ss}$). Ingestion of a high-fat, high-calorie meal did not affect the plasma PK of amantadine. Furthermore, sprinkling of the contents of the capsule on applesauce also did not alter the plasma PK of amantadine. Plasma amantadine was dose-proportional in the range of 68.5 mg – 274 mg.

Distribution: The volume of distribution and the extent of plasma protein binding are expected to be consistent with those reported for the IR formulation

[1] USPI – Symmetrel®

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Elimination: Mean apparent plasma clearance of amantadine was 0.27 L/hr/kg. Mean elimination half-life was approximately 16 hours. Renal clearance is the predominant elimination pathway for amantadine.

Metabolism: Amantadine is unlikely to be substrate or an inhibitor of CYP1A2, 2B6, 2C19, 2C8, 2C9, 2D6, 2E1, 3A4, and 3A5 CYP isoforms based on *in-vitro* drug interaction studies.

Excretion: Amantadine is primarly excreted unchanged in urine by both glomerular filtration and tubular secretion. Based on in vitro studies, amantadine is less likely to be a substrate or an inhibitor for MATE2-K, OAT1, OAT3 while it did not show inhibitory activity against p-gp, BCRP, OATP1B1 and OATP1B3 in the concentration range observed in the patients with Parkinson's disease. It was reported to be poor substrate to MATE1 based on *in-vitro* studies, while, *in-vivo* amantadine clearance increased by 33% in the presence of quinidine, OCT2 inhibitor.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The dosing recommendations for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications are an initial starting daily dose of 137 mg, administered orally at bedtime for one week and a daily maintenance dose of 274 mg at bedtime thereafter. This dosing regimen was tested in pivotal studies (ADS-AMT-PD-301 and ADS-AMT-PD-304).

The recommended dose for the treatment of Parkinson's Disease is 137 mg once daily used alone. The initial dose of GOCOVRI is 68.5 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 68.5 mg once daily, the dose may be increased to 137 mg once daily, if necessary. Occassionally, patients whose responses are not optimal with GOCOVRI at 137 mg once daily may benefit from an increase upto 274 mg once daily. However, such patients should be supervised closely by their physicians. These recommendations are based on the established BE between the proposed ER product and a generic version of the RLD product and are consistent with those listed in RLD's label.

Although the review team believes that GOCOVRI can be used for the treatment of Parkinson's Disease, the sponsor is seeking approval only for the dyskinesia indication (for which they have received orphan designation).

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2.2.2 Therapeutic individualization

Hepatic Impairment:

The impact of hepatic impairment on the exposures of plasma amantadine has not been assessed. Since renal clearance is the predominant elimination pathway for amantadine, no significant changes in amantadine exposures are expected with hepatic impairment and therefore, no dose adjustment is warranted in patients with hepatic impairment[2].

Renal Impairment:

Amantadine is extensively cleared by renal mechanisms, namely, glomerular filtration and tubular secretion. Based on literature reports, renal impairment may result in about 50% reduction in the elimination rate constant in subjects with moderate impairment relative to those with mild impairment. PK simulations were used for optimizing the dosing regimen for GOCOVRI (amantadine ER) in patients with renal impairment.

- Based on PK simulations in patients with moderate renal impairment, the steady state total exposures (AUC_{0-24}) were approximately 2-fold higher relative to patients with mild impairment. Therefore, dose reduction by 50%, both in the starting daily dose as well as the daily maintainence dose in patients with moderate impairment is recommended.
- In patients with severe renal impairment, the steady state exposures (AUC_{0-24}) were several fold higher than those with mild/moderate renal impairment. Exposures after daily dose of 68.5 mg appear to be within the range of those observed in patients with mild/moderate impairment and therefore, it was proposed in patients with severe renal impairment.
- GOCOVRI is not recommended in patients with ESRD who are on dialysis or otherwise, as amantadine is not efficiently removed by hemodialysis.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical pharmacology recommends the following labelling concepts to be included in the final package insert. The sponsor is seeking approval for only the dyskinesia indication at this time. However, we have also included dosing recommendations for the treatment of Parkinson's Disease (See Section 1).

[2] USPI - Symmetrel

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- The initial dosage of GOCOVRI is 137 mg administered orally once daily at bedtime for one week then the daily maintanence dose may be increased to 274 mg at bedtime for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications.
- The initial dosage of GOCOVRI is 137 mg once daily at bedtime when used alone for the treatment of Parkinson's Disease. The initial dosage of GOCOVRI is 68.5 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 68.5 mg once daily, the dose may be increased to 137 mg once daily, if necessary. Occassionally, in patients whose responses are not optimal with GOCOVRI at 137 mg once daily, it may be beneficial to increase the dose to 274 mg once daily. However, such patients should be supervised closely by their physicians.
- GOCOVRI can be taken with or without food. The capsules can be swallowed whole or by sprinkling the entire contents on a small amount (teaspoonful) of soft food, such as applesauce. The drug/food mixture should be swallowed immediately without chewing
- Do not use GOCOVRI with alcohol.
- No dose adjustment is necessary in patients with hepatic impairment
- Reduce the GOCOVRI initial dose and maintenance dose by half in patients with moderate renal impairment for both dyskinesia and Parkinson's Disease indications.
- A maximum total daily dose of up to 68.5 mg is recommended in patients with severe renal impairment depending on the indication.
- GOCOVRI is contraindicated in ESRD patients.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

GOCOVRI is an extended release formulation. The proposed product is a hard gelatin capsule filled with (b) (4) pellets containing the active ingradient, amantadine HCl. The (b) (4) pellets are (b) (4). The ER product used in two Phase 3 studies (ADS-AMT-PD301 and ADS-AMT-PD304) and in the BE study (ADS-AMT-PK111) is the same as the proposed to-be-marketed product.

GOCOVRI is available as 68.5 and 137 mg capsules. The indication under consideration for approval is the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications. There is no currently approved product for this indication and GOCOVRI has orphan drug designation. Furthermore, based on the established bioequivalence with the generic version of the RLD product and

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results from the key secondary endpoints, GOCOVRI can also be considered for the treatment of Parkinson's Disease indication.

This 505(b)(2) NDA relies partly on the Agency's findings of safety of SYMMETREL® (NDAs 16-020, 16-023, 17-118 and 18-101, Endo Pharmaceuticals), an immediate-release (IR) tablet formulation of amantadine HCl. Though SYMMETREL is no longer marketed in the US, generic products of the IR formulations are still being currently marketed for prophylaxis and treatment of influenza A, and for the treatment of Parksinson's disease and drug-induced extrapyramidal reactions. Therefore, the agency agreed upon using a generic version of the RLD.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The mechanism of action of amantadine HCl in the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications is not well understood. It is believed to act on the dopamine system and exert dopaminergic-like side effects such as hallucinations and dizziness.
Active moieties	Only the parent compound is believed to be active. One metabolite, an N-acetylated compound accounted for 0-15% in multiple studies, but, its contribution to efficacy/toxicity is not known.
QT Prolongation	The effect of QT prolongation was not studied in a dedicated thorough QT study. Amantadine's initial US approval was in 1968 and over the several decades it was marketed in the US, incidents of QT prolongation and torsade de pointes were reported only after overdose. Therefore, no significant new risk is expected with GOCOVRI.
General Information	
Bioanalysis	Amantadine HCl was measured using a validated LC/MS/MS method. The assay validation and sample analyses reports are acceptable. A summary of the

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	validation reports in included as Appendix 4.1.
Drug exposure at steady state following the therapeutic dosing regimen	The mean (CV) of $AUC_{0\text{-}24,\ ss}$ (ng.h/ml) and C_{max} (ng/ml) based on Study ADS-AMT-PK111 in healthy subjects after daily dose of 137 mg oral dose were 9946.7 (33.6) and 536.1 (31.3) respectively.
Dose proportionality	Plasma amantadine was dose-proportional in the dose range of 68.5 mg – 274 mg.
Accumulation at steady state	The steady-state exposures ($AUC_{0\text{-}Tau}$) were 20-30% higher than after single dosing (accumulation ratio ~1.2-1.3-fold).

Absorption

- Median Tmax for plasma amantadine was around 12 hours
  - Time to reach steady-state is approximately four days after the dose initiation.
  - Ingestion of high-fat, high-calorie meal did not affect the plasma PK of amantadine.
  - Adminstration by sprinkling of the contents of the capsule on applesauce also did not alter the plasma PK of amantadine
- Relative biovailability of the ER formulation with respect to the IR formulation is 93%. The steady-state exposures (Cmax, $AUC_{0\text{-}24}$) were bioequivalent with the IR formulation

Distribution

The values for volume of distribution and the extent of plasma protein binding are expected to be consistent with those of the IR formulation (as indicated in Symmetrel label).

Elimination

- Mean apparent plasma clearance of plasma amantadine was 0.27 L/hr/kg.
- Mean plasma amantadine elimination half-life was approximately 16 hours.
- Primary elimination pathway: renal clearance for amantadine.
- Metabolism and excretion:
  - neither a substrate nor an inhibitor of CYP1A2, 2B6, 2C19, 2C8, 2C9, 2D6, 2E1, 3A4, and 3A5 based on *in-vitro* studies.
  - neither a substrate nor an inhibitor for MATE2-K, OAT1, OAT3 and did not show inhibitory activity against p-gp, BCRP, OATP1B1 and OATP1B3 in the concentration range observed in the patients with Parkinson's disease.
  - reported to be poor substrate to MATE1 based on *in-vitro* studies, while, *in-vivo* amantadine clearance increased by 33% in the presence of quinidine, OCT2 inhibitor.
  - primarly excreted unchanged in urine by both glomerular filtration and tubular secretion.

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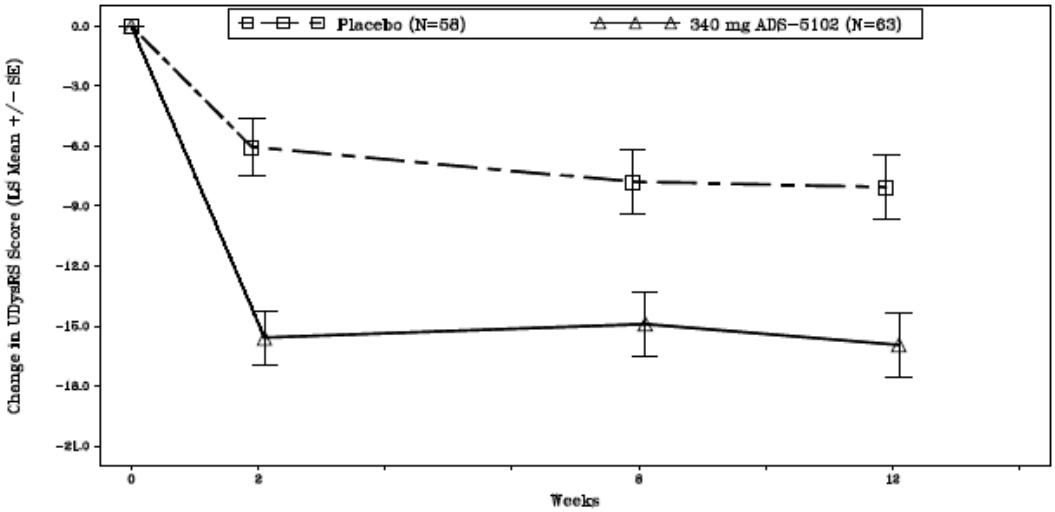
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications

The evidence of effectiveness is primarily supported by the reduction in the total score of the Unified Dyskinesia Rating Scale (UDysRS) relative to the baseline as compared to the placebo group from two phase 3 registration trials, ADS-AMT-PD-301 and ADS-AMT-PD-304. The results for the primary efficacy endpoint of these trials are shown in **Figure 1, Figure** 2. Additionally, a phase 2 dose-finding study also showed significant reduction in the in the total score of the Unified Dyskinesia Rating Scale (UDysRS) relative to the baseline compared with placebo and shown in **Figure 3.**

Figure 1 UDysRS Total Score Change over Time through Week 12 (LS Mean ± SE; MITT Population) in study ADS-AMT-PD301



LS Means and SEs were obtained from the MMRM model with change from baseline as the dependent variable and the baseline value as a covariate. The model included categorical effects for treatment group, visit (Weeks 2, 8, and 12), and the interaction between treatment group and visit.
Source: Study ADS-AMT-PD301, Figure 14.2.1.1.1

Note: 340 mg ADS-5012 is 270 mg GOCOVRI. Source: Clinical study report ADS-AMT-PD301 – Figure 4 on Page 64

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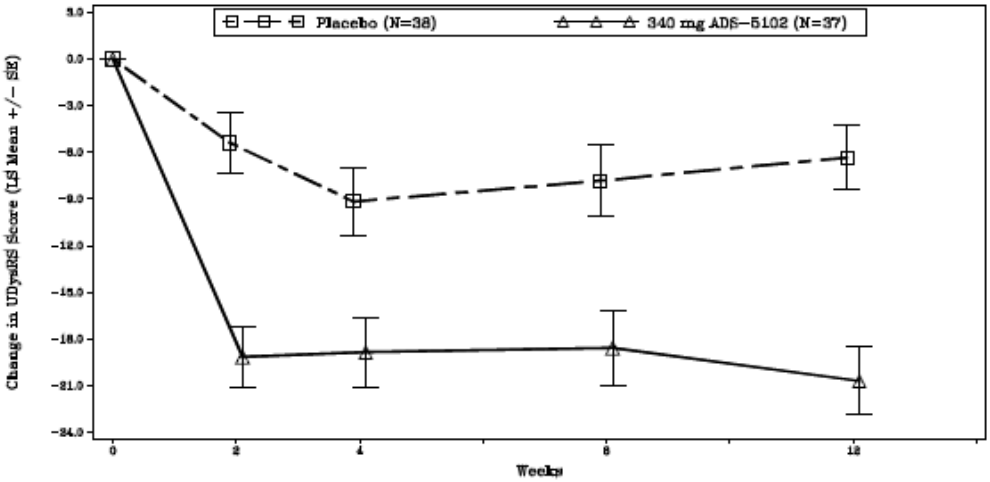
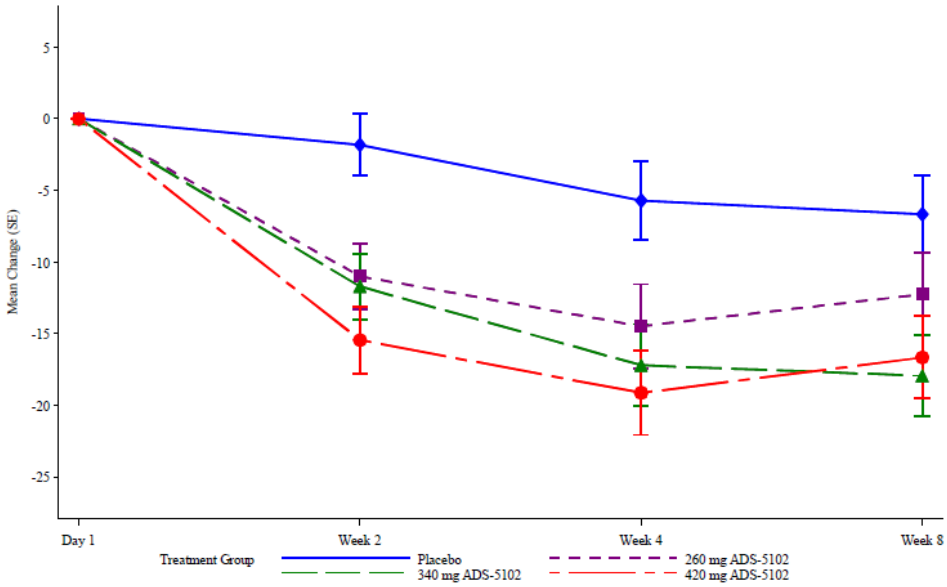
Figure 2 UDysRS Total Score Change over Time through Week 12 (LS Mean ± SE; MITT Population) in study ADS-AMT-PD304



Note: LS Means and SEs were obtained from the MMRM model with change from baseline as the dependent variable and the baseline value as a covariate. The model included categorical effects for treatment group, visit (Weeks 2, 4, 8, and 12), and the interaction between treatment group and visit.
Source: Study ADS-AMT-PD304, Figure 14.2.1.1.1

Note: 340 mg ADS-5012 is 270 mg GOCOVRI. Source: Clinical study report ADS-AMT-PD304 – Figure 4 on Page 64

Figure 3 UDysRS Total Score Change over Time through Week 8 (LS Mean ± SE; MITT Population) in study ADS-PAR-AM201



Results from Table 14.2.1.1, Analysis of covariance results for treatment differences in the change from baseline with the baseline value as a covariate.

Note: 260, 340, and 420 mg ADS-5012 correspond to 209.5, 270 and 338.5 mg GOCOVRI respectively. Source: Clinical study report ADS-PAR-AM201 – Figure 2 on Page 70

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Both the pivotal trials also showed significant improvement on the key secondary endpoints, namely, reduction in the daily OFF time and increase in the daily ON time without troublesome dyskinesia. *Please refer to Clinical and Statistical Reviews for additional details*.

Treatment of Parkinson's Disease

A bioequivalence study (ADS-AMT-PK111) established that the sponsor's ER product and a generic version of the reference listed drug (Symmetrel® immediate release tablets) met the bioequivalence criteria for steady state exposures ($C_{max,ss}$, $AUC_{0-24,\ ss}$) (please refer to Appendix 4.4) when they were administered as per their recommended regimens (i.e., once daily ER 137 mg vs. twice daily IR 80.6 mg).

SYMMETREL® is approved for the treatment of Parkinson's disease[3]. The approved usual dose of SYMMETERL is 80.6 mg taken twice daily when used alone (i.e., a daily dose of 161.2 mg). The recommended maximum daily dose is 322.4 mg (in divided doses, e.g., 161.2 mg BID) for patients whose response is not optimal with the usual dose. Aanalyses of secondary efficacy endpoints related to Parkinson's Disease from Studies ADS-AMT-PD301 and ADS-AMT-PD304, such as OFF time and ON time without troublesome dyskinesia favored GOCOVRI. *Please refer to the statistical review by Dr. Xiangmin Zhang, and clinical efficacy review by Dr. Kenneth J Bergmann for further details about the pivotal efficacy data on primary and secondary endpoints.* In addition, GOCOVRI had demonstrated bioequivalence to the generic version of SYMMETREL at the recommended daily dose of amantadine at steady-state. Therefore, we believe GOCOVRI can also be considered for the treatment of Parkinson's Disease.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications is a starting daily dose of 137 mg at bedtime for one week and a maintenance daily dose of 274 mg at bedtime is appropriate. This regime is same as that evaluated in both the registration trials ADS-AMT-PD-301 and ADS-AMT-PD-304. A consistent trend in the time course of the efficacy endpoint was observed in both the registration trials as well as the phase 2 dose-finding study. Further increase in doses beyond daily dose of 274 mg may not result in improved benefit/risk profile, as the dose-response for efficacy seem to plateau at the currently recommended dosing regimen (and it does not seem to show additional efficacy at 338.5 mg QD dose, as evaluated in the dose-finding study), and may potentially increase incidence rates for SAEs (e.g., hallucinations).

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[3] USPI – Symmetrel®: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016023s041,018101s016lbl.pdf

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The proposed dosing recommendation for the treatment of Parkinson's Disease is as follows:

- Initial dose of GOCOVRI is 137 mg once daily when used alone. This dosing regimen is appropriate based on the established BE between 137 mg of the proposed ER product and 80.6 mg BID of the generic version of the RLD and are also consistent with those listed under the RLD's label.
- Initial dose of GOCOVRI is 68.5 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 68.5 mg once daily, the dose may be increased to 137 mg once daily, if necessary. These recommendations are based on the fact that 68.5 mg of GOCOVRI can be considered bioequivalent to daily dose of 80.6 mg of RLDand 274 mg of GOCOVRI can be considered bioequivalent to daily dose of 322.4 mg of RLD, given that amantadine PK exhibits dose-proportionality in that dose range.
- Occassionally, patients whose responses are not optimal with GOCOVRI at 137 mg once daily may benefit from an increase upto 274 mg once daily (which is considered BE to proposed RLD dose of 322.4 mg in divided doses, i.e., 161.2 mg BID). However, such patients should be supervised closely by their physicians.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, dose adjustment in patients with renal impairment is necessary.

No dedicated renal impairment study was conducted with GOCOVRI. The reference listed drug SYMMTREL has dose adjustments recommended for patients with renal impairment[4]. The median values of the estimated GFR based on MDRD equation in patients from both the pivotal phase 3 trials indicated that most of them had either normal renal function (CrCL >90 ml/min/m^2) or mild renal impairment (CrCL in range of 60-89 ml/min/m^2). PK simulations were used to provide instructions for dose optimization for GOCOVRI in patients with various degrees of renal impairment, such that the exposures under each of the renal impairment scenario matched with those included in the pivotal efficacy trials (as the reference population). Please see Appendix 4.3 for details. The dosing instructions for GOCOVRI for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications are as follows:

[4] SYMMETREL: 200 mg on first day and 100 mg each day thereafter for subjects with CrCL values between 30-50 ml/min/1.73 m^2; 200 mg on first day followed by 100 mg on alternate days for subjects with CrCL values between 15-29 ml/min/m^2 and 200 mg every 7 days for subjects with CrCL values less than 15 ml/min/m^2.

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- No dose-adjustment is necessary in subjects with normal renal function and mild renal impairment, i.e., the dosing recommendation is 137 mg QD at bedtime for one week and 274 mg QD at bedtime thereafter.
- A 50% reduction is recommended in patients with moderate renal impairment to 68.5 mg QD at bedtime for one week and 137 mg QD at bedtime thereafter. In patients with severe renal impairment, a daily dose of 68.5 mg at bedtime is recommended.
- It is not recommended in patients with ESRD who are on dialysis or otherwise, as amantadine is not efficiently removed by hemodialysis.

Similarly, based on the established bioequivalence between 137 mg of the proposed ER product and 80.6 mg BID of the generic version of the RLD, PK simulations were used to derive the recommendations such that the exposures under each of the renal impairment scenarios matched with those simulated per dosing in general patient population (normal subjects or mildly renally impaired subjects). The dosing instructions for GOCOVRI for the treatment of patients with Parkinson's disease indication are as follows:

- No dose-adjustment is necessary in subjects with normal renal function and mild renal impairment, i.e., the dosing recommendation is 137 mg QD at bedtime and the maximum recommended daily dose is 274 mg at bedtime.
- A 50% reduction is recommended in patients with moderate renal impairment.
- In patients with severe renal impairment, 68.5 mg on alternate days and up to a maximum daily dose of 68.5 mg at bedtime is recommended.
- It is not recommended in patients with ESRD who are on dialysis or otherwise, as amantadine is not efficiently removed by hemodialysis.

No dose adjustments are needed for patients with hepatic impairment.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. In a food-effect study, ingestion of high-fat, high-calorie meal did not affect the plasma PK of amantadine and therefore, the food-drug interaction is not clinically relevant.

No clinically significant drug-drug interactions are expected based on *in-vitro* studies.

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4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The concentrations of amantadine in human plasma samples from each of the clinical pharmacology study in healthy subjects as well as Phase 2 study in patients with PD (ADS-PAR-AM201) were determined by a validated LC/MS/MS method. The method met the requirements for specificity, sensitivity, accuracy and precision (shown in **Table 1** below).

All the bioanalytical method validation consisted of at least 3 separate analytical runs. For each run, a calibration curve with 8 non-zero standards were processed and analyzed in duplicate. An internal standard was added to the matrix samples prior to processing and analysis. Accuracy (%nominal) and precision (percent coefficient of variation, %CV) of the method were assessed in a minimum of 3 method validation runs that used 3 QC samples. For all validation runs, the within-run (intra-assay) and between-run (inter-assay) precision was ≤ 15% and ≤ 20% at the LLOQ. Analysis of the QC samples showed that no more than 2/3 and no two at the same concentration deviated from the nominal values by more than ±15%.

Table 1 Validation summary of the bioanalytical method used to determine the amantadine concentrations in human potassium EDTA plasma

Study No.	Analytical Method Number	Internal Standard	Linear Range (ng/mL) and r^2	Accuracy (%nom) QCs at L, M, H	Accuracy (%nom) LLOQ QC Samples	Precision (%CV) QCs at L, M, H	Precision (%CV) LLOQ QC Samples
5103-C-101	LC/MS/MS 100-05001M.0	(b) (4)	2.00-400 r^2: 0.9968 to 0.9994	Intra-assay: 98.0-114 Inter-assay: 100-109	Intra-assay: 87.5-106 Inter-assay: 98.5	Intra-assay: 1.28-7.66 Inter-assay: 4.29-5.67	Intra-assay: 1.43-7.26 Inter-assay: 9.39
ADS-PAR-AM201	LC/MS/MS 000-11007M.0	(b) (4)	10.0-4000 r^2: 0.9996	Intra-assay: 95.0-108 Inter-assay: 97.0-106	Intra-assay: 106-112 Inter-assay: 109	Intra-assay: 0.416-3.08 Inter-assay: 2.25-2.60	Intra-assay: 1.20-4.49 Inter-assay: 3.96
ADS-AMT-PK110, ADS-AMT-PK111, ADS-AMT-PK112, and ADS-AMT-PK113	LC/MS/MS 000-14007M.0[a]	(b) (4)	API 5000 LC/MS/MS 5.00-1500 r^2: 0.9996 to 0.9998 API 4000 LC/MS/MS 5.00-1500 r^2: 0.9990	API 5000 LC/MS/MS Intra-assay: 90.1-105 Inter-assay: 95.6-102 API 4000 LC/MS/MS Intra-assay: 99.9-103	API 5000 LC/MS/MS Intra-assay: 87.8-106 Inter-assay: 99.4 API 4000 LC/MS/MS Intra-assay: 95.6	API 5000 LC/MS/MS Intra-assay: 1.97-7.31 Inter-assay: 3.28-7.57 API 4000 LC/MS/MS Intra-assay: 1.24-4.59	API 5000 LC/MS/MS Intra-assay: 5.56-13.6 Inter-assay: 12.2 API 4000 LC/MS/MS Intra-assay: 5.96

Abbreviations: %nom = % nominal; H = high; L = low; M = medium; r^2 = coefficient of determination.
Note: LLOQ is the lowest value in the range of the calibration curve for the method.
[a] Two LC/MS/MS instruments were cross validated and used to analyze samples from these studies. The linear ranges and intra-assay variability are provided for both methods.
Source: (b) (4) Validation Report Nos. 100-05001V, 000-11007V, 000-14007V, 000-14007V Addendum B and 000-14007V, Addendum D

Source: Summary of Clinical Pharmacology Studies Report: Table 4 on Page 68

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4.2 Summary of *In-vitro* Studies

Amantadine is not known to be a substrate, inhibitor or an inducer of CYP enzymes. Based on *in-vitro* studies performed by the sponsor (ADS-AMT-ME001, ADS-AMT-ME002, ADS-AMT-ME008, ADS-AMT-ME0012, ADS-AMT-ME0013, ADS-AMT-ME0015), it can be concluded that:

- Amantadine is unlikely to be substrate or an inhibitor of CYP1A2, 2B6, 2C19, 2C8, 2C9, 2D6, 2E1, 3A4, and 3A5 CYP isoforms at concentrations observed in human plasma following dose of 274 mg of ADS-5102 (upto 9.9µM, or 1500 ng/ml)
- Amantadine is unlikely to be a substrate or an inhibitor for MATE2-K, OAT1, OAT3 while it did not show inhibitory activity against p-gp, BCRP, OATP1B1 and OATP1B3 in the concentration range observed in the patients with Parkinson's disease. It was reported to be poor substrate to MATE1, with a 1.2 fold higher in uptake that may not be clinically meaningful.
- While *in-vivo* amantadine clearance increased by 33% in the presence of quinidine, OCT2 inhibitor, based on study reported in literature, *in-vitro* study conducted by the sponsor showed 1.3-fold higher uptake but this may not be clinically meaningful.

4.3 Dosing in Patients with Renal Impairment

4.3.1 Sponsor's Analysis

The key objective was to propose dosing recommendations in patients with renal impairment. The sponsor adopted the following workflow:

- Step 1: A one-compartment PK model was developed to characterize the single-dose plasma PK of amantadine and also evaluated for its predictive performance. Data from a phase 1 study (ADS-AMT-PK-111) following oral administration of ADS-5102 capsules with rich PK sampling after single-dose were used for this purpose.
- Step 2: A correlation between creatinine clearance (CrCL) and elimination rate constant (K_{10}) in population ranging from healthy to high degrees of renal impairment was developed based on values of these parameters from four studies available in the literature.
- Step 3: Based on the correlation, the values for the elimination rate constant under various renal impairment scenarios were used to simulate the steady state PK. The final dosing recommendations were based on these simulations.

The model parameter estimates based on the sponsor's one-compartment PK model are shown in **Table 2**. Furthermore, the single-dose predicted PK was overlaid with the observed PK to

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evaluate the model's predictive performance and is shown in **Figure 4**. Lastly, the steady-state PK simulations (using the same PK model) were overlaid with the observed data and shown in **Figure 5**

Table 2 Mean (SD) and Median One-Compartment PK Parameter Estimates

		ADS-5102	
Parameter	**Units**	**Mean (SD)**	**Median**
V	L	450.914 (130.23)	443.705
K_{01}	1/h	0.283 (0.179)	0.229
K_{10}	1/h	0.0585 (0.015)	0.0577
T_{lag}	h	4.02 (1.21)	3.58

V = Volume of distribution, K_{01} = absorption rate constant, K_{10} = elimination rate constant, T_{lag} = lag time of absorption

Source: PK report ADS-5102-CR-2016-002, Table-8 on page 21

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Figure 4 Single Dose PK– Predicted vs. Observed Amantadine Concentrations

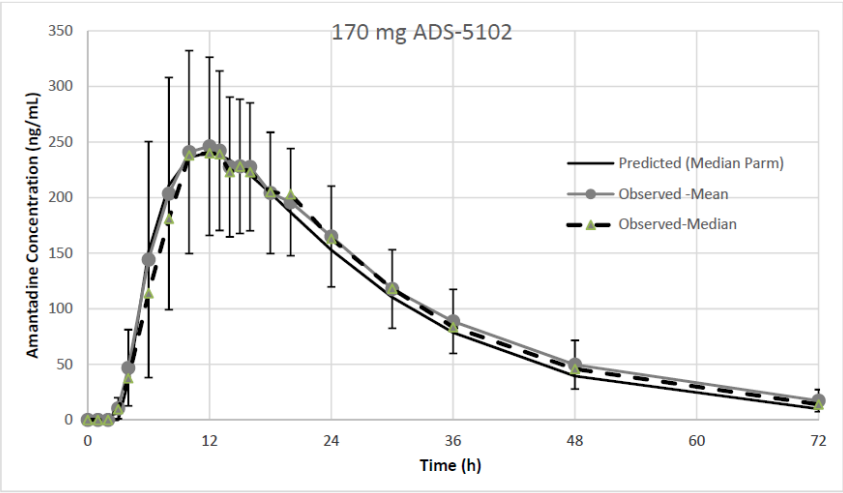
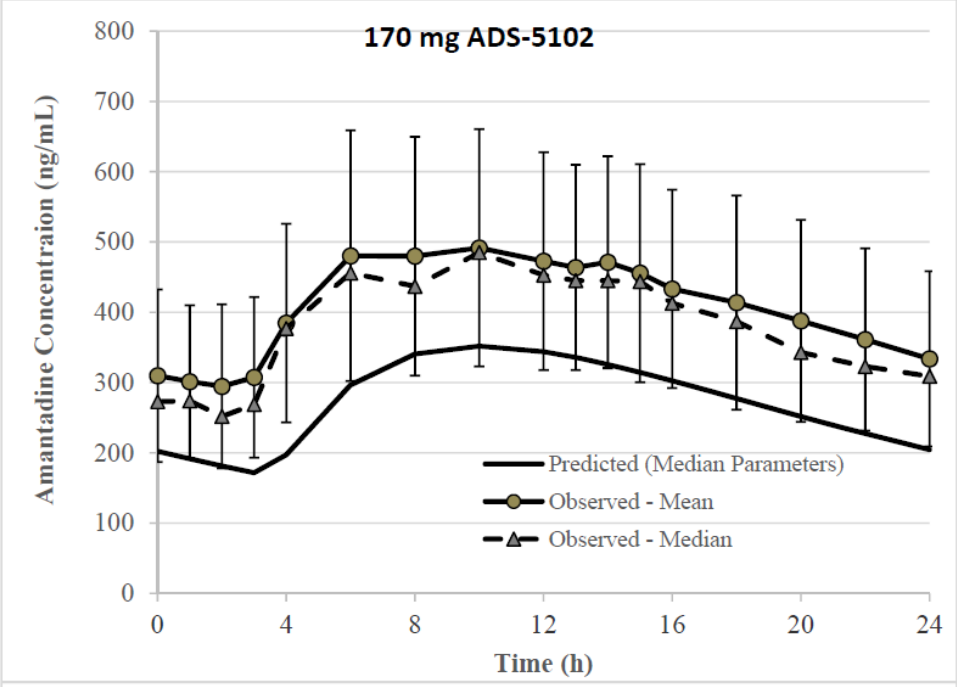


Figure 5 Steady State PK – Predicted vs. Observed Amantadine Concentrations



Source: PK report ADS-5102-CR-2016-002, Figures-3, 5 on pages 22, 25

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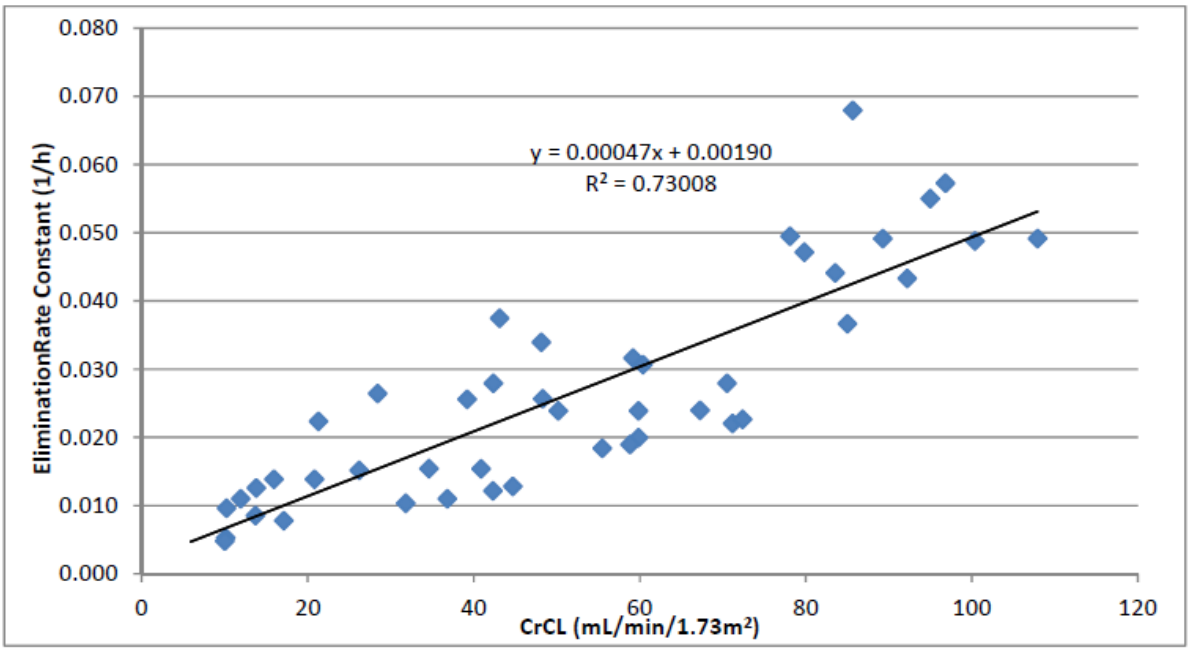
The correlation between elimination rate constants (K_{10}) and CrCL is shown in **Figure 6** and values of parameters in **Table 3**.

Figure 6 Correlation between elimination rate constant of Amantadine and Creatinine Clearance



Source: PK report ADS-5102-CR-2016-002, Figure-1 on page 9

Studies from literature used to develop the correlation include the following:

1. *Horadam V, Sharp J, et al. Pharmacokinetics of amantadine hydrochloride in subjects with normal and impaired renal function. Annals of Int Med. 1981; 4(1) 454-458.*
2. *Wu M, Soung L, Daugirdas J, Hano J, Gandhi V. Amantadine hydrochloride pharmacokinetics in patients with impaired renal function. Clinical Nephrol. 1982; 17(1): 19-23.*
3. *Aoki F, Sitar D, Ogilvie R. Amantadine kinetics in healthy young subjects after long-term dosing. Clinical Pharmacology Therapeutics. 1979; 26(6): 729-736.*
4. *Aoki F, Sitar D. Amantadine kinetics in healthy elderly men: implications for influenza prevention. Clinical Pharmacology Therapeutics. 1985; 37(2): 137-144*

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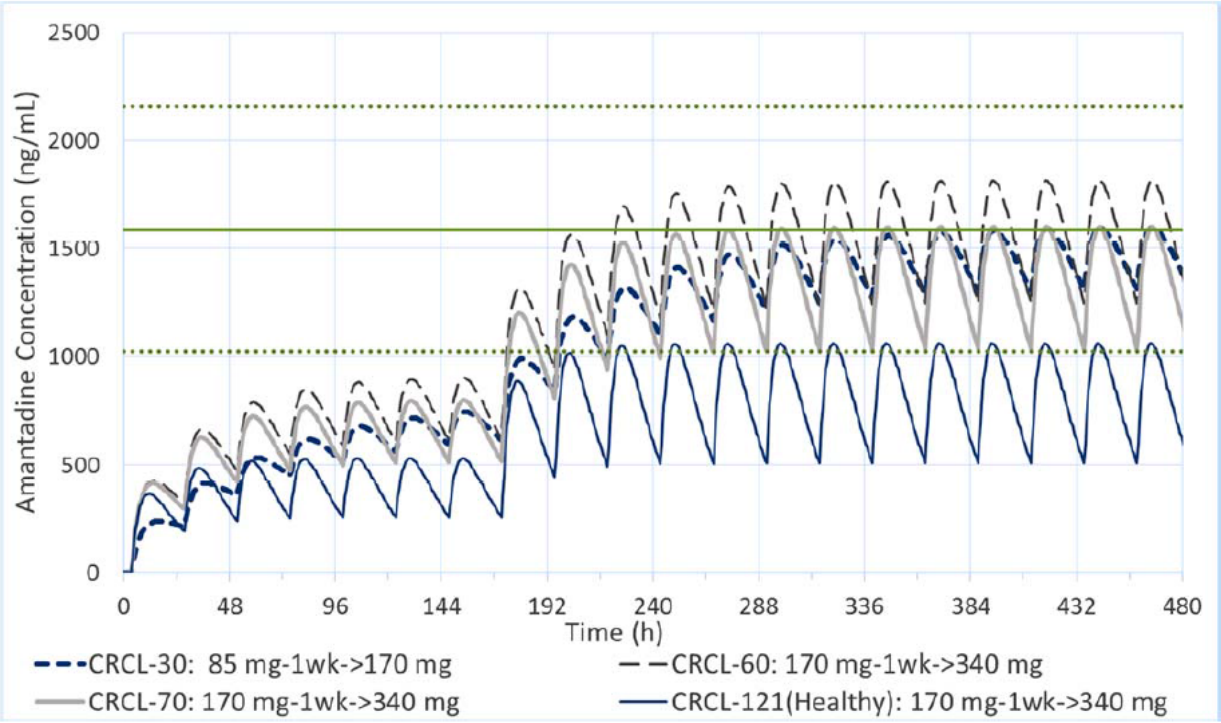
Table 3 Final parameter estimates used for simulations in renal impairment scenarios

CrCL (mL/min/1.73m^2)	K_{10} (1/h)	$t_{1/2}$ (h)
30	0.0160	43.31
60	0.0301	23.02
70	0.0348	19.91
121 (Healthy)	0.0588	11.79

Source: PK report ADS-5102-CR-2016-002, Table-3 on page 9

The simulated plasma amantadine profiles based on the sponsor's final dose recommendations in patients with varied degrees of renal impairment are shown in **Figure 7**.

Figure 7 Simulated amantadine plasma concentration profile based on dosing recommendations in patients with renal impairment



Source: Report ADS-5102-CR-2016-002, Attachment 2
Note: The solid line at 1600 ng/mL reflects the mean (SD) amantadine plasma concentration in Study ADS-PAR-AM201 of 1590.9 (567.86) ng/mL. The dotted lines depict ± 1 standard deviation.

Source: PK report ADS-5102-CR-2016-002, Table-3 on page 9

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Reviewer's comments:

Overall, the sponsor's workflow to derive the dosing recommendations in patients with renal impairment seems reasonable. However, there are a few major issues with their analyses. During step 1, the sponsor used only the rich PK data sampled after single-dose for developing the PK model and did not provide a rationale for excluding the steady-state PK, given the understanding of linearity in the dose range of 68.5-274 mg. The model parameter estimates seem acceptable and the model simulations seem to be in good agreement with the observed data after single-dose. However, the simulations of the steady state PK seem to be consistently lower than the observed data.The sponsor's argument for this inconsistency (see below) does not seem to be not scientifically sound.

The correlation relationship developed by the sponsor was based on four studies from the literature in step 2. While the estimation method for calculating the elimination rate constant in each of these studies is acceptable, adequate characterization of the terminal phase plasma amantandine concentrations in the context of the analytical method sensitivity seems unclear. There can be additional uncertainity in accurately quantifying the urinary and serum concentrations of creatinine. Of the four studies included, only two studies included CrCL values normalized by the individual's body surface area (BSA) while in the other two, it was normalized to the BSA using published individual body weight and median height values based on study 5103-C101. In general, this strategy seems reasonable, but may contribute at least in part to potential inaccuracies in establishing the correlation. The values of the elimination rate constant at different degrees of renal impairment for simulation of exposures was based on the correlation relationship and estimates from the one-compartment PK model developed using only single-dose PK data. The sponsor clearly and accurately stated the assumptions in using the model developed using PK from healthy adults to simulate the steady-state exposures in renally impaired subjects and are reasonable. However, given the potential issues with using only single-dose data and clear discordance of the steady-state simulations with the observed data as discussed above, the simulated steady state exposures under various renal impairment scenarios can potentially be misleading. Lastly, the sponsor's proposed argument for increasing all the steady-state simulated concentration profiles by 50% (25% increase based on accumulation from multiple dosing and another 20% increase to account for the higher exposures in females) is not reasonable.

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4.3.2 Reviewer's Analysis

Introduction

There seem to be few major issues with the PK model developed using the single-dose PK data in adequately characterizing the steady-state PK data in healthy subjects as discussed above. The reviewer performed independent analysis to develop the PK model using both single-dose and steady-state data and better characterize the disposition of amantadine. Additionally, the reviewer used the parameter estimates from the model to derive the values of the elimination rate constant in different degrees of renal impairment based on the established correlation of elimination rate constant and creatinine clearance. Last, the reviewer performed simulations in different degrees of renal impairment using the derived values of the elimination rate constant to inform the dosing recommendations in patients with renal impairment for both the indications, namely treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications and treatment of Parkinson's Disease.

Objective

To adequately characterize the single-dose and steady-state PK of amantadine in healthy subjects after oral administration of ADS-5102 capsules and to determine the dosing regimen in patients with renal impairment, which match the exposures in the pivotal trials in treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications or per the proposed general dosing recommendations in Parkinson's Disease (based on the established BE of the proposed ER product with the RLD as well as key secondary endpoints).

Datasets

Datasets used in the analyses are embedded in the project file sent by the sponsor.

Software

Phoenix WinNonlin 6.4, Build 7.0.0.2535; Certara USA, Inc., 100 Overlook Center, Suite 101, Princeton, NJ 08540 USA

Methods

The observed PK data after single- and multiple-doses from study ADS-AMT-PK111 was used to develop a PK model that can adequately characterize the disposition of amantadine. In order to account for multiple-dosing arm in the study, new rows were added to reflect the additional

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doses and were implemented in the "Dose_mg" column at the respective dosing timepoints in "N_Time_h".

Results

The final model parameter estimates of the PK model developed using both single- and multiple-doses are shown in **Table 4**. Except for the T_{lag} parameter, the values from the reviewer's analysis suggests, higher volume of extravascular distribution, slower absorption rate and a faster elimination rate as compared with the sponsor's analysis. Furthermore, the model performance of the PK model is shown **Figure 8**. The model simulations seem to be very consistent with the observed data both after single-dose and also at steady-state.

Table 4 Descriptive statistics of the model parameter estimates – Reviewer's analysis

		Sponsor's results		*Reviewer's Analysis*	
Parameter	Units	Mean (SD)	Median	*Mean (SD)*	*Median*
V	L	450.91 (130.23)	443.71	*523.84 (136.23)*	*522.26*
K_{01}	l/h	0.283 (0.179)	0.229	*0.419 (0.332)*	*0.368*
K_{10}	l/h	0.0585 (0.015)	0.0577	*0.037 (0.010)*	*0.03588*
T_{lag}	h	4.02 (1.21)	3.58	*3.53 (1.09)*	*3.41*

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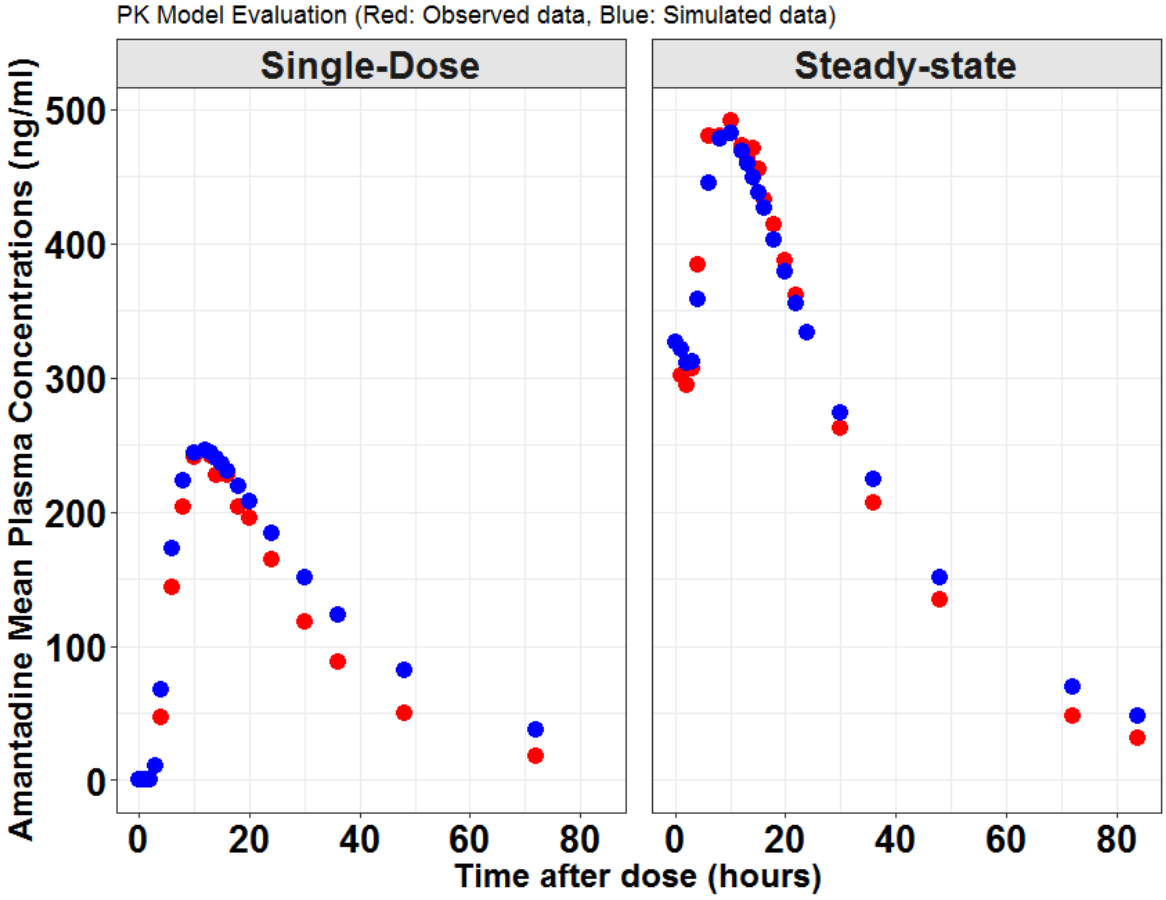
Figure 8 PK Model performance – Reviewer's Analysis



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Based on the final PK model parameter estimates, the elimination rate constant values at various degrees of renal impairment were derived based on the correlation relationship reported by the sponsor and shown in **Table 5**.

The median (range) values of eGFR for patients enrolled in the two pivotal trials at baseline were 86 (55 – 174) ml/min/1.73 m^2 and 97 (53 – 155) ml/min/1.73 m^2 respectively, suggesting most of them were characterized as subjects with normal or mild renal impairment. Therefore, the final PK model parameter estimates and elimination rate constant derived from the correlation relationship were used to derive the exposures in normal subjects and those with mild renal impairment based on the dosing regimen administered in the pivotal trial to serve as the reference population, and are shown in **Figure 9 Figure** 10. The reviewer evaluated the adequacy of different dosing regimens in various degrees of renal impairment that either match or are within reasonably acceptable margin of the exposures in the reference population in the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications.

The final dosing recommendations based on the simulation of the exposures in different categories of renal impairment in the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications are shown in **Table 6**. The exposures ranging from, normal subjects (CrCL.121) to mildly renally impaired subjects (CrCL.60) was represented as shaded areas and the simulated profiles per the dosing recommendations in subjects with moderate and severe renal impairment in the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications are shown in **Figure 11,Figure** 12.

Table 5 Values of elimination rate constant for final simulation in patients with renal impairment

Renal Impairment	CrCL Value (ml/min/1.73 m^2)	Elimination rate constant (1/h)
Normal	90	0.02822
	121	0.03752
Mild	60	0.01922
	89	0.02792

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Moderate	30	0.01022
	59	0.01892
Severe	15	0.00572
	29	0.00992

Table 6 Final dosing recommendations in renal impairment for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications – Reviewer's analysis

Creatinine Clearance	Dosing Recommendations
≥ 60 ml/min/1.73 m^2	Daily bedtime dose of 137 mg dose for a week, and 274 mg QD at bedtime thereafter
30-59 ml/min/1.73 m^2	Daily bedtime dose of 68.5 mg dose for a week, and 137 mg QD at bedtime thereafter
15-29 ml/min/1.73 m^2	Daily bedtime dose of 68.5 mg dose
< 15 ml/min/1.73 m^2	Not recommended

The proposed recommendations in treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications under the renal impairment scenarios were consistent with those for Symmetrel, especially for normal, mild and moderate renal impairment categories. However, for severely renally impaired subjects, the total daily weekly dose (595 mg, i.e., with the salt form) was slightly higher than that for Symmetrel (500 mg, i.e., with the salt form), but the simulated exposures fall well within the margin of those in normal subjects/mildly renally impaired (reference population)

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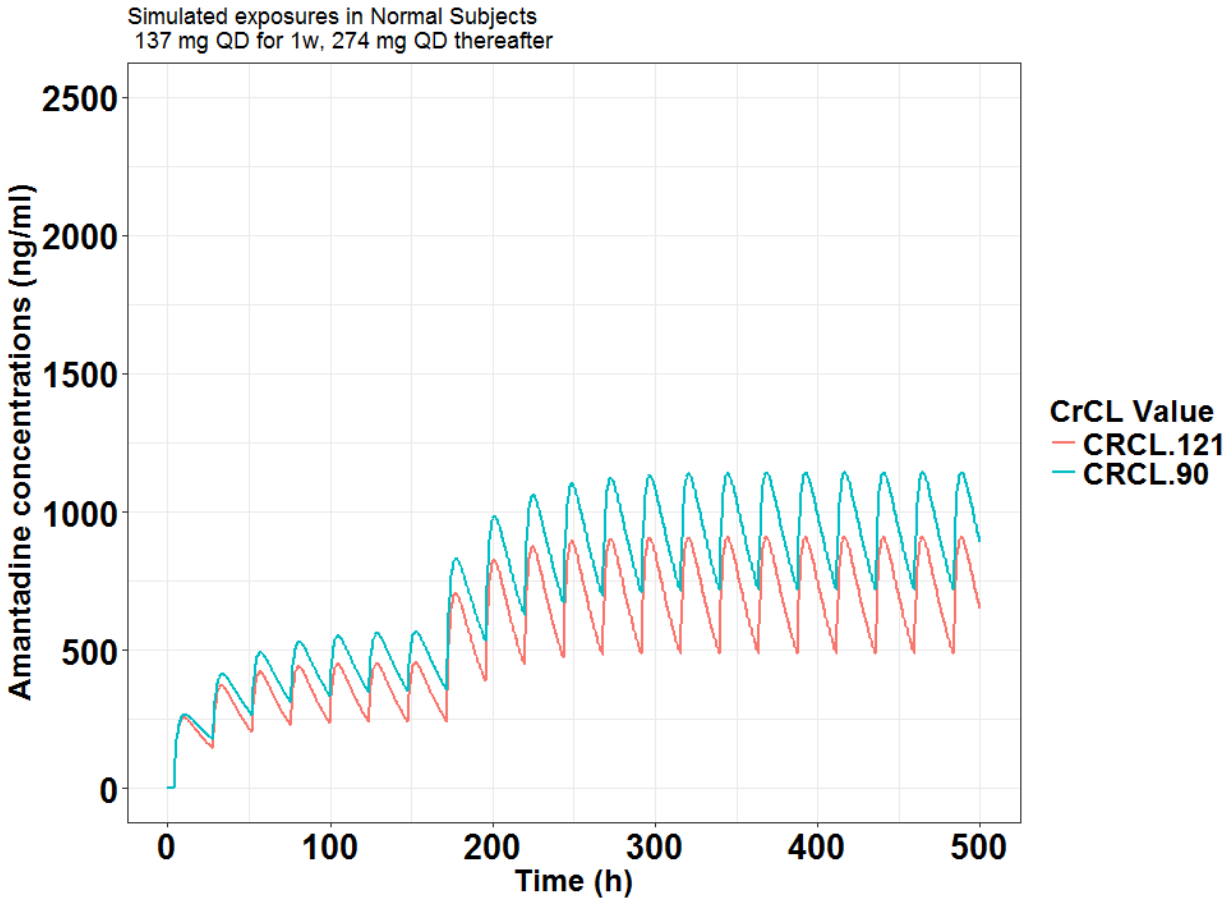
Figure 9: Simulated exposures in patients with normal renal function



Dosing recommendation in normal renal function: 137 mg QD at bedtime for 1 week and 274 mg QD at bedtime thereafter. The simulated profiles represent the extremes for the margins (>CrCL90)of the creatinine clearance of subjects with normal renal function

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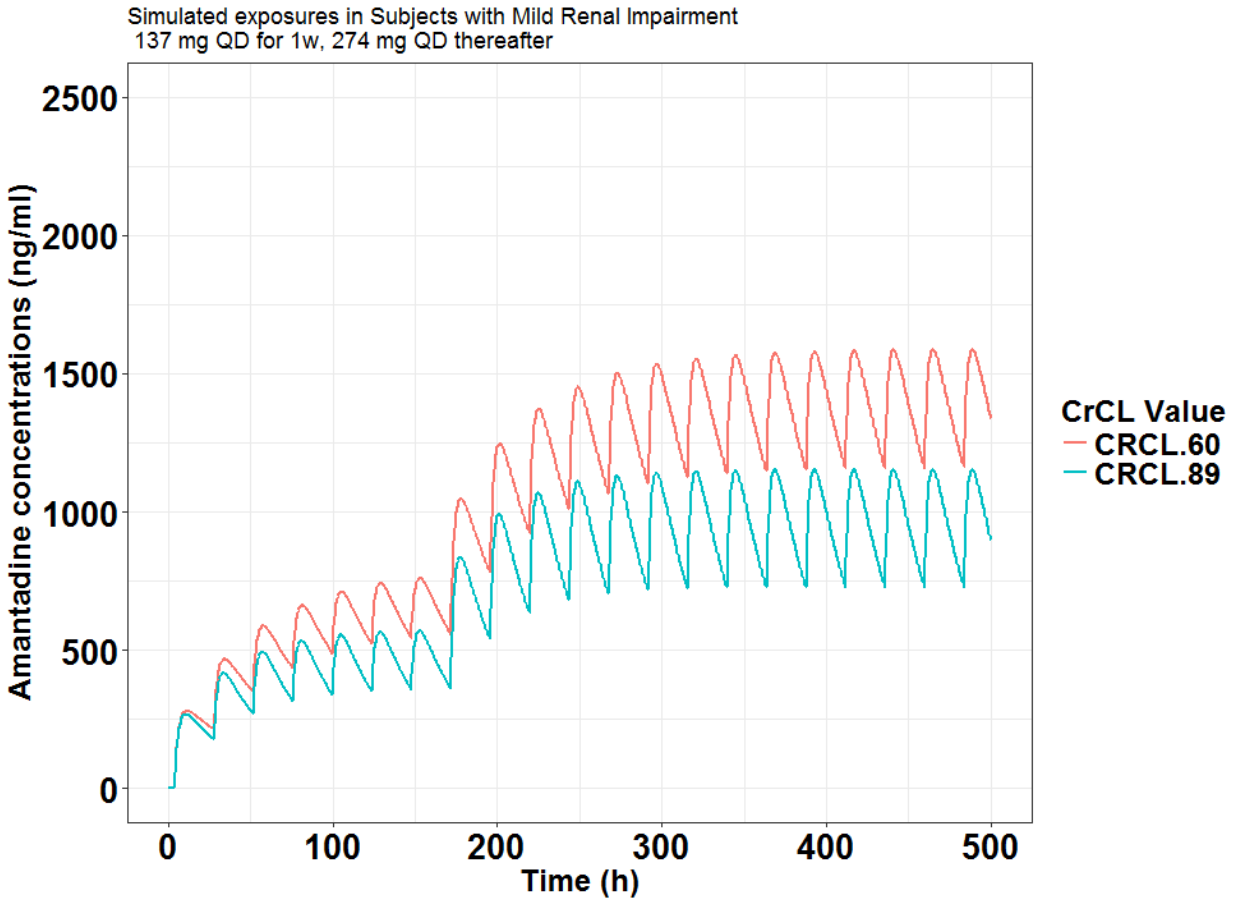
Figure 10 Simulated exposures in patients with mild renal impairment



Dosing recommendation in mild renal impairment: 137 mg QD at bedtime for 1 week and 274 mg QD at bedtime thereafter. The simulated profiles represent the extremes for the margins (CrCL60 – CrCL89) of the creatinine clearance of subjects with mild renal impairment

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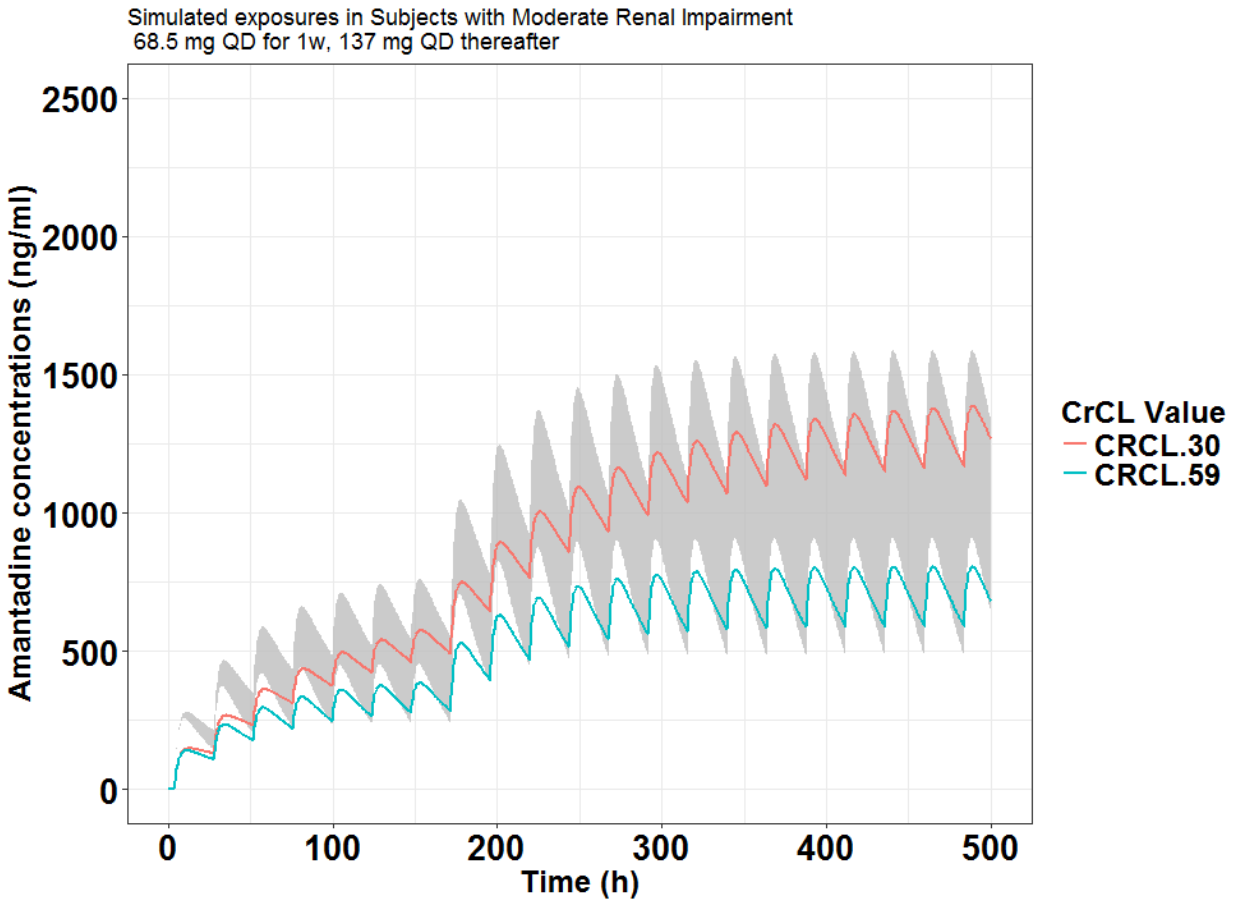
Figure 11 Simulated exposures in patients with moderate renal impairment



Dosing recommendation in moderate renal impairment: 68.5 mg QD at bedtime for 1 week and 137 mg QD at bedtime thereafter. The simulated profiles represent the extremes for the margins (CrCL30 – CrCL59) of the creatinine clearance of subjects with moderate renal impairment. The grey shaded area represents exposures in the margins of renal impairment (CrCL60 and CrCL121) in normal subjects and mildly renally impaired subjects (reference population).

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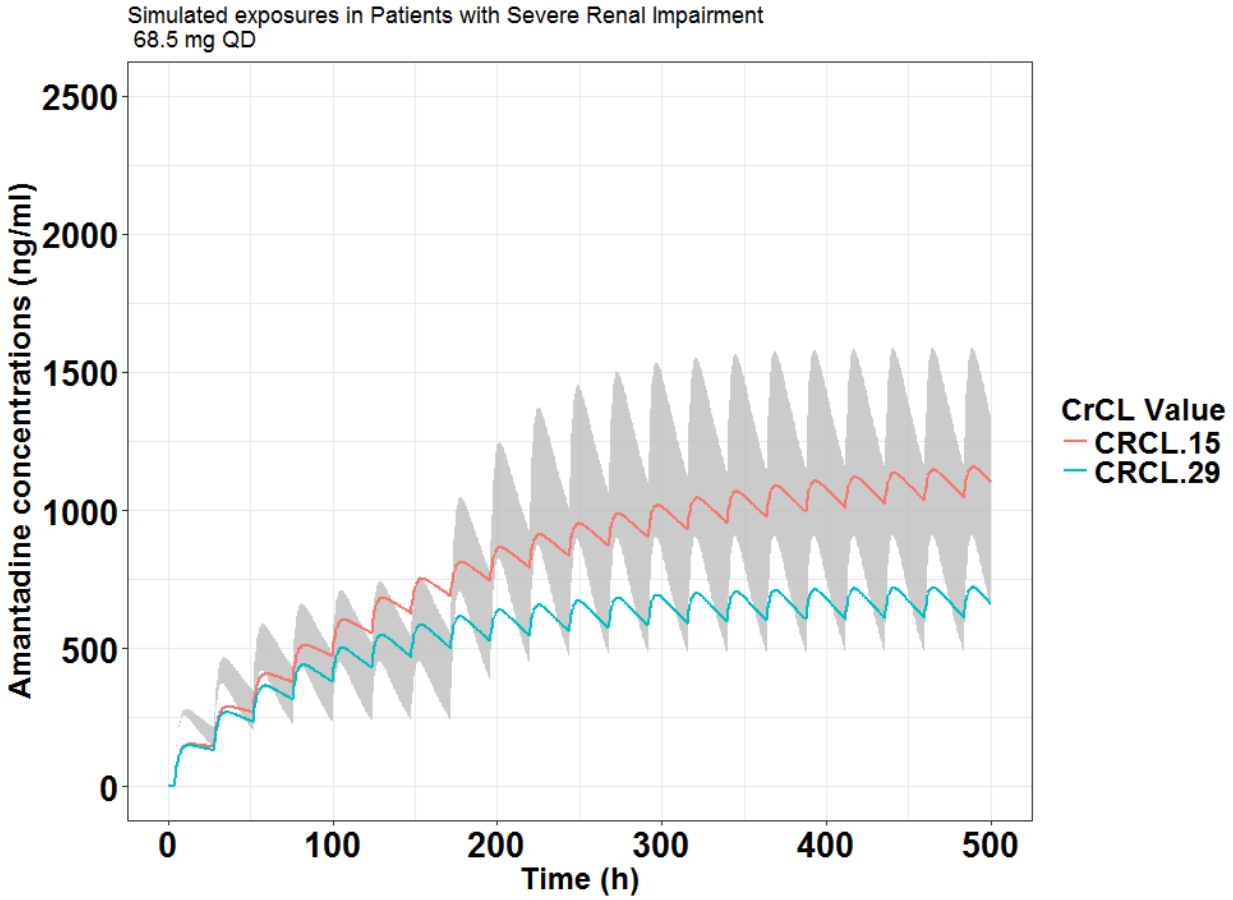
Figure 12 Simulated exposures in patients with severe renal impairment



Dosing recommendation in severe renal impairment: 68.5 mg QD at bedtime. The simulated profiles represent the extremes for the margins (CrCL15 – CrCL29) of the creatinine clearance of subjects with severe renal impairment. The grey shaded area represents exposures in the margins of renal impairment (CrCL60 and CrCL121) in normal subjects and mildly renally impaired subjects (reference population)

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Similarly, based on the values of the final PK model parameter estimates and the elimination rate constant values at various degrees of renal impairment listed in **Table 5**, exposures were derived for the dosing recommendations in the general population per the usual dose (137 mg QD at bedtime) and maximum recommended daily dose (274 mg QD at bedtime) assuming normal subjects/mild renal impairment (serve as the reference population) Subsequently, the reviewer evaluated the adequacy of different dosing regimens in various degrees of renal impairment that either match or are within reasonably acceptable margin of the exposures in the reference population for treatment of Parkinson's Disease indication.

The final dosing recommendations based on the simulation of the exposures in different categories of renal impairment for treatment of Parkinson's Disease indication are shown in **Table 7**. The exposures ranging from, normal subjects (CrCL.121) to mildly renally impaired subjects (CrCL.60) was represented as shaded areas and the simulated profiles per usual dosing recommendations in subjects with moderate and severe renal impairment for treatment of Parkinson's Disease indication are shown in **Figure 13** and **Figure 14**.

Table 7 Final dosing recommendations in renal impairment for the treatment of patients with Parkinson's Disease– Reviewer's analysis

Creatinine Clearance	Based on usual daily dose of 137mg for treatment of PD	Based on maximum recommended daily dose of 274 mg for treatment of PD
30 to 59 mL/min/1.73 m^2	68.5 mg once daily at bedtime	137 mg once daily at bedtime
15 to 29 ml/min/1.73 m^2	68.5 mg on alternate days at bedtime	68.5 mg once daily at bedtime
below 15 mL/min/1.73 m^2	Contraindicated	

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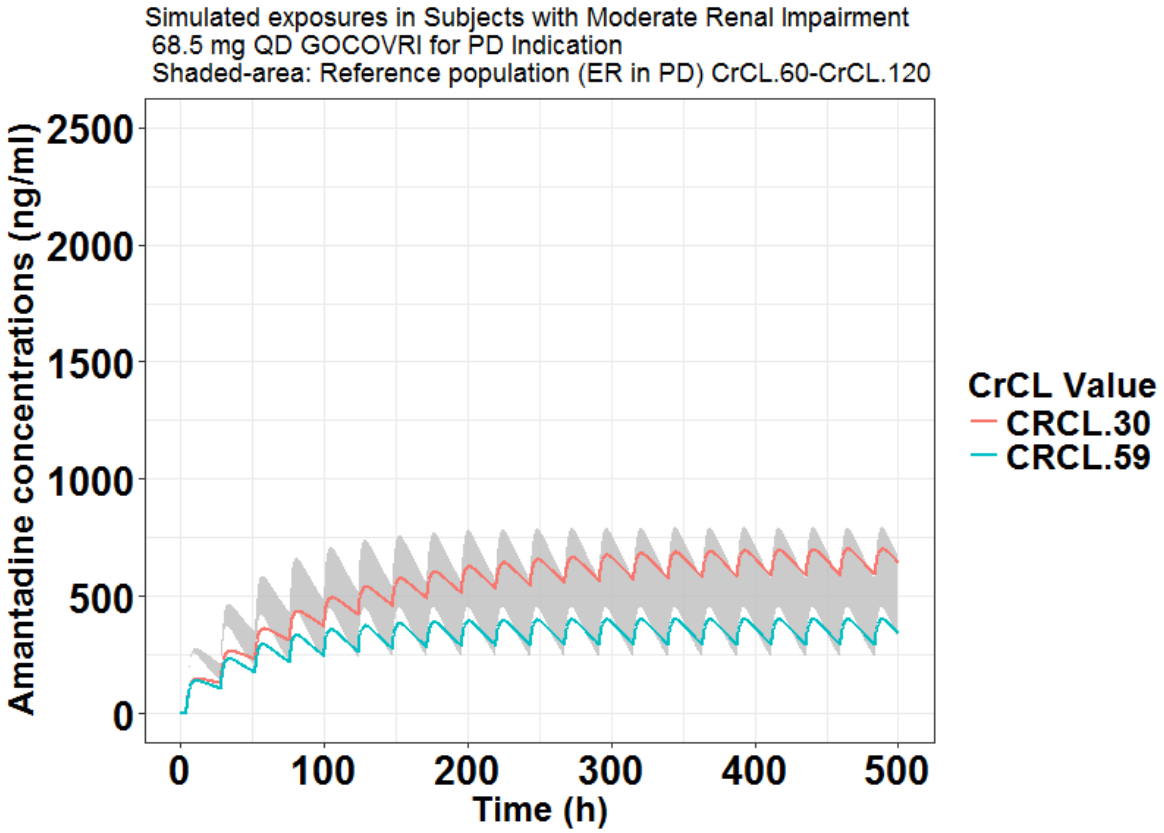
Figure 13 Simulated exposures in patients with moderate renal impairment for treatment of PD indication per the usual dosing recommendation



Dosing recommendation in moderate renal impairment for the treatment of PD indication: 68.5 mg QD. The simulated profiles represent the extremes for the margins (CrCL30 – CrCL59) of the creatinine clearance of subjects with moderate renal impairment. The grey shaded area represents exposures in the margins of renal impairment (CrCL60 and CrCL121) in normal subjects and mildly renally impaired subjects (reference population) per the usual dosing recommendation.

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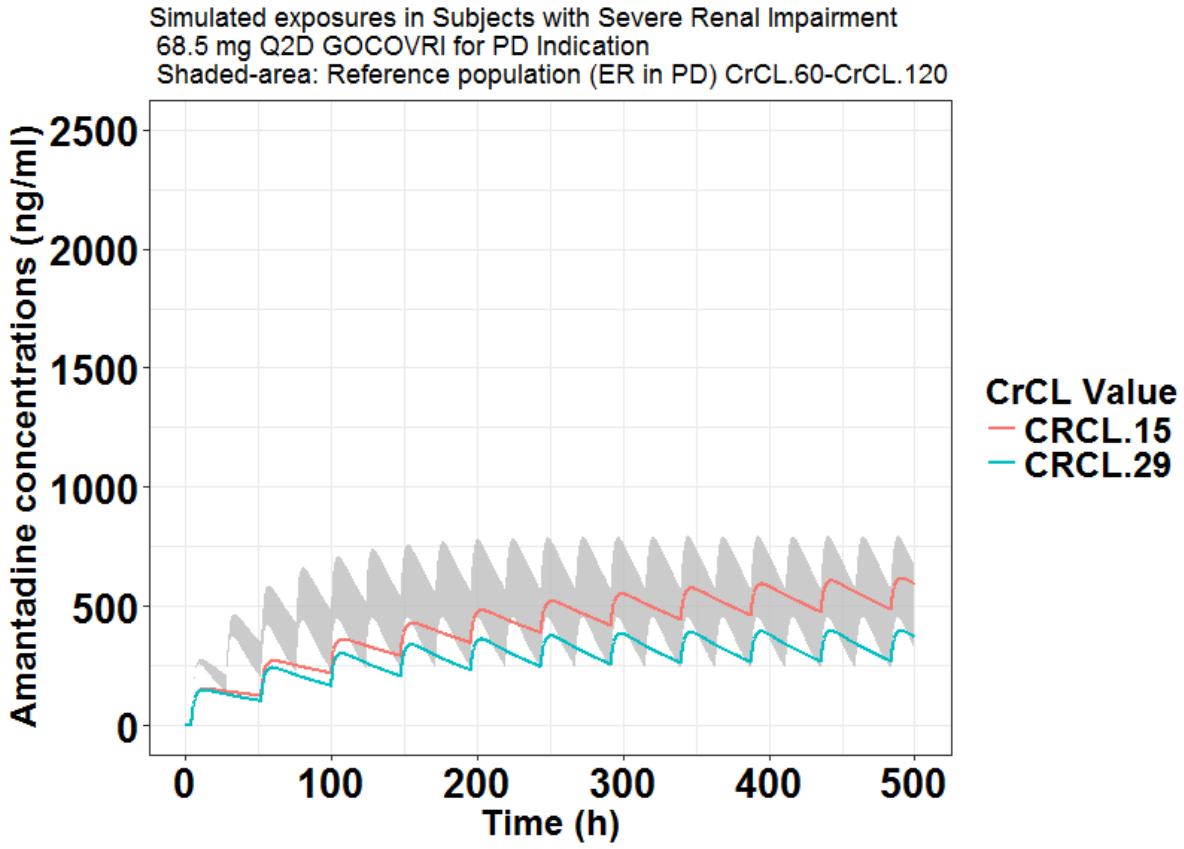
Figure 14 Simulated exposures in patients with severe renal impairment for treatment of PD indication per the usual dosing recommendation



Dosing recommendation in severe renal impairment for the treatment of PD indication: 68.5 mg QD on alternate days. The simulated profiles represent the extremes for the margins (CrCL15 – CrCL29) of the creatinine clearance of subjects with severe renal impairment. The grey shaded area represents exposures in the margins of renal impairment (CrCL60 and CrCL121) in normal subjects and mildly renally impaired subjects (reference population) per the usual dosing recommendation.

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List of Analysis Codes and Output files

Filename	Description	Link to PM Review Shared Drive
Reviewer_PKModel.phxproj	PK model developed by the reviewer using single-dose and stead-state PK data. This is a Phoenix model file which embeds the dataset. ERsswalldoses_reviewer is the dataset prepared by the reviewer	\\cdsnas\Pharmacometrics\Reviews\Ongoing PM Reviews\Amantadine_NDA208944_GG\FDA Review\QBR
Reviewer_RenalSimulations.phxproj	Model file for simulating different dosing regimens for subjects with various degrees of renal impairment, namely, normal, mild, moderate, severe.	
FinalPK_Parameters.csv	Final PK model parameters based on the model developed by the reviewer	
FinalPKSSwSD.csv	Final PK model evaluation: simulated data after single dose and at steady-state	
Finalplots.R	Post processing of the data for descriptive purposes and also for plotting	
Notes_workflow.csv	Document listing invidual steps as performed by the reviewer	
Sim_<RI>.csv	Simulated datasets for various degrees of renal impairment (RI)	
CrCL-Ke-CL_Calculations.csv	Calculation of Ke used for simulations of various degrees of renal impairment	

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4.4 Bioequivalence Assessment

4.4.1 Sponsor's Analysis

ADS-AMT-PK111 was an open-label, single-center, multiple-dose, 2-period, 2-treatment, balanced crossover study in which 24 healthy subjects were randomly assigned in a 1:1 ratio to receive 1 of 2 dosing treatment sequences (AB or BA) with 12 subjects per sequence:

Treatment A (Test):

- ADS-5102 ER as one 137 mg capsule administered at approximately 20:00 hours on Day 1
- No dosing on Days 2 and 3
- ADS-5102 ER as one 137 mg capsule administered QD at approximately 20:00 hours for 7 days (Days 4 to 10)

Treatment B (Reference):

- Amantadine IR as two 80.6 mg tablets administered at approximately 20:00 hours on Day 1
- No dosing on Days 2 and 3
- Amantadine IR 80.6 mg administered BID at approximately 20:00 hours and 08:00 hours for 7 days (Days 4 to 11; last dose on the morning of Day 11)

There was a 7-day drug-free washout between the last dose in Period 1 and the start of dosing in Period 2.

The key objective was to compare the steady-state PK (observed maximum concentration at steady-state [Cmax,ss], and AUC from time zero to 24 hours post-dose at steady-state [AUC0-24,ss]) of ADS-5102 ER capsules once daily (QD) at a total daily dose of 137 mg (test) versus amantadine IR tablets twice daily (BID) at a total daily dose of 161.2 mg (reference). The plasma amantadine concentration time profiles at steady-state are shown in **Figure 15** below.

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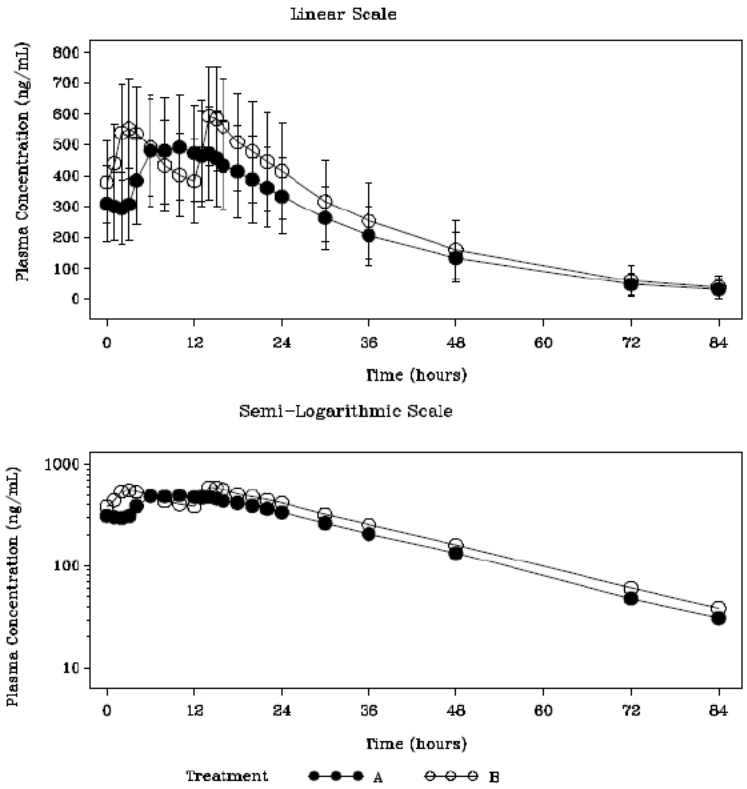
Figure 15 Mean (±SD) plasma amantadine concentration time profiles at steady-state



Abbreviations: BID, twice daily; ER, extended release; IR, immediate release; QD, once daily.
Note: Subject (b) (6) was excluded from the pharmacokinetic analysis populations due to vomiting on Day 1 of Period 1.
Study drug administered at 8PM (or 20:00 hours) for QD administration and 8PM and 8AM (20:00 hours and 08:00 hours) for BID administration.
Treatment A = ADS-5102 ER (170 mg, QD, single and multiple doses).
Treatment B = Amantadine IR (200 mg, QD, single dose and 100 mg, BID, multiple doses).

Source: Study ADS-AMT-PK111 Clinical Study Report: Figure 4 on page 64

The bioequivalence was used using a linear mixed-effect model with the natural log-transformed PK parameters as the dependent variable; treatment, period, and sequence as fixed effects; and subject nested within sequences as a random effect. The results are shown in **Table 8**

Table 8. Bioequivalence assessment – Sponsor's Analysis

Parameter	Treatment	N	Geometric LS Means	Ratio (%) of Geometric LS Means (A/B)	90% CI of the Ratio (%)	Inter-subject CV	Intra-subject CV
$AUC_{0\text{-}24,ss}$ (ng•h/mL)	A	23	9472.8	85.68	(81.45, 90.14)	30.8	10.0
	B	23	11055.7				
$C_{max,ss}$ (ng/mL)	A	23	512.6	86.49	(81.53, 91.76)	27.5	11.7
	B	23	592.7				

Treatment A = ADS-5102 ER (137 mg, QD multiple doses);Treatment B = Amantadine IR (80.6 mg, BID, multiple doses).

Source: Study ADS-AMT-PK111 Clinical Study Report: Table 12, on page 70

Reviewer's comments:

Overall, the sponsor's workflow to assess the bioequivalence between the steady-state exposures of GOCOVRI and IR formulation is acceptable. The results suggest that the analysis meets the bioequivalence criteria and therefore, can be considered bioequivalent based on the steady-state exposures, $C_{max,ss}$ and $AUC_{0\text{-}24h,\ ss}$, more specifically.

4.4.2 Reviewer's Analysis

Introduction

The sponsor is seeking the indication in treating levodopa-induced dyskinesia in patients with Parkinson's disease for GOCOVRI. In the light of the results for the secondary efficacy endpoints, the assessment of bioequivalence is critical to extend to broader indication for the treatment of Parksinson's disease. Therefore, the reviewer performed independent analysis to assess if the steady state exposures, $C_{max,ss}$ and $AUC_{0.24h,ss}$ do indeed meet the bioequivalence criteria.

Objective

To compare the steady-state PK (observed maximum concentration at steady-state [Cmax,ss], and AUC from time zero to 24 hours post-dose at steady-state [AUC0-24,ss]) of ADS-5102 ER

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capsules once daily (QD) at a total daily dose of 137 mg (test) versus amantadine IR tablets twice daily (BID) at a total daily dose of 161.2 mg (reference).

Datasets

Datasets used in the analyses are shown in **Table 9** below.

Table 9: Summary of datasets used

Filename	Description	Link to EDR
dpc.xpt	Pharmacokinetic plasma concentrations analysis dataset	\\cdsesub1\evsprod\nda208944\0001\m5\datasets\ads-amt-pk111\analysis\legacy\datasets\dpc.xpt
dpp.xpt	Pharmacokinetic parameters analysis dataset	\\cdsesub1\evsprod\nda208944\0001\m5\datasets\ads-amt-pk111\analysis\legacy\datasets\dpp.xpt

Software

Phoenix WinNonlin 6.4, Build 7.0.0.2535; Certara USA, Inc., 100 Overlook Center, Suite 101, Princeton, NJ 08540 USA

Methods

First, the steady-state exposures, $C_{max,ss}$ and $AUC_{0-24,ss}$ following the administration of the ER and IR formulations were estimated using non-compartmental analysis. Subsequently, bioequivalence was assessed using a linear mixed-effect model with the natural log-transformed PK parameters, namely, $AUC_{0-24h,ss}$, $C_{max,ss}$ as the dependent variable; treatment, period, and sequence as fixed effects; and subject nested within sequences as a random effect.

Results

The reviewer's results were comparable to the sponsor's results (shown in **Table 10** below)

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Table 10 BE- Assessment – Reviewer's analysis

Parameter	Treatment	N	Geometric LS Means	Ratio of Geometric LS Means	90% CI of Ratio (%)	Inter Subject CV (%)	Intra Subject CV (%)
$AUC_{0-24,ss}$ (ng.h/ml)	*Capsule*	*23*	*9473.43*	*85.71*	*(81.47, 90.17)*	*30.8*	*10*
	Tablet	*23*	*11053.08*				
$C_{max,ss}$ (ng/ml)	*Capsule*	*23*	*512.61*	*93.24*	*(87.27, 99.61)*	*27.1*	*13.1*
	Tablet	*23*	*549.79*				
Sponsor's results							
$AUC_{0-24,ss}$ (ng.h/ml)	Capsule	23	9472.8	85.68	(81.45, 90.14)	30.8	10
	Tablet	23	11055.7				
$C_{max,ss}$ (ng/ml)	Capsule	23	512.6	86.49	(81.53, 91.76)	27.5	11.7
	Tablet	23	592.7				

In conclusion, given the significant results on the key secondary efficacy endpoints and meeting the bioequivalence criteria with the reference listed drug, GOCOVRI indication can be extended to treatment of Parkinson's disease

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List of analyses: Codes and Output files

Filename	Description	Link to PM Review Shared Drive
Reviewer_BE.phxproj	Independent BE assessment by the reviewer with embedded datasets with the exposure metrics ($C_{max,ss}$, $AUC_{0-24,ss}$) calculated from the raw plasma concentration data	\\cdsnas\Pharmacometrics\Reviews\Ongoing PM Reviews\Amantadine_NDA208944_GG\FDA Review\BE_Assessment
auc24ss.csv	Final dataset with $AUC_{0-24h,ss}$ for both the formulations	
cmaxss.csv	Final dataset with $C_{max,ss}$ for both formulations	
cpt_ss.csv	Dataset of the plasma concentration data at steady state	
Reviewer_BE.R	Pre-processing for dataset compilation	

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/s/

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08/23/2017

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