CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209510Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Memorandum

Joint Summary Review (Cross Discipline Team Leader / Signatory)

From	Erica Lyons, MD, Medical Team Leader, Division of Gastroenterology and Inborn Errors Products (DGIEP) Jessica Lee, MD, MMSc., Associate Director, DGIEP Victor Crentsil, MD, Deputy Office Director (Acting), ODE III
Subject	Joint Summary Review (Cross Discipline Team Leader / Signatory)
NDA #	209510
Applicant	Acacia Pharma Ltd.
Date of Submission	August, 26, 2019 (Class 2 Resubmission)
PDUFA Goal Date	February 26, 2020
Proprietary Name / Established (USAN) names	BARHEMSYS (amisulpride) injection, for intravenous use
Pharmacologic Class	Dopamine-2 (D_2) antagonist
Dosage forms / Strength	Injection: 5 mg/2 mL (2.5 mg/mL) in a single-dose vial.
Dosing Regimen	5 and 10 mg
Proposed Indications	BARHEMSYS is indicated in adults for: • Prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class. • Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis.
Recommended Action:	Approval

The original NDA for Barhemsys (IV amisulpride) was submitted on October 5, 2017. The NDA met conditions for approval except for issues regarding the manufacturing site (b) (4), (b) (4). The facilities reviewer concluded that "there appears to be significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history and relevant experience." For additional details, please refer to the October 5, 2018 Multidisciplinary Review. Due to the above-mentioned deficiencies at the manufacturing site, the Office of Product Quality (OPQ) made a recommendation of a Complete Response (CR) action for this NDA per 21 CFR 314.125(b)(13), and the Agency issued a CR on October 5, 2018. The CR letter indicated that approval of the NDA will require resolving the issues identified at the manufacturing site. Specifically, the CR letter stated the following: "During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility at the close of the inspection. Satisfactory resolution of these observations is required before this

NDA may be approved."

A resubmission of the application was received on November 5, 2018. A repeat inspection found that the deficiencies that were identified at the manufacturing facility (b) (4) (b) (4) in the previous review cycle had not been resolved. The facilities reviewer concluded that "there appears to be significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience." As a result, OPQ made a recommendation of a CR action for this NDA per 21 CFR 314.125(b)(13). For full details, please see the April 24, 2019 OPQ review. The Agency issued a second CR on May 2, 2019. The CR letter indicated that approval of the NDA will require resolving the issues identified at the manufacturing site. The CR letter restated the following: "During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility at the close of the inspection. Satisfactory resolution of these observations is required before this NDA may be approved."

A second resubmission for this application was received on August, 26, 2019. In this submission, Acacia Pharma proposed a new amisulpride drug substance supplier, (b) (4) (b) (4) in addition to retaining (b) (4) as an amisulpride drug substance supplier to support approval of NDA 209510 as they attested that the previous deficiencies that prevented approval at the (b) (4) site had been satisfactorily resolved. Additionally, Acacia Pharma proposed revisions to the proposed USPI (b) (4) (b) (4) for Agency review. As this study was completed on August 13, 2018 and there have been no ongoing nonclinical or clinical studies for amisulpride since NDA 209510 was resubmitted to FDA in November 2018, a Safety Update was not provided with this resubmission. For details from the most recent Safety Update, please see the May 1, 2019 clinical review from Dr. Marjorie Dannis.

A consultation from the Interdisciplinary Review Team for Cardiac Safety Studies was obtained to review the results of study DP10022. Please see the December 16, 2019 and January 24, 2020 reviews by Christine Garnett, Pharm.D. for full details. In summary, the team concluded, "Study #DP10022 is not a thorough QT (TQT) study and the QTc effects are not appropriately characterized. (b) (4) (b) (4) Revisions to the proposed label were recommended (b) (4) (b) (4) (b) (4). In the October 5, 2018 Multi-Disciplinary Review, the following recommendations were made in the Benefit-Risk Assessment for NDA 209510, (pg. 22):

(b) (4)

(b) (4)

According to the January 24, 2020 review by Dr. Garnett, 10 mg of amisulpride infused intravenously over 1 minute has a maximal predicted (95% upper predication interval) ΔΔQTcF of 13.4 (15.1) milliseconds. Concentration-dependent prolongation of the QTc interval for ondansetron was established in the TQT study #S3A115458 under NDA 020007, (see October 15, 2012 and December 15, 2012 QT-IRT Reviews by Dr. Jeffry Florian). Based on the concentration-QT relationship established by in study #S3A115458, the maximum mean (95% upper predication interval) ΔΔQTcF for a Cmax of 90 mg/ml of ondansetron was predicted to be 3.7 (4.4) milliseconds. In study #DP10022, the mean Cmax from a 4 mg intravenous dose of ondansetron infused over 1 minute was 85.3 ng/ml. The maximal predicted prolongation from a 4 mg intravenous dose of ondansetron infused over 1 minute (the approved dose for PONV) was approximated to be 3.6 milliseconds based on the mean Cmax from study #DP10022 (85.3 ng/ml) relative to the Cmax from study #S3A115458 (90 ng/ml) and the established concentration-response relationship.

Using the predicted values, the total effect of a 10 mg dose of amisulpride given with a 4 mg dose of ondansetron, each infused intravenously over 1 minute, would be approximately 17 milliseconds (13.4 milliseconds from amisulpride and 3.6 milliseconds from ondansetron). As per the October 2015 Guidance for Industry: *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*, "The data on drugs that prolong the mean QT/QTc interval by more than around 5 and less than 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk. Drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic, and might have clinical arrhythmic events captured during drug development." Given the limited anticipated contribution of ondansetron to the total maximal predicted ΔΔQTcF, ECG monitoring during co-administration of ondansetron and amisulpride infusion should be adequate; (b) (4) (b) (4). For additional details regarding the estimation and assessment of the impact of co-administration of amisulpride and ondansetron on the QTc interval, please see the February 21, 2020 Clinical Pharmacology review by Dr. Dilara Jappar.

The recommendation to conduct ECG monitoring in patients with pre-existing arrhythmias/cardiac conduction disorders, electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, and in patients taking other medicinal products (e.g., ondansetron) or with other medical conditions known to prolong the QT interval was retained in both the *Highlights of Prescribing Information* and section 5, *Warnings and Precautions* of the label. ECG monitoring was also maintained as a recommendation for patients taking other drugs known to prolong the QT interval in section 7, *Drug Interactions*, of the label.

Additionally, Acacia Pharma proposed a labeling revision (b) (4) (b) (4) in section 6.2, *Postmarketing Experience*. To assist with the evaluation of this request, the Office of Surveillance and Epidemiology/Division of Pharmacovigilance was consulted. Office of Surveillance and Epidemiology/Division of Pharmacovigilance recommended (b) (4)

(b) (4) section 6.2 and confirmed that the terms selected to describe adverse events in the section were acceptable and reflect chronic use of oral amisulpride. Please see the November 13, 2019 review by Michelle Hines, Pharm.D. for full details. We agreed with the Office of Surveillance and Epidemiology/Division of Pharmacovigilance's recommendations. After additional discussions with the Applicant, the listed adverse events were refined to exclude those that were not relevant to the single dose regimen of Barhemsys (IV amisulpride) for the prevention or treatment of PONV.

To assess the status of the previously identified deficiencies that resulted in CR actions on October 5, 2018 and May 2, 2019, both facilities (b) (4) (b) (4) underwent inspections in January 2020. Following these inspections, Acacia Pharma was notified of the general facilities status and 483 items for which a response was needed. According to the facilities reviewer, "(b) (4) has provided adequate information in response to the 483 issued for the January 27-31, 2020 inspection and there are no inspectional issues identified that require further questions for review". On February 21, 2020, Acacia Pharma submitted an update to the application to remove (b) (4) as a manufacturing facility for the application. As a result, the Office of Process and Facilities (OPF) has made a final overall "Approval" recommendation for the facilities involved in this application. For additional details, please see the February 24, 2020 Office of Product Quality (OPQ) review.

The following PMRs will be issued for this application:

REQUIRED PEDIATRIC ASSESSMENTS / PREA PMRs

3478-1 Confirmatory repeat dose toxicity study of intravenous amisulpride in juvenile rats (Study BGX0023).

Study Completion: 06/2020
Final Report Submission:10/2020

This juvenile animal toxicity study is required to support the safety of amisulpride in pediatric patients. The full report of the study must be submitted for the Agency's review to assess the safety of IV amisulpride in pediatric patients prior to initiation of pediatric clinical trials.

3478-2 Randomized, double-blind, placebo-controlled, dose-ranging study of Barhemsys (amisulpride) for I.V. injection as prophylaxis for postoperative nausea and vomiting in children aged 0-17 years.

Draft Protocol Submission: 10/2020
Final Protocol Submission: 08/2021
Study/Trial Completion: 12/2023
Final Report Submission: 06/2024

3478-3 Randomized, double-blind, active-controlled, dose-ranging study of Barhemsys (amisulpride) for I.V. injection as treatment of children aged 0-17 years with postoperative nausea and vomiting.

Draft Protocol Submission: 10/2020
Final Protocol Submission: 08/2021
Study/Trial Completion: 12/2023
Final Report Submission: 06/2024

The goals of PMRs 3478-2 and 3478-3 are to obtain safety and efficacy data in order to inform labeling for pediatric use.

POSTMARKETING REQUIREMENTS UNDER 505(o)

3874-4 A pharmacokinetic study following a single dose of Barhemsys (IV amisulpride) in patients with severe renal impairment and end-stage renal disease (i.e., eGFR < 30 mL/min/1.73 m^2) and healthy subjects as a control group.

Draft Protocol Submission: 07/2020
Final Protocol Submission: 10/2020
Study/Trial Completion: 05/2021
Final Report Submission: 11/2021

PMR 3874-4 was issued because the pharmacokinetics of Barhemsys (IV amisulpride) in patients with severe renal impairment/end-stage renal disease needs to be adequately characterized for dosing recommendations that avoids serious risks. For details on the limitations of the available data from NDA 209510 for evaluation of the effects of severe renal impairment and end-stage renal disease on the pharmacokinetics of Barhemsys (IV amisulpride), please see the October 5, 2018 NDA Multi-Disciplinary Review and Evaluation.

From the clinical perspective, the benefit-risk profile of Barhemsys (IV amisulpride) for the proposed indications are acceptable (See the Multidisciplinary Review and Evaluation dated 10/5/2018 for complete details on NDA 209510 including the benefit and risk analysis for Barhemsys [IV amisulpride]). We agree with OPQ's recommendation for approval of this NDA because the deficiencies at the manufacturing facility have been satisfactorily resolved.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Office of Clinical Pharmacology Review

NDA or BLA Number	209510
Link to EDR	\\CDSESUB1\evsprod\NDA209510\209510.enx
Submission Date	08/26/2019
Submission Type	Class 2 resubmission in response to 5/2/19 CR issued due to manufacturing facility deficiencies
Brand Name	Barhemsys
Generic Name	Amisulpride
Dosage Form and Strength	Injection: 5 mg/2 mL (2.5 mg/mL) in a single-dose vial
Dosing Regimen	5 and 10 mg
Pharmacological Class	dopamine-2 (D2) antagonist
Proposed Indication	• Prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class. • Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or who have not received prophylaxis.
Applicant	Acacia Pharma Ltd
PDUFA goal date	February 26, 2020
OCP Review Team	Dilara Jappar, Ph.D. (Clinical Pharmacology Reviewer) Insook Kim, Ph.D. (Clinical Pharmacology Team Leader)

1. EXECUTIVE SUMMARY

The original NDA 209510 for amisulpride injection (APD421) was submitted on 10/05/2017. Due to the deficiencies in facility inspection, NDA 209510 amisulpride injection had received a complete response (CR) on 10/05/2018. The NDA received a 2nd CR on 5/2/19 in response to Applicant's 11/5/18 resubmission because the facility issues were not adequately addressed.

During the 1st cycle, the clinical pharmacology program for NDA 209510 was fully evaluated by Dr. Sojeong Yi (please refer to Multidisciplinary Review and Evaluation dated on 10/5/18).

This current NDA submission was submitted on 8/26/19 in response to the 5/2/19 CR letter. In this current submission, in addition to addressing the facility inspection issue, the Applicant had also submitted a new study report, DP10022 titled "A Randomized, Double-blind, Placebo-controlled, Crossover Study in Healthy Adult Subjects to Investigate the Effect of Intravenous APD421, with and without Ondansetron, on Cardiac Conduction." Applicant also proposed QT related labeling changes in their draft proposed PI submitted with the 8/26/19 resubmission. In this study, the impact of 10 mg IV amisulpride on QT prolongation with and without ondansetron was evaluated as well as the PK of 10 mg IV dose amisulpride and ondansetron . The newly obtained PK data at 10 mg IV amisulpride infused over 1 minute was proposed to be included in the label.

Effects on QT Prolongation:

In the 1st cycle submission dated 10/05/2017, the Applicant conducted a thorough QT (tQT) study (Study DP10013) in which amisulpride prolonged the QT interval in a concentration-dependent manner. In the tQT study, amisulpride at the 5-mg dose proposed for the prevention of PONV did not have a significant effect of amisulpride on the QT interval (ΔΔQTcF 90% CI upper bound: 7.1 ms). On the other hand, at a supra-therapeutic dose (40 mg infused over 8 min, mean Cmax of 1305 ng/mL), a significant effect on the QT interval was observed with the largest ΔΔQTcF of 23.4 ms (90% CI upper bound: 25.5 ms). The effects of amisulpride 10 mg on the QT interval were not studied in the tQT study but were predicted to be 12.6 ms (90% upper CI: 14.1 ms) based on the QT-IRT team's concentration-QT relationship analysis.

In this current submission, QT-IRT team was consulted to review the QT data from the newly submitted study DP10022 which evaluated the effect of 10 mg IV amisulpride infused over 1 minute on QT interval, with and without 4 mg ondansetron infused over 1 minute. Please refer to the QT-IRT consult review dated 12/16/2019 and the addendum dated 1/24/2020 by Dr. Girish Bende for further details. According to the QT-IRT team's review, the effects on the QTc interval are not appropriately characterized as the study did not include a positive control or had a sufficiently large exposure margin to waive the requirement for a positive control. (b) (4)

(b) (4)

Instead, the QT-IRT team predicted the ΔΔQTcF of 10 mg amisulpride infused over 1 minute based on the newly obtained observed PK data in Study DP10022 using the concentration-QT relationship model developed in previous review (QT-IRT Review dated 01/12/2018) with non-linear Emax model. The predicted ΔΔQTcF of 10 mg amisulpride infused over 1 minutes was 13.4 msec at the Cmax (451 ng/mL) and predicted to return to <5 msec within 10 min after 10 mg dose (Table 1). However, there was an approximlatey of 5-10 minutes delay observed between the peak amisulpride concentration and the maximum increase in the QT interval; therefore, it may take longer than 10 min from the completion of dosing (Figure1) for ΔΔQTcF to return to <5 msec.

Table 1: Predicted ΔΔQTcF for 10 mg amisulpride infused over 1 minute in study DP10022 (FDA analysis)

ECG parameter	**Time Post Dose** (min)	**Mean Plasma Concentration** (ng/mL)	ΔΔ**QTcF** (msec)	*90% CI* (msec)
QTc	Tmax (3.18 min)	451	13.4	(11.7 to 15.1)
QTc	10 min	140	4.9	(3.9 to 6.0)
QTc	20 min	86	2.8	(2.0 to 3.7)
QTc	30 min	68	2.0	(1.3 to 2.9)
QTc	60 min	43	0.9	(0.2 to 1.8)
QTc	120 min	34	0.5	(-0.2 to 1.4)

Source:

- *CSR study DP10022, Table 14.2.3.1 and Table 14.2.3.3 for time course & plasma concentration*
- *QT-IRT consult review dated 12/16/2019 and addendum dated 1/24/2020 by Dr. Girish Bende*
- *Predicted based on an Emax model as described in the QT-IRT review of the thorough QT study DP10013 (Dt: 01/12/2018).*

In this study, when 4 mg IV ondansetron was infused over 1 minute with simultaneous infusion of 10 mg IV amisulpride over 1 minute, ondansetron mean Cmax was 85.3 ng/mL, which was similar to the Cmax of 8 mg IV ondansetron infused over 15 minutes (90 ng/mL) (Refer to Pharmacometric review of NDA 20007 by Dr. Jeffry Florian dated 12/15/2012). The maximum mean (95% upper confidence bound) ΔΔQTcF was 5.6 (7.4) msec for 8 mg IV ondansetron infused over 15-minute (Refer to Zofran Injection label), and was predicted to be 3.7 (4.4) msec at 90 ng/mL based on the conc.-QT relationship (Refer to Pharmacometric review of NDA 20007 by Dr. Jeffry Florian dated 12/15/2012).

When ondansetron is simultaneously administered with amisulpride, the additive effects of QT prolongation from ondansetron component is anticipated to be less than 5.6 msec. As the potential QT prolongation from 10 mg amisulpride is expected to be approximately 13.4 msec, ECG monitoring is recommended when patients taking amisulpride with other medicinal products known to prolong the QT interval such as ondansetron.

RECOMMENDATION:

From the clinical pharmacology standpoint, there is no remaining issue that preclude the approval provided a mutual agreement is reached for the labeling.

The proposed labeling in Section 12.3 regarding the PK data on 10 mg IV amisulpride infused over 1 minute is acceptable. (b) (4)

(b) (4)

(per QT-IRT consult. The labeling language is under negotiation.

INDIVIDUAL STUDY REVIEW

Study DP10022

Title: A randomised, double-blind, placebo-controlled, crossover study in healthy adult subjects to investigate the effect of intravenous APD421, with and without ondansetron, on cardiac conduction

Clinical Site: (b) (4) Early Phase Clinical Unit (EPCU) London
Study Date: 07/04/2018 to 08/13/2018

Objective:

- To assess the effect of a rapid infusion of 10 mg intravenous (IV) APD421 on the corrected QT (QTcF) interval
- To assess the effect of a single IV dose of 10 mg APD421 when coadministered with a single IV dose of 4 mg ondansetron on the QTcF interval

Study Design: This was a single-center, randomized, double-blind, placebo-controlled, three-period, crossover phase I study in healthy adult subjects to investigate the effect of IV APD421, with and without ondansetron, on cardiac conduction.

Investigational Products: APD421 (amisulpride) Solution for IV Injection (2.5 mg/mL) at 10 mg administered as an IV infusion over 1 min.

Treatments:

1. IV Placebo infused over 1 min, followed by second identical placebo infusion 2 h later
2. Infusion of IV APD421 10 mg, over 1 min, followed by second identical APD421 infusion 2 h later
3. Infusion of IV APD421 10 mg, over 1 min, plus simultaneous infusion of ondansetron 4 mg, over 1 min; followed by placebo infusion 2 h later

Figure 1 Study Sequence

Period 1*	Washout ≥2 complete days	Period 2*	Washout ≥2 complete days	Period 3*
APD421		IV-P		APD421+OND
IV-P		APD421+OND		APD421
APD421+OND		APD421		IV-P

*Example sequences shown
APD421 = APD421 at 10 mg infused over 1 min
APD421+OND = APD421 at 10 mg and ondansetron at 4 mg, both infused over 1 min
IV-P = intravenous placebo infused over 1 min

Study Population: The study included healthy males and non-pregnant, non-lactating females ages between 18-65 with good health. This study enrolled 30 subjects and 29 of completed the study as planned (one withdrawal).

Pharmacokinetic Measurements:

Table 2: Timing of Assessments, Periods 1-3

Protocol Time (hh:mm)	Study Drug Administration	PK Blood Sampling (APD421)	PK Blood Sampling (OND)	12-Lead ECG	ECG Extraction
Pre-dose		X			X[c]
00:00	X				
00:01	(End of infusion)	X[a]	X[a]		X
00:05		X	X		X
00:10		X	X	X	X
00:20		X	X		X
00:30		X	X		X
01:00		X	X		X
02:00	X	X[b]	X[b]		X
02:01	(End of infusion)	X[a]			X
02:05		X			X
02:10		X		X	X
02:20		X			X
02:30		X			X
03:00		X			X

04:00		X	X		X
06:00		X			X

a PK sample drawn immediately after completion of dosing infusion (delayed accordingly if infusion slowed or interrupted)
b PK sample drawn immediately prior to dosing
c 3 time points prior to dosing (-45, -30 and -15 min)

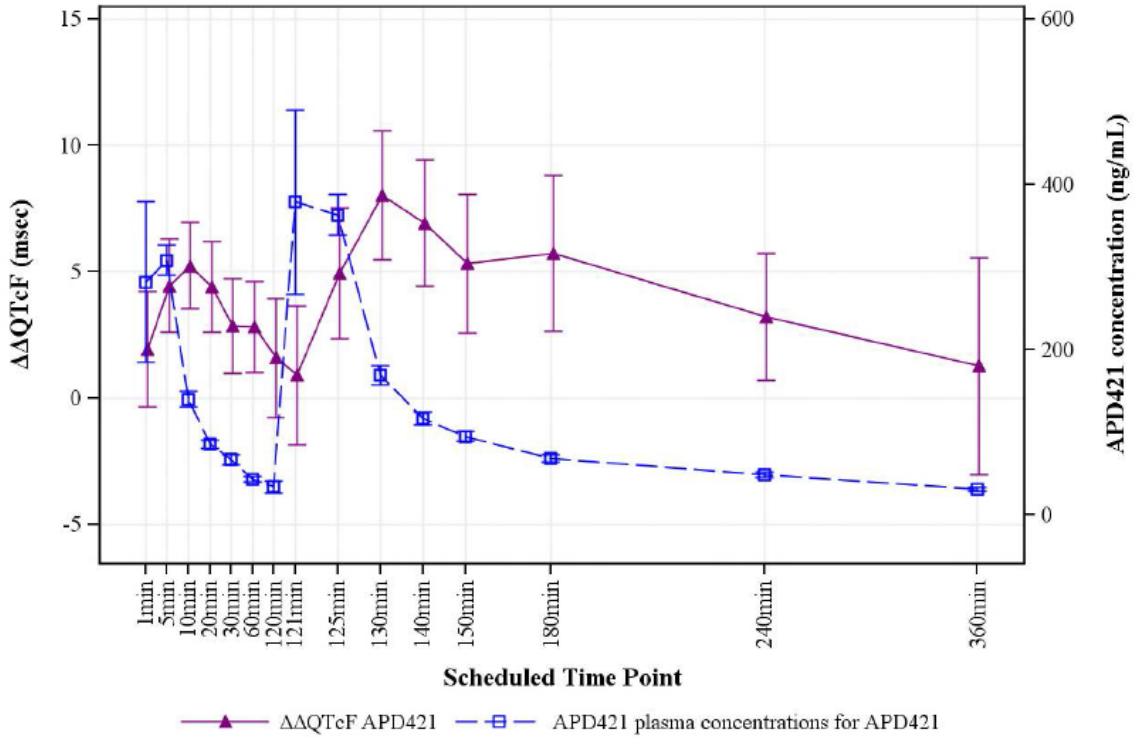
Results:

QT Prolongation (ECG): The QT-IRT Team was consulted to evaluate the ECG data to assess the QT prolongation potential of 10 mg IV APD421 infused over 1 minute with and without ondansetron. Please refer to the QT-IRT consult review dated 12/16/2019 and addendum dated 1/24/2020 by Dr. Girish Bende for further details. According to the QT-IRT team's review, the effects on the QTc interval are not appropriately characterized in this study as the study did not include a positive control or had a sufficiently large exposure margin to waive the requirement for a positive control. (b) (4)

(b) (4).

In addition, QT-IRT team noted that there was a delay observed between peak amisulpride concentration and maximum increase in the QTc interval (Figure 1). The Applicant's analysis did not account for this delay which will negatively bias the slope of the concentration-QTc relationship and result in an underprediction of the increase in QTc at higher concentrations.

Figure 1: Plasma concentration and ΔΔQTcF Versus Time profile [Study # DP10022]



Source: Cardiac Safety Report, Figure 14.2.2.6.1.1

APD421 (amisulpride) PK:

Table 3: Descriptive Statistics of APD421 Plasma PK Parameters

Treatment A: 10 mg APD421 infused over 1 min (n=29): APD421 administered twice at 0, and 2 hours.

Parameter	C_{1max} ng/mL	T_{1max} hr	C_{2max} ng/mL	T_{2max} hr	$AUC_{(0-2)}$ h*ng/mL	$AUC_{(0-inf)}$ h*ng/mL	t½ h	CL L/h	Vss L
Mean	451.03	0.053	515.90	2.049	135.87	545.13	2.619	39.02	156.8
SD	229.635	0.0337	234.321	0.0339	27.948	150.395	0.4956	9.498	36.74
Geometric mean	411.24	0.041	475.33	2.049	133.16	527.94	2.577	37.88	151.7
Median	335.00	0.083	443.00	2.017	134.2	512.22	2.464	39.05	149.2
Range	277-1120	0.02-0.08	261-1260	2.02-2.08	96.0-192.2	319.2-1075.9	2.03-3.89	18.6-62.7	50-230

Treatment B: 10 mg APD421+4 mg Ondansetron, both infused over 1 min (n=30): ADP421 administered once.

Parameter	C_{max} ng/mL	T_{1max} hr	$AUC_{(0-inf)}$ h*ng/mL	t½ h	CL L/h	V_{ss} L
Mean	463.03	0.037	289.10	3.798	35.65	149.7
SD	256.565	0.0311	51.391	0.9413	6.315	40.23
Geometric mean	409.17	0.027	284.76	3.689	35.12	144.5
Median	389.00	0.017	278.19	3.724	35.95	143.7
Range	164.0- 1170.0	0.02-0.08	202.4-398.0	2.05-6.36	25.1-49.4	79-261

C1max and C2max refer to the Cmax for phase 1 (time 0:00 to 2:00) and phase 2 (time 2:00 to 6:00), respectively. Cmax: peak plasma concentration; AUC(0-inf): area under concentration curve from time zero to infinity; t½: half-life; CL: clearance; Vss: volume of distribution at steady state
Source: CSR study DP10022, Table 15, (page 66)

Ondansetron PK: When IV ondansetron 4 mg was infused over 1 minute with simultaneous infusion of IV APD421 10 mg over 1 minute, ondansetron mean (SD) C_{max} was 85.3 (81.08) ng/mL and AUC_{0-inf} was 142.24 (46.59) ng·h/ml with a half-life of 4.52 (1.6) hr.

APPENDIX:

Bioanalytical Assay Method:

Amisulpride

Concentrations of amisulpride in human plasma (K_2 EDTA) were measured by a validated LC/MS/MS at (b) (4) according to the validation report titled "Validation of an LC-MS/MS method for the measurement of amisulpride in human plasma" (Project No: (b) (4) 115501QB02). This was the same bioanalytical method that was used in the previous clinical pharmacology studies for NDA 209150. Please refer to Multidisciplinary Review and Evaluation for NDA 209510 dated 0/5/18 for further details on the bioanalytical method validation report.

Plasma samples were stored frozen at -20°C until analysis. Samples were stored for a maximum of 29 days between the date of collection and the date of sample extraction. This is within the validated sample storage period of 259 days when stored in a freezer set at -20°C.

Table 4: Bioanalytical assay of APD421 (amisulpride)

Lower limit of quantification	2.00 ng/mL
Standard Curve:	2.00-2000 ng/mL with linear regression ($1/X^2$ weight)
Quality Control (QC) levels	6.00 ng/mL, 60.0 ng/mL, 1500 ng/mL
Analytical method	Liquid-liquid extraction with LC-MS/MS detection

Incurred sample reproducibility (ISR)	ISR acceptance criteria met (79% of samples within 20% of their mean value)

- During sample analysis the back-calculated concentrations of the amisulpride calibration standards were within ±15% RE of the nominal value (±20% RE at the LLOQ) for at least 75% of the calibration standards in each accepted analytical batch.
- The accuracy values of the amisulpride QC samples were within ±15% RE of the nominal values for at least two-thirds of the QC samples (at least 50% at each concentration level) in each accepted batch. The mean precision and accuracy for the low, medium and high QC samples were ≤8.9% CV and were within 1.3% to 5.3% RE, respectively, indicating that the method performed reliably during the analysis of study samples.

Ondansetron:

Concentrations of ondansetron in human plasma (dipotassium EDTA) were measured by a validated HPLC/MS/MS method at (b) (4) according to the validation report titled "Quantitation of Ondansetron in Human Plasma via HPLC with MS/MS Detection," (Project No: P1434.01).

- Plasma samples were stored frozen at -20°C until analysis. Samples were stored for a maximum of 68 days between the date of sample collection (07/04/2018 to 08/13/2018) and the date of sample analysis (09/04/2018 to 09/10/2018) and were analyzed within the demonstrated long-term storage stability in human plasma containing dipotassium EDTA at -20 °C (135 days).
- Each calibration curve was calculated using a linear (1/concentration² weighted) least-squares regression algorithm During sample analysis, the back-calculated concentrations of the ondansetron calibration standards (0.05 to 250 ng/mL) were within ±15% RE of the nominal value (CV%<6.88% & RE of -2.36% to 3.52%).
- The accuracy values of the QC samples (1.25, 3.00, 12.0, 40.0, and 190 ng/mL) were within ±15% RE of the nominal values for at least two-thirds of the QC samples. The mean precision was CV% ≤6.74% and accuracy (RE) were within -1.88% to 1.33%, indicating that the method performed reliably during the analysis of study samples.
- 10% of the samples re-analyzed as the incurred samples reanalysis (ISR) to demonstrate the reproducibility. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20% in all studies.
- There was no interference for measurement of ondansetron when samples were fortified with amisulpride.

Table 5: Bioanalytical Method Validation for Ondansetron

Bioanalytical Method:	Quantitation of Ondansetron in Human Plasma via HPLC with MS/MS Detection
Lower limit of quantification	0.05 ng/mL
Upper limit of quantification	250 ng/mL
Standard Curve Range:	0.500, 0.900, 1.80, 5.50, 22.0, 75.0, 200, and 250 ng/mL with linear regression ($1/X^2$ weight)
Quality Control (QC) levels	0.05, 1.25, 3.00, 12.0, 40.0, and 190 ng/mL
Intra-assay Precision	<7.81%

Intra-assay Accuracy	-1.56% to 12.3%
Inter-assay Precision	< 8.80
Inter-assay Accuracy	0.371% to 7.26%
Recovery	>93%
Stability at -20^{o}C	135 days
Stability at 2 to 8^{o}C	29 Days
Stability at Room Temperature	25 hours
Freeze-thaw at -70^{o}C	5 cycles
Freeze-thaw at -20^{o}C	5 cycles
Stability in whole blood	2 hours on ice & at room temperature

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/s/

DILARA JAPPAR
02/21/2020 02:24:28 PM

INSOOK KIM
02/21/2020 02:40:37 PM

Safety Update Review

This Safety Update Report summarizes the latest worldwide safety experience with amisulpride from June 18, 2018 to October 26, 2018.

Clinical Trial Data

Since the original submission of the NDA, there has been one clinical trial involving 30 healthy volunteers, 29 of whom received three administrations of a 10-mg IV amisulpride dose during a one-week period (total administered dose 30 mg, maximum 20 mg in one day), and one of whom received one 10-mg administration (total administered dose 10 mg).

Between June 18, 2018 and October 26, 2018, 30 healthy volunteers have been given up to three doses, infused by syringe driver over 1 minute, in the Applicant's Phase 1 Study DP10022, designed to obtain additional pharmacokinetic data on single and repeat dosing of 10 mg amisulpride. This double-blind, cross-over study included a placebo control dosing period and was conducted at a single, specialist Phase 1 unit in the United Kingdom. There were no deaths or serious adverse events reported in Study DP10022. One subject chose to discontinue from the study after experiencing moderate pain during placebo study drug infusion. The pain lasted for 4 minutes and resolved without sequelae and without the need for medication. A total of 37 adverse events were reported in subjects during two periods of amisulpride dosing; all events appeared to be mild or moderate in severity. A further 23 events were reported in subjects during one period of placebo administration. As displayed in Table 1 below, adverse events which occurred in amisulpride and placebo appeared to be similar in nature and frequency. Administration site conditions, such as mild, transient infusion site pain, occurred commonly in Study DP10022, but not more commonly during amisulpride infusions than during placebo infusions. Accordingly, there is no significant incidence of any other event and no change in the general nature and frequency of adverse events compared to the original NDA.

Table 1: Adverse Events Reported in Study DP10022 (Healthy Volunteers)

	Period A APD421 10 mg* N = 29 n (%) E	Period B APD421 10 mg† N = 30 n (%) E	Period C Placebo§ N = 30 n (%) E
All AEs	9 (31.0%) 19	11 (36.7%) 18	15 (50.0%) 23
Deaths	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
AEs leading to discontinuation	0 (0.0%) 0	0 (0.0%) 0	1 (3.3%) 1
Serious AEs	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Severe AEs	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Moderate AEs	5 (17.2%) 7	2 (6.7%) 2	5 (16.7%) 5
Mild AEs	8 (27.6%) 12	10 (33.3%) 16	12 (40.0%) 18
AEs considered related to IMP	9 (31.0%) 17	11 (36.7%) 16	12 (40.0%) 19
AEs reported (preferred term):			
Allergy to arthropod bite	0 (0.0%)	0 (0.0%)	1 (3.3%)
Back pain	1 (3.4%)	1 (3.3%)	0 (0.0%)
Catheter site swelling	0 (0.0%)	0 (0.0%)	1 (3.3%)
Constipation	0 (0.0%)	1 (3.3%)	0 (0.0%)
Cough	0 (0.0%)	0 (0.0%)	1 (3.3%)
Dizziness	0 (0.0%)	2 (6.7%)	1 (3.3%)
Headache	4 (13.8%)	3 (10.0%)	2 (6.7%)
Hordeolum	0 (0.0%)	0 (0.0%)	1 (3.3%)
Infusion site discomfort	0 (0.0%)	1 (3.3%)	0 (0.0%)
Infusion site pain	8 (27.6%)	8 (26.7%)	12 (40.0%)
Nausea	1 (3.4%)	0 (0.0%)	0 (0.0%)
Palpitations	0 (0.0%)	0 (0.0%)	1 (3.3%)
Stomatitis	1 (3.4%)	0 (0.0%)	0 (0.0%)

n = number of subjects experiencing an event; E = number of events
* Two infusions two hours apart, each infused over 1 minute
† One infusion, infused over 1 minute
§ Identical composition to APD421 except for absence of active ingredient, infused over 1 minute

ADP421=amisulpride

Source: Table 1 pg 3-4 of Safety Update Report dated October 18, 2018

Worldwide Experience

A re-query of the Eudravigilance database for suspected adverse drug reactions appears to indicate that, in the year since the original submission of this NDA, the range and frequency of events are consistent with previous experience.

In conclusion, there does not appear to be any significant change in the safety profile of oral or IV amisulpride.

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/s/

MARJORIE F DANNIS
05/01/2019 11:22:40 PM

ANIL K RAJPAL
05/01/2019 11:23:28 PM

Memorandum

Joint Summary Review (Cross Discipline Team Leader / Signatory)

From	Anil Rajpal, MD, MPH, Medical Team Leader, DGIEP Dragos Roman, MD, Division Director (Acting), DGIEP Victor Crentsil, MD, Deputy Office Director (Acting), ODE III
Subject	Joint Summary Review (Cross Discipline Team Leader / Signatory)
NDA #	209510
Applicant	Acacia Pharma Ltd.
Date of Submission	November 5, 2018 (Class 2 Resubmission)
PDUFA Goal Date	May 5, 2019
Proprietary Name / Established (USAN) names	BARHEMSYS (amisulpride) injection, for intravenous use
Pharmacologic Class	Dopamine-2 (D_2) antagonist
Dosage forms / Strength	Injection: 5 mg/2 mL (2.5 mg/mL) in a single-dose vial.
Dosing Regimen	5 and 10 mg
Proposed Indications	BARHEMSYS is indicated in adults for: • Prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class. • Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis.
Recommended Action:	Complete Response

The original NDA for Amisulpride was submitted on October 5, 2017. The NDA met conditions for approval except for issues regarding the manufacturing site (b) (4). The facilities reviewer concluded that "there appears to be significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history and relevant experience." See details in the Multidisciplinary Review (dated October 5, 2018). Due to the above-mentioned deficiencies at the manufacturing site, the Office of Product Quality (OPQ) reviewer made a recommendation of a Complete Response (CR) action for this NDA per 21 CFR 314.125(b)(13). The Agency issued a CR on October 5, 2018. The CR letter indicated that approval of the NDA will require resolving the issues identified at the manufacturing site. Specifically, the CR Letter stated the following: "During a recent inspection of the (b) (4) (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility at the close of the inspection. Satisfactory resolution of these observations is required before this NDA may be approved."

This resulted in a new submission on November 5, 2018. A repeat inspection found that the deficiencies that were identified at the manufacturing facility (b) (4) in the

previous review cycle have not been resolved. Specifically, the facilities reviewer concluded that "there appears to be significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience." These findings preclude approval of this NDA (see the Office of Product Quality (OPQ) Executive Summary dated April 24, 2019 for details).

I agree with the OPQ recommendations that satisfactory resolution of the deficiencies at the manufacturing facility is required before this NDA may be approved.

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/s/

ANIL K RAJPAL
04/30/2019 06:58:52 PM

DRAGOS G ROMAN
04/30/2019 07:39:17 PM

VICTOR CRENTSIL
04/30/2019 08:00:14 PM

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	New Drug Application (NDA)
Application Number(s)	209510
Priority or Standard	Standard
Submit Date(s)	10/05/2017
Received Date(s)	10/05/2017
PDUFA Goal Date	10/05/2018
Action Goal Date	10/5/2018
Division/Office	Division of Gastroenterology and Inborn Errors Products (DGIEP)/ Office of Drug Evaluation III (ODE III)
Review Completion Date	10/4/2018
Established Name	Amisulpride
(Proposed) Trade Name	Barhemsys
Pharmacologic Class	Dopamine-2 (D_2) antagonist
Applicant	Acacia Pharma Ltd.
Formulation(s)	Injection: 5 mg/2 mL (2.5 mg/mL) in a single-dose vial
Dosing Regimen	5 and 10 mg
Applicant Proposed Indication(s)/Population(s)	1) Prevention of postoperative nausea and vomiting (PONV), either alone or in combination with other antiemetics. 2) Treatment of (b) (4) postoperative nausea and vomiting in patients (with or without prior postoperative nausea and vomiting prophylaxis)
Recommendation on Regulatory Action	Complete Response (CR)
Recommended Indication(s)/Population(s) (if applicable)	Not Applicable

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Reviewers of Multi-Disciplinary Review and Evaluation

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Product Quality Application Team Leader	Hitesh Shroff	OPQ/OBP/DBRRIV	Sections: 4.2	Select one: _X__ Authored _____Acknowledged _X__ Cleared
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Nonclinical Reviewer	Dinesh Gautam	OND/ODEIII/DGIEP	Sections: 5.0 and 11.1	Select one: _X__ Authored _____Acknowledged _X__ Cleared
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Nonclinical Team Leader	Sushanta Chakder	OND/ODEIII/DGIEP	Sections: 5.0 and 11.1	Select one: _X__ Authored _____Acknowledged _X__ Cleared
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Statistical Team Leader	George Kordzakhia	OTS/OB/DBIII	Sections: 7.1, 7.2, 8.1, 8.2, 8.3, 8.5, 8.6	Select one: _X__ Authored _____Acknowledged _X__ Cleared
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Clinical	Marjorie Dannis	OND/ODEIII/DGIEP	Sections: 1.1, 1.4, 2, 3, 8.2, 8.6, 9, 12, 13	Select one: _X__ Authored _____Acknowledged _____Cleared
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Clinical Team Leader and Cross Discipline Team Leader	Anil Rajpal	OND/ODEIII/DGIEP	Sections: authored 1.2, 1.3 reviewed/cleared all	Select one: _X__ Authored _____Acknowledged _X___Cleared
	Signature: Anil K. Rajpal -S Digitally signed by Anil K. Rajpal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Anil K. Rajpal -S, 0.9.2342.19200300.100.1.1=1300170204 Date: 2018.10.05 09:40:04 -04'00'			

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Acting Deputy Division Director (DBIII)	Lei Nie	OTS/OB/DBIII	Sections: 7.1, 7.2, 8.1, 8.2, 8.3, 8.5, 8.6	Select one: ____ Authored ____ Acknowledged _X__ Cleared
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Nonclinical ODE Acting Associate Director	Ronald Wange	ONDIO	Sections: 5.0 and 11.1	Select one: _____Authored _____Acknowledged _X__ Cleared
	Signature: Ronald L. Wange -S Digitally signed by Ronald L. Wange -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300236480, cn=Ronald L. Wange -S Date: 2018.10.04 15:18:49 -04'00'			
Acting Division Director (DGIEP)	Dragos Roman	OND/ODEIII/DGIEP	Sections: All	Select one: _____Authored _X__ Acknowledged _X__ Cleared
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Acting Deputy Office Director (ODEIII)	Victor Crentsil	OND/ODEIII	Sections: All	Select one: _____Authored _X__ Acknowledged _X__ Cleared
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Additional Reviewers of Application

OPQ	RPM: Oumou Barry Hitesh Shroff (ALT) Drug Product: Hong Cai/Moo Jhong Rhee Drug Substance: Joseph Leginus/Donna Christner Biopharm: Ge (Larry) Bai/Kimberly Raines Microbiology: Peggy Kriger/John Arigo Manufacturing Facility: Laurie Nelson/Juandria Williams Process: Li Shan Hsieh/Nallaperumal Chidambaram EA: James Laurensen
OPDP	Meeta Patel
OSI	Susan Leibenhaut/Susan Thompson
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OSE/DRISK	Yasmeen Abou-Sayed/Donella Fitzgerald
DMPH	RPM: Matthew Bacho DPMH Peds: Jacqueline Spaulding DPMH Maternal: Carrie Ceresa
IRT-QT	RPM: Devi Kozeli
NDA Project Manager	CAPT Mimi T. Phan

OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management
DPV = Division of Pharmacovigilance

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AUC	area under the curve
BCRP	breast cancer resistance protein
BLA	biologics license application
BRF	Benefit Risk Framework
BW	body weight
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CG	control group
CI	confidence interval
CL	clearance
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
Crl: WI	Charles River Wistar
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P
D2	dopamine type 2
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DGIEP	Division of Gastroenterology and Inborn Errors Products
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DRISK	Division of Risk Management
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EPS	extrapyramidal symptoms
ETA(CL)	interindividual variability of clearance
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice

GRMP	good review management practice
HD	high dose
5-HT3	5-hydroxytryptamine (serotonin) type 3
ICH	International Conference on Harmonization
ICS	inhaled corticosteroids
IM	intramuscular
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LC-MS/MS	liquid chromatography-coupled tandem mass spectrometry
LD	low dose
MACE	major adverse cardiovascular event
MATE	multidrug and toxin extrusion protein
MD	middle dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOAEL	no adverse event level
OAT	organic anion transporter
OCS	Office of Computational Science
OF	objective function
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PONV	postoperative nausea and vomiting
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
QD	daily
REMS	risk evaluation and mitigation strategy
RF	renal function

SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SGE	special government employee
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Acacia Pharma Ltd. submitted this New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for amisulpride injection, for intravenous use (hereafter referred to as amisulpride, proposed proprietary name Barhemsys). Amisulpride, a dopamine-2 (D_2) receptor antagonist, is a new molecular entity (NME). The proposed indications in adult patients are:

- Prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class.
- Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or who have not received prophylaxis.

The proposed dose for the prevention of PONV is 5 mg as a single intravenous dose infused over 1 to 2 minutes at the time of induction of anesthesia. The proposed dose for the treatment of PONV is 10 mg as a single intravenous dose infused over 1 to 2 minutes.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy of amisulpride for prevention of postoperative nausea and vomiting, either alone or in combination with an antiemetic of a different class, was demonstrated in two randomized, double-blind, placebo-controlled, multi-center trials in patients undergoing general anesthesia for elective surgery (Study DP10015 and Study DP10017). In Study DP10015, the patients received monotherapy with amisulpride. In Study DP10017, the patients received amisulpride in combination with one other intravenously administered, non-dopaminergic antiemetic (ondansetron, dexamethasone or betamethasone). In both trials, patients were administered amisulpride at the induction of anesthesia. A dose of 5 mg as a single intravenous injection infused over 1 to 2 minutes at the time of induction of anesthesia is supported by efficacy and safety data from these clinical trials.

Efficacy of amisulpride for treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class, or have not received prophylaxis, was demonstrated in two randomized, double-blind, placebo-controlled, multi-center trials in patients experiencing PONV after general anesthesia for elective surgery (Study DP10018 and Study DP10019). Study DP10018 enrolled patients who had not received prior PONV prophylaxis. Study DP10019 included patients who had received and failed PONV prophylaxis with an antiemetic of another class. Patients were excluded if they had received a D_2 receptor antagonist antiemetic. A dose of 10 mg as a single intravenous injection infused over 1-2 minutes in the event of nausea and/or vomiting after a surgical procedure is supported by efficacy and safety

data from these clinical trials.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Postoperative nausea and vomiting (PONV) is a common and distressing complication of surgery. In general, the incidence of postoperative nausea and vomiting are approximately 50% and 30%, respectively (Gan et al. 2014); however, in high-risk patients, the rate of PONV can be as high as 80%.

Pharmacologically, amisulpride is a D_2 antagonist. D_2 receptors are located in the chemoreceptor trigger zone (CTZ) in the medulla oblongata and respond to the dopamine released from the nerve endings. Activation of CTZ relays stimuli to the vomiting center and leads to emesis.

The efficacy and safety of amisulpride for prevention of PONV (either alone or in combination with an antiemetic of a different class), and for treatment of PONV (in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis) has been adequately assessed in this application.

Amisulpride was evaluated for prevention of PONV in two randomized, double-blind, placebo-controlled, multi-center trials in patients undergoing general anesthesia for elective surgery (Study DP10015 and Study DP10017). In Study DP10015, patients received monotherapy with amisulpride; in Study DP10017, patients received amisulpride in combination with one other intravenously administered, non-dopaminergic antiemetic (ondansetron, dexamethasone or betamethasone). In both trials, patients were administered amisulpride at the induction of anesthesia.

Study DP10015 was conducted in 342 patients (176 in the amisulpride 5 mg arm and 166 in the placebo arm). Study DP10017 was conducted in 1,147 patients (572 in the amisulpride 5 mg arm and 575 in the placebo arm). The primary efficacy endpoint in both trials was Complete Response (CR), defined as absence of any episode of emesis and absence of use of rescue medication within the first 24 hours postoperatively. The treatment difference (drug to placebo) was 12% (95% CI: 2%, 22%) in Study DP10015 (monotherapy) and 11% (95% CI: 5%, 17%) in Study DP10017 (combination with ondansetron, dexamethasone or betamethasone).

Amisulpride was evaluated for treatment of PONV in two randomized, double-blind, placebo-controlled, multi-center trials in patients experiencing PONV after general anesthesia for elective surgery (Study DP10018 and Study DP10019). Study DP10018 enrolled patients who had not received prior PONV prophylaxis; Study DP10019 included patients who had received and failed PONV prophylaxis with an antiemetic

of another class. Patients were excluded if they had received a D_2 receptor antagonist antiemetic.

Study DP10018 was conducted in 369 patients (188 in the amisulpride 10 mg arm and 181 in the placebo arm). Study DP10019 was conducted in 465 patients (230 in the amisulpride 10 mg arm and 235 in the placebo arm). The primary efficacy endpoint in both trials for treatment was CR, defined as absence of any episode of emesis and absence of use of rescue medication within the first 24 hours after treatment (excluding emesis within the first 30 minutes). The treatment difference (drug to placebo) was 10% (95% CI: 1%, 19%) in Study DP10018 and 13% (95% CI: 5%, 22%) in Study DP10019.

The amisulpride safety database consisted of 1,385 patients who received a single dose in placebo-controlled trials. A total of 967 received a dose of 5 mg for prevention of PONV (of whom 572 received another antiemetic concomitantly) and 418 received 10 mg for treatment of PONV.

The most common adverse reactions in Studies DP10015 and DP10017 (for prevention of PONV) were increased blood prolactin levels (amisulpride 5 mg 3% versus placebo 0%), procedural hypotension (3% versus placebo 2%), hypokalemia (3% versus placebo 2%), chills (3% versus placebo 2%), and abdominal distension (2% versus placebo 1%). The most common adverse reaction in Studies DP10015 and DP10017 (for treatment of PONV) was infusion site pain (amisulpride 10 mg 6% versus placebo 4%).

There was one adverse event (AE) leading to discontinuation (peritonitis) in a patient who had received amisulpride (5-mg dose). This AE was not considered to be treatment-related because the peritonitis appeared to be related to the laparoscopic abdominal surgery (hysterectomy) rather than the study drug.

There was one death in a patient receiving amisulpride (5-mg dose). This death does not seem attributable to the study treatment because the patient had multiple comorbidities (including diabetes, morbid obesity, and hypertension) and a complex open abdominal surgery followed by a complicated postoperative course (including systemic inflammatory response syndrome, acute renal failure requiring dialysis, metabolic acidosis, hyperglycemia, hypocalcemia and tachycardia). It should be further noted that amisulpride has a short half-life (4 to 5 hours) and the death occurred 3 days after the patient was given amisulpride, (see Section 8.4.4 Safety Results – Deaths in this Multidisciplinary Review).

There were minor imbalances in serious adverse event (SAE) frequency across the treatment groups but there was no consistent pattern and the numbers were too small to draw definitive conclusions.

In a thorough QT study, amisulpride was shown to cause dose-dependent prolongation of the QT interval. The magnitude of QT prolongation for amisulpride 5 mg is not predicted to exceed the threshold of risk identified in the ICH Guideline E14 (10 ms); however, the magnitude of QT prolongation for amisulpride 10 mg is predicted to exceed this threshold of risk (see Section 6.3.2.2.3 QT Prolongation of this Multidisciplinary Review). Because amisulpride could be administered in combination with ondansetron (which also prolongs the QT interval) for the treatment of PONV, we considered the potential QT effect for this drug combination. Based on whether the magnitude of QT prolongation predicted would exceed the threshold of risk identified in the ICH Guideline E14 (10 ms), we concluded the following:

- Simultaneous or sequential administration of 5 mg amisulpride with 4 mg ondansetron IV (the approved dose of ondansetron for PONV) would be acceptable.
- After administration of amisulpride 10 mg, there must be a delay of at least 30 minutes before administration of ondansetron 4 mg.
- After administration of ondansetron 4 mg, there must be a delay of at least 10 minutes before administration of amisulpride 10 mg.

An analysis of extrapyramidal symptoms (EPS) and neuroleptic malignant syndrome (known adverse events (AEs) with D_2 antagonists) showed that the frequency of possible EPS appears similar for placebo and for both doses of amisulpride, and that there were no events of neuroleptic malignant syndrome identified in the amisulpride clinical development program.

In conclusion, the benefit-risk profile for amisulpride for the indications sought is favorable. PONV is a serious disease because nausea and vomiting can cause serious electrolyte imbalances and dehydration; nausea and vomiting have a significant impact on how patients function. Although there are FDA-approved products with an acceptable risk-benefit profile for the prevention and for the treatment of PONV, amisulpride offers an alternative or additive option for prevention and the treatment of PONV. Efficacy of amisulpride 5 mg for prevention of PONV (either alone or in combination with an antiemetic of a different class) and of amisulpride 10 mg for treatment of PONV (in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis) was demonstrated in the trials submitted. While QT prolongation is a known class risk for D_2 antagonists (including amisulpride), the risks of QT prolongation have been adequately evaluated and can be adequately managed with specific dosing recommendations in drug labeling (particularly for co-administration with ondansetron which also has QT effects). It should be further noted that patients receiving this single IV dose of amisulpride will be subject to intensive monitoring post-administration as the drug will be administered in the operating room and/or post-anesthesia care unit.

While the benefit-risk profile of Barhemsys (amisulpride injection) is favorable for the indications sought, this New Drug Application (NDA) will not be approved during this review cycle because of the deficiencies that have been identified at the manufacturing facility in (b) (4) (b) (4). The Applicant does not have an alternative drug substance manufacturing facility for this NDA; therefore, satisfactory resolution of the deficiencies at the manufacturing facility is required before this NDA may be approved (refer to Section 4.2).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	PONV is a common and distressing complication of surgery (Gan et al. 2014). Risk factors for developing PONV include the following: (1) female gender; (2) nonsmoking status; (3) history of PONV; and (4) postoperative opioid use. The most likely causes of PONV are volatile anesthetics, nitrous oxide, and postoperative opioids.	PONV is a serious disease because nausea and vomiting can cause serious electrolyte imbalances and dehydration. Nausea and vomiting have a significant impact on how patients function.
Current Treatment Options	Approved intravenous anti-emetics for prevention of PONV (by class of anti-emetic) include the following: (1) 5-HT_3 Receptor Antagonists: (a) Zofran (ondansetron) approved in 1991; (b) Anzemet (dolasetron) approved in 1997; and (c) Aloxi (palonosetron) approved in 2003. (2) D_2-Receptor Antagonists: (a) Inapsine (droperidol) approved in 1968; and (b) Reglan (metoclopramide) approved in 1979. (3) H_1 Receptor Antagonists: Phenergan (promethazine) approved in 1956. (The indication wording is "Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.") Approved intravenous anti-emetics for treatment of PONV (by class of anti-emetic) include the following: (1) 5-HT_3 Receptor Antagonists: (a) Zofran (ondansetron) approved in 1991 (The indication includes a statement that "For patients who do not receive prophylactic ZOFRAN Injection and experience nausea and/or vomiting postoperatively, ZOFRAN Injection may be given to prevent further episodes."); (b) Anzemet (dolasetron) approved in 1997. (2) H_1 Receptor Antagonists: Phenergan (promethazine) approved in 1956. (The indication wording is "Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.")	There are FDA-approved products with an acceptable risk-benefit profile for the prevention and treatment of PONV.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Barhemsys (amisulpride injection) was evaluated for prevention of PONV, either alone or in combination with an antiemetic of a different class (ondansetron, dexamethasone or betamethasone) in two randomized, double-blind, placebo-controlled, multi-center trials in patients undergoing general anesthesia for elective surgery. The primary efficacy endpoint in both trials for prevention was complete response (CR), defined as absence of any episode of emesis and absence of use of rescue medication within the first 24 hours postoperatively. The treatment difference (drug to placebo) was 12% for monotherapy and 11% when given in combination with ondansetron, dexamethasone or betamethasone. Barhemsys was evaluated for treatment of PONV in patients who had received antiemetic prophylaxis with an agent of a different class or had not received prophylaxis in two randomized, double-blind, placebo-controlled, multi-center trials in patients experiencing PONV after general anesthesia for elective surgery. The primary efficacy endpoint in both trials for treatment was CR, defined as absence of any episode of emesis and absence of use of rescue medication within the first 24 hours after treatment (excluding emesis within the first 30 minutes). The treatment difference (drug to placebo) was 10% in patients who had not received prior PONV prophylaxis and 13% in patients who had received and failed PONV prophylaxis with an antiemetic from a class different from that of amisulpride.	Efficacy of Barhemsys (amisulpride injection) for prevention of PONV, either alone or in combination with an antiemetic of a different class was demonstrated in patients undergoing general anesthesia for elective surgery. Efficacy of Barhemsys for treatment of PONV in patients who had received antiemetic prophylaxis with a drug from a different class or had not received prophylaxis was demonstrated in two randomized, double-blind, placebo-controlled, multi-center trials in patients experiencing PONV after general anesthesia and elective surgery.
Risk and Risk Management	The most common adverse reactions in studies for prevention of PONV were increased blood prolactin levels (Barhemsys 5 mg 3% versus placebo 0%), procedural hypotension (Barhemsys 5 mg 3% versus placebo 2%), hypokalemia (Barhemsys 5 mg 3% versus placebo 2%), chills (Barhemsys 5 mg 3% versus placebo 2%), and abdominal distension (Barhemsys 5 mg 2% versus placebo 1%). The most common adverse reaction in studies for	The risks associated with Barhemsys can be mitigated with labeling. None will require a Risk Evaluation Mitigation Strategy (REMS) to ensure the benefits of Barhemsys outweigh the risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment of PONV was infusion site pain (Barhemsys 10 mg 6% versus placebo 4%). The rates of serious adverse events (SAEs) were similar in the amisulpride group and the placebo group. SAEs occurring at a higher rate than placebo included the following: peritonitis, postoperative wound infection, and acute respiratory failure.[1] There were five patients with QT prolongation in the Barhemsys 5 mg group and two in the placebo group. Of the five cases of QT prolongation in the Barhemsys 5 mg group, one was considered moderate (and classified as a SAE) with a time to onset of 19 hours; we considered the event to be not treatment-related because of the time to onset.[2] Of the remaining four cases of QT prolongation in the Barhemsys 5 mg group, all were considered mild and occurred 2 to 29 hours after treatment; one of these four cases was a patient who had received Barhemsys in combination with ondansetron for prevention of PONV. The magnitude of QT prolongation for Barhemsys 5 mg is not predicted to be greater than the threshold of risk identified in the ICH Guideline E14 (10 ms) (see Section 6.3.2.2.3 QT Prolongation of this Multidisciplinary Review). The mean C_{max} for Barhemsys 10 mg infused over 1 minute is predicted to be 390 ng/mL, which translates to a ΔΔQTcF of 12.6 ms (90% upper CI: 14.1), and is predicted to be greater than the threshold of risk identified in the ICH	To mitigate the identified risks associated with Barhemsys treatment, important recommendations should be included in labeling: • To reduce the risk of QT prolongation associated with use of Barhemsys, we recommend Barhemsys should be avoided in patients with congenital long QT syndrome or severe renal impairment or patients taking droperidol. Also, electrocardiogram (ECG) monitoring should be undertaken when Barhemsys is given to patients with pre-existing arrhythmias/cardiac conduction disorders, electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, and in patients taking other medicinal products or with other medical conditions known to prolong the QT interval.

[1] Summary of Clinical Safety Page 19

[2] Page 91 of Report for Study DP10017.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Guideline E14 (10 ms). However, the QT interval is predicted to return to <5 ms within 30 minutes after the 10-mg dose (see Section 6.3.2.2.3 QT Prolongation of this Multidisciplinary Review). Thus, we recommend waiting at least 30 minutes after Barhemsys 10 mg to administer ondansetron 4 mg in light of the QT effects of both Barhemsys and ondansetron. Furthermore, we recommend waiting at least 10 minutes after a 4-mg dose of ondansetron to administer Barhemsys 10 mg because the QTc increase will fall below 5 ms within a short time (10 minutes). Extrapyramidal symptoms (EPS) and neuroleptic malignant syndrome are known AEs associated with this class of drugs (D_2 antagonists). Based on the SMQ "Extrapyramidal syndrome," which comprises four SMQs (akathisia, dyskinesia, dystonia, and Parkinson-like events), the following eight AEs have been reported in the Barhemsys clinical trial program: Restlessness, laryngospasm, muscle spasms, muscle spasticity, muscle tightness, hypertonia, dysphonia, and tremor. The frequency of possible EPS appears to be similar for placebo and for both doses of amisulpride. There was no event of neuroleptic malignant syndrome identified in the Barhemsys clinical development program. The effects of severe renal impairment on Barhemsys pharmacokinetics were not adequately characterized. Barhemsys pharmacokinetics data were only available from one patient with severe renal impairment (AUC_∞ in that patient was 2.1-fold higher than that observed in patients with normal renal function).	• (b) (4) Because the effects of severe renal impairment on Barhemsys pharmacokinetics has not been adequately characterized, we recommend that the Applicant conduct the following study: • A pharmacokinetic study following a single dose of Barhemsys (amisulpride injection) in patients with severe renal impairment (i.e., eGFR <30 mL/min/1.73 m^2) and healthy subjects as a control group. It is especially important that the potential increase in systemic exposure in patients with severe renal impairment is adequately characterized because amisulpride is known to cause concentration-dependent prolongation of the QT interval. The results of the proposed study may be used to develop safe dosing recommendations for patients with severe renal impairment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Although the benefit-risk profile of Barhemsys (amisulpride injection) is favorable for the indications sought, this New Drug Application (NDA) will not be approved during this review cycle because of the deficiencies identified at the manufacturing facility in (b) (4) (b) (4). The Applicant does not have an alternative drug substance manufacturing facility for this NDA; therefore, satisfactory resolution of the deficiencies at the manufacturing facility is required before this NDA may be approved.

5-HT_3 = 5-hydroxytryptamine (serotonin) type 3; AUC = area under the curve; CR = Complete Response; eGFR = estimated glomerular filtration rate; MedDRA = Medical Dictionary for Regulatory Activities; PI = prescribing information; PK = pharmacokinetics; PMR = postmarketing requirement; PONV = postoperative nausea and vomiting; SA = standard anti-emetic; SAE = serious adverse event; SMQ = standard medical query

1.4. Patient Experience Data

The Applicant stated that "the NDA does not include this type of data."[3]

Patient Experience Data Relevant to this Application (check all that apply)

	The patient experience data that was submitted as part of the application, include:							Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as						
			□	Patient reported outcome (PRO)				
			□	Observer reported outcome (ObsRO)				
			□	Clinician reported outcome (ClinRO)				
			□	Performance outcome (PerfO)				
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)						
	□	Patient-focused drug development or other stakeholder meeting summary reports						
	□	Observational survey studies designed to capture patient experience data						
	□	Natural history studies						
		Patient preference studies (e.g., submitted studies or scientific publications)						
□	Patient experience data that was not submitted in the application, but were considered in this review.							
	□	Input informed from participation in meetings with patient stakeholders						
	□	Patient-focused drug development or other stakeholder meeting summary reports						
	□	Observational survey studies designed to capture patient experience data						
X	Patient experience data was not submitted as part of this application.							

[3] Email from applicant received August 23, 2018.

2. Therapeutic Context

2.1. Analysis of Condition

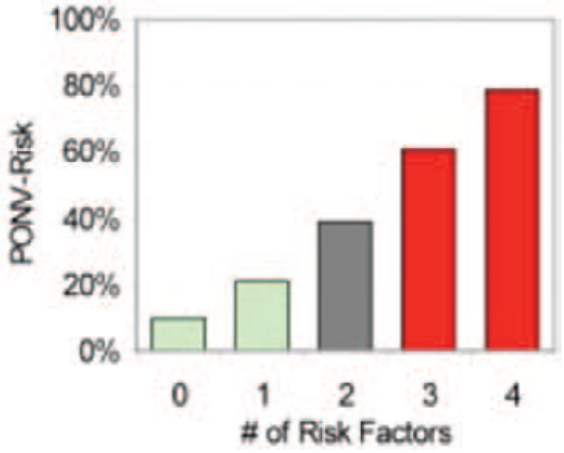
PONV is a complication of surgery experienced by 25% to 30% of surgical patients overall, and 70% to 80% of patients with multiple risk factors. Although several factors have been associated with an increased risk of PONV, most are only weakly associated. The factors associated with a greater risk of PONV include (1) female gender, (2) history of PONV and/or susceptibility to motion sickness, and (3) non-smoking status. Other risk factors include duration of anesthesia and possibly, the type of surgical procedure, gynecological, 'intra-abdominal laparoscopic, breast, plastic, and eye surgery being of particular high-risk. The use of inhaled volatile general anesthetics, nitrous oxide and administration of opioids intraoperatively and postoperatively may also increase the risk of PONV.

An important factor in defining the potential risk for PONV is the number of risk factors a patient has. A risk score can be calculated to determine the risk of PONV. The simplified risk score from Apfel et al. (See Figure 1 below) is a widely used risk calculator tool in adults (Apfel et al. 1999). Accordingly, the higher the risk score, the higher the probability of PONV.

Patients with multiple risk factors for PONV (≥3) can require more than one drug for prevention and/or treatment. The incidence of PONV with the presence of 0, 1, 2, 3, and 4 risk factors is about 10%, 20%, 40%, 60%, and 80%, respectively. An expert panel from the Society for Ambulatory Anesthesiology considers patients with 0 to 1, 2 or 3, and more than 3 risk factor as “low,” “medium,” and “high” risk categories, respectively.” Although risk scores are an objective approach to assessing the patient’s risk for PONV, they are not completely predictive, with sensitivity and specificity of between 65% and 70% (Gan et al. 2014).

Figure 1. The Modified Risk Score from Apfel et al. (Apfel et al. 1999)

Risk Factors	Points
Female Gender	1
Non-Smoker	1
History of PONV	1
Postoperative Opioids	1
Sum =	0 ... 4



2.2. Analysis of Current Treatment Options

There are several approved therapies for the prevention and/or treatment of PONV (see Table 1). Currently, the most effective and widely used approved therapies are in the class 5-HT_3 receptor antagonists. Other drugs approved for the prevention of PONV are D_2 receptor antagonists, such as droperidol and metoclopramide. Corticosteroids, although not approved for PONV, are also frequently used for prevention or treatment of PONV.

Apfel et al. demonstrated that the effects of antiemetics acting on different receptors are additive. Adults at moderate or high risk for PONV could receive benefit from combination therapy with drugs from different classes as the efficacy is optimized when a combination of drugs with different mechanisms of action are administered (Gan et al. 2014).Thus, providing additional options for the prevention/treatment of PONV would expand a practitioner's therapeutic armamentarium and increase PONV treatment alternatives available to patients.

Table 1. Summary of Treatment Options Relevant to Proposed Indication

Drug Class		PONV	
		Prevention	Treatment
5-HT_3 Receptor Antagonists			
Zofran (ondansetron)	IV	√	
	Oral	√	
Anzemet (dolasetron)	IV	√	√
	Oral		
Aloxi (palonosetron)	IV	√	
	Oral		
NK_1 Receptor Antagonists			
Emend (aprepitant)	Oral	√	
D_2-Receptor Antagonists			
Droperidol	IV, IM	√	
Metoclopramide	IV	√	
H_1 Receptor Antagonists			
Phenergan (promethazine)*	Oral	√#	√#
	Suppository	√#	√#
	IV, IM	√#	√#
Anticholinergics			
Transderm Scop (scopolamine)	Trans-dermal	√	
Other			
Tigan (trimtho-benzamide HCl)	IM		√
	Oral		√

* Also dopamine (D_2) antagonist and acetycholine (M_1) antagonist (although not in the label); 1/10 potency of prochlorperazine on D_2
# Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery
5-HT_3 = 5-hydroxytryptamine (serotonin) type 3; IM = intramuscular; IV = intravenous; PONV = postoperative nausea and vomiting; NK_1 = tachykinin type 1; H_1 = histamine type 1

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Amisulpride is a new molecular entity (NME) that is not currently marketed in the United States. However, oral amisulpride (50 mg tabs) is approved/marketed in Europe (for over 30 years) for treatment of schizophrenia at 50 to 1200 mg/day (recommended dose is 400 to 800 mg).

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2. Relevant Clinical Presubmission Regulatory Background

Date	Action
October 2012	Type B Meeting: End of Phase 2 Proposed Indication: Prevention of postoperative nausea and vomiting Use of the 5-mg dose in the phase 3 clinical trials may be reasonable as low-dose D_2 receptor antagonists have been used for prevention and treatment of PONV, but the dose-response relationship does not appear to be well understood. The absence of PK data in study DN10006 prevents determination of an exposure-response. Trial population: The proposed trial population (adults undergoing elective surgery who are at moderate to high risk for PONV) is acceptable. For non-inferiority comparisons, it will be important to enroll a population that is at high risk for PONV, in order to assure that the lack of observed treatment difference reflects treatment effect and not a population effect. FDA has observed that males with high risk features are less likely to respond to treatment in antiemetic trials. For this reason, for a non-inferiority trial we believe that the population may need to be nearly all female or will have to be of such a large size that the impact of a small proportion of males would not undermine the non-inferiority evaluation. FDA agreed that a placebo-controlled trial would be an acceptable design and stated that two placebo-controlled trials would be acceptable, and that an active control trial would not be required. The acceptable primary endpoint was defined as: The proportion of patients with no vomiting/retching and no use of rescue medication during the first 24 hours after completion of surgery ("Complete Response").
February 2015	Type B Meeting: Prephase 3 To discuss Sponsor's clinical development plans for amisulpride intravenous to support the following proposed indications (amended): (1) Prevention of PONV, either alone or in combination with other antiemetics, and (2) Rescue treatment of (b) (4) PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis. (b) (4) Sponsor proposed and FDA agreed one monotherapy and one combination therapy phase 3 study, if both positive, could support a combination prophylaxis indication. Sponsor proposed and FDA agreed that if the Sponsor provides rescue therapy data from two successful phase 3 trials, one with and one without prior prophylaxis, this package, in conjunction with the two proposed prophylaxis trials could support both monotherapy and combination therapy indications in both prophylaxis and rescue treatment settings. FDA reiterated its recommendation to conduct additional dose exploration in the rescue therapy setting, including PK assessment.
August 2015	Type B Meeting: End of Phase 2 To discuss their clinical and nonclinical development plans for intravenous and oral amisulpride for new proposed indication: prevention of nausea and vomiting associated with cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Discussion of completed and proposed trials for amisulpride IV, and oral amisulpride through the May 28, 2015 meeting request. Sponsor's proposed phase 3 studies were not compliant with FDA's usual standard for these trials regarding key design elements. Phase 2 data were equivocal.

Date	Action
March 2017	Pre-NDA Meeting: FDA agreed to ISE for prophylaxis indication; ISE for rescue treatment indication; and single ISS supporting both indications. FDA requested: • Summary of AEs seen in the postmarketing safety database for amisulpride (i.e., for the oral dosage form approved in other countries). • Details of AEs of special interest reported during your clinical trials. AEs of special interest should include QT prolongation, extrapyramidal symptoms (EPS), and neuroleptic malignant syndrome; we noted these AEs were reported with chronic oral dosing in schizophrenic patients. • Details of all cardiac AEs (e.g., bradycardia, hypokalemia, hypotension, palpitations, QT prolongation, and Torsades de Pointes) reported during your clinical trials including details about the use of concomitant medications.
October 2017	NDA 209510 was submitted.

AE = adverse event; D_2 = dopamine type 2; EPS = extrapyramidal symptoms; ISE = integrated summary of effectiveness; ISS = integrated summary of safety; IV = intravenous; NDA = new drug application; PK = pharmacokinetics; PONV = postoperative nausea and vomiting; QD = daily

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Inspections for this NDA consisted of inspections of five clinical investigator sites and the Sponsor Acacia Pharma Ltd. Three of the clinical sites and the Sponsor have the final or preliminary classification of No Action Indicated (NAI). Two of the clinical sites have the final or preliminary classification of Voluntary Action Indicated (VAI). No significant regulatory findings or data integrity issues were noted. Thus, the data generated by these sites and the Sponsor are acceptable in support of the application. See separate review by Susan Leibenhaut, M.D. (finalized June 15, 2018).

4.2. Product Quality

The active pharmaceutical ingredient, amisulpride, is a white to almost white crystalline powder. It is a racemic mixture of equal amount of R and S enantiomers and it shows no optical rotation. There are no known polymorphs of amisulpride. It is manufactured by (b) (4). The CMC information is provided in DMF (b) (4) from the manufacturer. This DMF was reviewed and was deemed adequate. The active pharmaceutical ingredient is controlled to conform to the requirements (specification) to produce amisulpride injection, 5 mg/2 mL.

(b) (4)

Amisulpride injection is supplied in a 2 mL clear glass vial containing 5 mg of amisulpride. The drug product does not contain any preservatives or antioxidants. It is manufactured by (b) (4) (b) (4). The manufacturing process consists of (b) (4) (b) (4) The drug product manufacturing process was reviewed and was deemed acceptable.

The overall control strategy for the drug product's identity, strength, purity and quality is deemed adequate based on raw material controls, and drug product specification including appearance, identity, assay, impurities, extractable volume, particulate matter, pH, osmolality, bacterial endotoxin limits, and sterility.

The environmental monitoring (b) (4) (b) (4)

(b) (4) as well as the microbiology related attributes in the drug product specification including endotoxins, sterility and container closure integrity etc. were reviewed and deemed adequate for drug product sterility assurance.

A claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31 was deemed acceptable.

A pre-approval inspection of the drug substance manufacturing facility, (b) (4) was performed between July 16 – July 20, 2018. The facilities reviewer concluded the following: there appears to be significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history and relevant experience. Therefore, the facilities are determined unacceptable to support approval of this NDA.

Because of this conclusion, the Office of Process and Facilities (OPF) has *not* made an overall "Adequate" recommendation.

From OPQ perspective this NDA is recommended for ***Complete Response*** per 21 CFR 314.125(b)(13).

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Amisulpride (Barhemsys) is a dopamine D_2/D_3 receptor antagonist. The applicant is seeking approval for the prevention and treatment of PONV. The maximum recommended adult dose for Barhemsys is 10 mg (0.167 mg/kg for a 60 kg individual), administered by intravenous infusion over 2 minutes.

In support of the safety of amisulpride, the applicant submitted the following nonclinical studies: pharmacodynamic studies, a 4-week repeat-dose IV toxicity study in rats, and a battery of genotoxicity and reproductive and developmental toxicity studies. The applicant also submitted published pharmacology studies in which the binding affinities of amisulpride to dopamine D_2/D_3 receptors have been determined.

Amisulpride is a dopamine D_2 receptor antagonist with a K_i value of 2.8±0.4nM. It also binds to dopamine D_3 receptors with a K_i of 3.2±0.3nM. Amisulpride has low binding affinities for 5-HT_{2B} (K_i=13nM) and 5-HT_7 (K_i=11.5nM) receptors. Amisulpride has no binding affinity for dopamine D_1 and D_4 receptors, alpha-adrenergic, histaminergic, muscarinic, gamma-aminobutyric acid (GABA) type A (IC_{50}>100μM), GABAB (IC_{50}>100μM), or N-methyl-D-aspartic acid (NMDA) (IC_{50}>100μM) receptors. Amisulpride demonstrated anti-emetic activity in a ferret model of morphine- and apomorphine-induced emesis following IV and subcutaneous (SC) administrations at dose levels of 3 mg/kg and 1 μg/kg, respectively.

In an in vitro hERG assay, amisulpride showed hERG channel inhibitory effects with an IC_{50} of ~100μM, suggesting a low risk for clinical QT prolongation. Amisulpride was rapidly absorbed and widely distributed in tissues with highest concentrations observed in the gastrointestinal tract contents following IV administration in rats. Amisulpride was eliminated via urine (55%) and feces (40%) in rats following IV administration.

Based on extensive clinical experience with amisulpride, outside of the Unites States, at higher doses, the Division agreed that a 28-day repeat dose toxicity in a single species would be adequate for the proposed indication in which only a single dose will be administered. In the 28-day toxicity study in rats, amisulpride was administered IV to Charles River Wistar (Crl:WI(Han)) rats at doses of 0, 2, 5 and 10 mg/kg/day. One male in the high dose group died on day 15, and the cause of death was not known. Animals in the high dose group showed reddening of the pinnae and noisy/labored breathing immediately after dosing. These clinical signs were less pronounced in the mid dose group and were not observed in the low dose group. Histopathological examination revealed acinar cell proliferation in mammary gland of males and females in all dose groups, which is related to the pharmacological action of the drug.

Amisulpride was negative in the Ames test, the in vitro mammalian chromosome aberration assay in human peripheral blood lymphocytes and the in vivo micronucleus assay in rats by oral gavage.

An oral (gavage) fertility and early embryonic development study with amisulpride was conducted in male and female Crl:WI (Han) rats. Amisulpride was administered at dose levels of 0, 60, 100 and 160 mg/kg/day for 14 days before and during pairing. Majority of females (90% to 95%) failed to mate at all dose levels, and the treatment was stopped for both males and females after 10 days of pairing. Following the cessation of the treatment, the animals remained in the pairing cages for up to 10 days. The effects of amisulpride on mating and fertility in rats were reversible following the cessation of treatment. There were no effects of treatment on the uterine/implantation parameters.

Embryo fetal development studies were conducted in pregnant rat and rabbits. In rats, amisulpride was administered orally at dose levels of 0, 60, 100 and 160 mg/kg/day from gestation day 6 through gestation day 17. In rabbits, amisulpride was administered orally at doses of 0, 50, 100 and 210 mg/kg/day from gestation day 6 through gestation day 18. In both rabbits and rats, amisulpride had no effects on the pregnancy or fetal parameters at any dose levels, and no test item-related macroscopic, visceral or skeletal malformations were noted. The no adverse event levels (NOAELs) for maternal toxicity and for embryo-fetal development in rats and rabbits were 160 and 210 mg/kg/day, respectively; the highest doses tested.

In a prenatal and postnatal development study in rats, amisulpride was administered daily by oral gavage (0, 60, 100 and 160 mg/kg/day) to pregnant rats from gestation day 6 to lactation day 20. No treatment-related effects were noted on the F_0 generation, including pregnancy parameters or litter survival and pups body weights. Amisulpride treatment had no effects on body weight gain, development, behavior or reproductive function, or pregnancy parameters of the F_1 generation. The NOAEL for maternal toxicity and prenatal and postnatal developmental effects was 160 mg/kg/day; the highest doses tested.

The abuse potential of amisulpride was assessed in rats following IV administration of 0.25 and 1.0 mg/kg infusion doses. The study showed that amisulpride had no abuse potential.

5.2. Referenced NDAs, BLAs, DMFs

IND 114207: Amisulpride, for postoperative nausea and vomiting (PONV); Acacia Pharma, Ltd.

5.3. Pharmacology

5.3.1. Primary Pharmacology

Amisulpride is a dopamine D_2/D_3 receptor antagonist with K_i values of 2.8±0.4nM and 3.2±0.3, respectively (Schoemaker et al. 1997).

In a receptor screening assay, amisulpride has no affinity for D_1 and D_4 receptors, alpha-adrenergic, histaminergic, muscarinic, gamma-aminobutyric acid type A (GABA), GABAB, or N-methyl-D-aspartic acid (NMDA) receptors (Perrault et al. 1996). Amisulpride showed weak affinity to 5-HT_{2B} (K_i=13nM) and 5-HT_{7a} (K_i=11.5nM) receptors (Abbas et al. 2009).

Study: Evaluation of amisulpride for antagonizing apomorphine, morphine or cisplatin-induced emesis in the ferret (SC or IV administration) (Study # 10.005/25).

Amisulpride was studied for the antagonism of apomorphine-, morphine- or cisplatin-induced emesis following SC (1, 10 and 100 μg/kg) or IV (3, 6 and 12 mg/kg) administration in male ferrets. Amisulpride was administered subcutaneously 30 minutes before apomorphine (0.25 mg/kg, SC), 5 to 10 minutes before morphine (0.4 mg/kg, intraperitoneal; IP), and 5 minutes before cisplatin (10 mg/kg, IP).

Amisulpride, at 1 μg/kg SC, administered 30 minutes before apomorphine, reduced the incidence of emesis, compared with the vehicle control group (6.0±2.2 versus 14.8±4.8 retches; 0.0±0.0 versus 1.0±0.5 vomits; 1.5±0.6 versus 3.3±0.9 emesis periods; not statistically significant). Amisulpride, 10 and 100 μg/kg, caused a complete inhibition of apomorphine-induced emesis, when compared with the vehicle control group.

Amisulpride, at IV doses of 3, 6 and 12 mg/kg, administered 5 or 10 minutes before morphine, had no consistent anti-emetic effects in ferrets challenged with morphine, as compared to the vehicle control group. However, a significant decrease in vomiting episodes was seen at 3 mg/kg (0.0±0.0 versus 1.6±0.7) and a decrease in the number of emesis periods was seen at 6 mg/kg (3.3±1.1 versus 7.5±1.5).

Amisulpride (0.2, 0.6, 2 and 6 mg/kg, IV), administered 5 minutes before cisplatin, reduced the emetic effects of cisplatin as compared with the vehicle control (23.3±10.8 retches at 0.2 mg/kg, 62.2±59.0 retches at 0.6 mg/kg, 3.3±2.5 retches at 2 mg/kg and 11.7±3.8 retches at 6 mg/kg versus 79.8±22.2 retches in the vehicle control group; 0.2±0.2 vomits at 0.2 mg/kg, 1.3±1.1 vomits at 0.6 mg/kg, 0.2±0.2 vomits at 2 mg/kg, and 1.2±1.0 vomits at 6 mg/kg, versus 3.0±1.1 vomits in the vehicle control group and 3.7±2.0 emesis periods at 0.2 mg/kg, 6.5±5.3 emesis periods at 0.6 mg/kg, 0.5±0.3 emesis periods at 2 mg/kg, and 3.7±1.3 emesis periods at 6 mg/kg versus 10.7±2.8 emesis periods in the vehicle control group).

In conclusion, apomorphine-induced emesis in ferrets was completely inhibited by subcutaneous administration of amisulpride at doses of 10 and 100 μg/kg. Intravenously administered amisulpride (3, 6 and 12 mg/kg) had no consistent anti-emetic effects on morphine-induced emesis in ferrets. Intravenous administration of amisulpride at doses of 0.2, 0.6, 2 and 6 mg/kg showed significant anti-emetic effects on cisplatin-induced emesis in ferrets.

5.3.2. Secondary Pharmacology

No secondary pharmacology studies were submitted. Literature cited by the applicant that assessed activity at related receptors is reviewed in section 5.3.1, above.

5.3.3. Safety Pharmacology

Study 1 Effect of Acacia Pharma Test Substances on hERG Tail Current Recorded from Stably Transfected HEK293 Cells (Study # ZNA34471).

The effects of droperidol, amisulpride and sulpiride on hERG tail currents were assessed in stably transfected HEK293 cells. The IC_{50} values for droperidol, amisulpride and sulpiride for hERG channel inhibition were 0.1, 44 and ~100μM, respectively.

Study 2 Effect of (S)-amisulpride compared with racemic amisulpride on hERG tail current recorded from stably transfected Chinese hamster ovary cells (Study # CYP1369-R1/R2).

Amisulpride is a chiral drug with two enantiomers, (R)- and (S)-amisulpride. The effect of (S)- and (R)-amisulpride on hERG tail current was assessed in stably transfected Chinese hamster ovary (CHO) cells. The concentrations of both enantiomers used were from 0.08μM to 250μM. Quinidine was used as a positive control. The result showed that neither (R)-amisulpride nor (S)-amisulpride produced 50% or greater inhibition of hERG current at the concentrations tested. At the highest concentration (250μM), both (R)-amisulpride and (S)-amisulpride produced similar levels of inhibition (36.7% and 35.3%, respectively). The IC_{50} values for quinidine were 1.36±0.385μM.

Study 3 Manual patch-clamp profiling of two compounds against the hERG ion channel (Study # ACAC-001).

In this study, the effects of ondansetron and amisulpride on hERG tail currents were assessed in stably transfected HEK293 cells. The concentrations of ondansetron used ranged from, 0.1 to 10μM and the concentration of amisulpride ranged from 1 to 100μM. The IC_{50} and IC_{10} values for ondansetron were 1.3μM and 135nM, respectively, and the IC_{50} and IC_{10} values for amisulpride were 68μM and 2.82μM, respectively.

In another experiment, hERG tail current inhibition was assessed for amisulpride and ondansetron alone, or in combination of amisulpride and ondansetron at their IC_{10} concentrations (2.82µM and 135nM). The levels of hERG channel inhibition were 18±1% and 5±0.2% at IC_{10} of ondansetron and amisulpride, respectively. When amisulpride and ondansetron were used in combination, the inhibition of hERG channels was increased from 5±0.2% to 15±0.5% and 18±1% to 26±0.9%. The result showed that there was an additive effect of the combination of amisulpride and ondansetron at their IC_{10} values. The hERG channel inhibition was 100% with cisapride.

In conclusion, amisulpride caused hERG channel inhibition alone or in combination with ondansetron, but the finding is not suggestive of a high risk for QT prolongation because the effects on the hERG channel were small and observed at very high concentrations compared to therapeutic plasma concentrations.

5.4. ADME/PK

Table 3. ADME Studies

Type of Study	Major Findings
Absorption	No absorption studies were submitted.
Distribution	
[^{14}C] amisulpride: Preclinical enabling studies for clinical metabolism programme (Study Number # APL/03).	Radiolabelled amisulpride was administered to male rats at a single IV dose of 10 mg/kg (3.7 MBq/kg). amisulpride was widely distributed into tissues following a single IV dose. At 6 hours after dosing, the highest concentrations of radioactivity were observed in components of the gastrointestinal tract, contents of the urinary bladder, liver, uveal tract, small intestinal mucosa, whole eye, pigmented skin, urinary bladder wall, kidney medulla, seminal vesicles, epididymis, pituitary and kidney as a whole. At 336 hours or 14 days after dosing, low to moderate levels of radioactivity were detected at the uveal tract, eye and meninges. By 840 hours or 35 days after dosing, radioactivity was detected in the uveal tract (0.402 µg/g tissue) and whole eye (0.133 µg/g tissue). The levels of radioactivity detected in the meninges up to 336 hours and uveal tract up to 840 hours post-dose suggest an affinity of amisulpride for the melanin pigmented tissues.
Metabolism	No metabolism studies were submitted.
Excretion	
[^{14}C] amisulpride: Preclinical enabling studies for clinical metabolism programme (Study Number # APL/03).	After a single intravenous dose of [^{14}C] amisulpride to male rats, approximately 55% of radioactivity was detected in urine and 40% in feces. Elimination was rapid, with more than 90% of urinary excretion within 12 hours. More than 90% of fecal elimination was within 24 hours.

Type of Study	Major Findings
Toxicokinetic data from general toxicology studies	
Amisulpride: intravenous (slow bolus) 28-day toxicity study in the rat with a 14-day treatment free period (Study # BGX0002).	Rat *$T_{1/2}$: (days 1 and 28; M/F, all doses)* 0.7 to 3.3 hours T_{max} *(days 1 and 28; M/F, all doses)* 0.083 hours in males and females *AUC_{inf} (day 1; M/F)* 2 mg/kg/day: 538/521 ng.h/mL 5 mg/kg/day: 1560 ng.h/mL (males) 10 mg/kg/day: 3870/3350 ng.h/mL *AUC_{inf} (day 28; M/F)* 2 mg/kg/day: 635/643 ng.h/mL 5 mg/kg/day: 1840/2010 ng.h/mL 10 mg/kg/day: 4200/3700 ng.h/mL C_{max} *(day 1; M/F)* 2 mg/kg/day: 735/771 ng/mL 5 mg/kg/day: 2140/2260 ng/mL 10 mg/kg/day: 4920/4920 ng/mL C_{max} *(day 28; M/F)* 2 mg/kg/day: 848/704 ng/mL 5 mg/kg/day: 2280/2420 ng/mL 10 mg/kg/day: 5410/4580 ng/mL *Accumulation:* No evidence of accumulation. *Dose proportionality:* Increased dose-related, but not dose proportional. A five-fold increase in dose caused more than 5-fold increase in exposure.
Toxicokinetic data from reproductive toxicology studies	
Amisulpride: Oral (Gavage) Fertility and Early Embryonic Development Study in the Rat with Toxicokinetic Sampling (Study # BGX0009).	Rat *$T_{1/2}$: (days 1 and 14; M/F, all doses)* 1.6 to 4.1 hours T_{max}: *(days 1 and 14; M/F, all doses)* 1 to 3 hours *AUC_{inf} (day 1; M/F)* 60 mg/kg/day: 1890/1410 ng.h/mL 100 mg/kg/day: 5970/3370 ng.h/mL 160 mg/kg/day: 11500/8940 ng.h/mL *AUC_{inf} (day 14; M/F)* 60 mg/kg/day: 2540/NA ng.h/mL 100 mg/kg/day: 7000/3890 ng.h/mL 160 mg/kg/day: 13400/13600 ng.h/mL C_{max} *(day 1; M/F)* 60 mg/kg/day: 542/342 ng/mL 100 mg/kg/day: 1350/774 ng/mL 160 mg/kg/day: 2540/2060 ng/mL C_{max} *(day 14; M/F)* 60 mg/kg/day: 691/246 ng/mL 100 mg/kg/day: 1430/490 ng/mL 160 mg/kg/day: 2110/1610 ng/mL *Accumulation:* There was no accumulation over the 14-day period in males and females at low and mid doses. Slight accumulation was noticed in females at HD (1.5-fold). *Dose proportionality:* C_{max} and AUC increased generally more than dose-proportionally in both sampling days (days 1 and 14).

Type of Study	Major Findings
Amisulpride: Oral (Gavage) Embryo-Fetal Development Study in the Rat (Study # BGX0012).	Rat *$T_{1/2}$: (days 6 and 17; F, all doses)* 2.5 to 3.3 hours T_{max}: *(days 6 and 17; F, all doses)* 3 hours *AUC_{inf} (day 6; F)* 60 mg/kg/day: 2670 ng.h/mL 100 mg/kg/day: 7380 ng.h/mL 160 mg/kg/day: 16400 ng.h/mL *AUC_{inf} (day 17; F)* 60 mg/kg/day: 4280 ng.h/mL 100 mg/kg/day: 12100 ng.h/mL 160 mg/kg/day: 17300 ng.h/mL C_{max} *(day 6; F)* 60 mg/kg/day: 642 ng/mL 100 mg/kg/day: 1760 ng/mL 160 mg/kg/day: 3050 ng/mL C_{max} *(day 17; F)* 60 mg/kg/day: 997 ng/mL 100 mg/kg/day: 2150 ng/mL 160 mg/kg/day: 3150 ng/mL *Accumulation:* There was slight accumulation of amisulpride over the 12-day dosing period in female rats in 60 and 100 mg/kg/day dose groups, but no accumulation in the 160 mg/kg/day dose group. *Dose proportionality:* Exposures increased more than the dose-proportionally.
Oral (Gavage) Embryo-Fetal Development Study in the Rabbit with Toxicokinetic Sampling (Study # BGX0011).	Rabbit *$T_{1/2}$: (days 16; F, all doses)* 2.3 to 4.9 hours T_{max}: *(day 16; F, all doses)* 0.5 to 1 hours *AUC_{inf} (day 16; F)* 50 mg/kg/day: 7500 ng.h/mL 100 mg/kg/day: 39600 ng.h/mL 210 mg/kg/day: 184000 ng.h/mL C_{max} *(day 16; F)* 50 mg/kg/day: 4230 ng/mL 100 mg/kg/day: 16000 ng/mL 210 mg/kg/day: 38400 ng/mL *Dose proportionality:* Exposures increased more than dose-proportionally.

AUC = area under the curve; HD = high dose

5.5. Toxicology

5.5.1. General Toxicology

Study title/number: Amisulpride: Intravenous (Slow Bolus) 28-Day Toxicity Study in the Rat with a 14 Day Treatment Free Period (Study # BGX0002).

Key Study Findings

One death (Male #47) in the high dose (10 mg/kg/day) on day 15 after dosing. Cause of death was not confirmed following macroscopic and microscopic examinations.

Microscopic examinations showed changes in the mammary area (feminization in surviving males and acinar proliferation/secretory activity in surviving females) in all dose groups. These findings were reversed following 14-day treatment free period.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 4. Methods of 28-Day Toxicity Study in the Rat

Parameter	Details
Dose and frequency of dosing:	0, 2, 5 and 10 mg/kg/day (2.5 mL/kg), once daily for 28 days
Route of administration:	IV slow bolus
Formulation/Vehicle:	5M NaOH with a pH 5
Species/Strain:	Crl:WI(Han) Rat
Number/Sex/Group:	15/sex in the control and high dose groups and 10/sex in the low and mid dose groups.
Age:	5 to 6 weeks
Satellite groups/unique design:	For toxicokinetic studies, 3/sex in control and 9/sex in low, medium and high dose groups
Deviation from study protocol affecting interpretation of results:	None.

Crl:WI = Charles River Wistar; IV = intravenous

Table 5. Observations and Results: Changes from Control

Parameters	Major findings
Mortality	One male (#47) from the 10 mg/kg/day group died on day 15 after dosing.
Clinical Signs	Animals in the 10 mg/kg/day dose group showed reddening of the pinnae and noisy/labored breathing immediately after dosing. These clinical signs were also noticed in the 5/mg/kg/day dose groups but with low prevalence and regressed 30 minutes after dosing.
Body Weights	No adverse effects on body weight were observed.
Ophthalmoscopy	No ocular changes were observed.
Hematology	MD males: 18% decrease in lymphocytes and 15% decrease in total white blood cells HD males: 24% decrease in lymphocytes and 19% decrease in total white blood cells HD males: up to 63% increase in neutrophils Reversed after 14-day dose free period.
Clinical Chemistry	HD males: 29% increase in plasma glucose, 17% increase at the end of 14-day dose free period LD females: 19% increase in plasma glucose, reversed after 14-day drug free period.
Urinalysis	No treatment-related changes.
Gross Pathology	No treatment-related macroscopic findings.
Organ Weights	Relative to body weight (%) HD males: 9% decrease in heart wt., 14% decrease in spleen wt., 6% decrease in liver wt., and 8% decrease in kidney wt. MD males: 6% decrease in heart wt. and 7% decrease in kidney wt. These changes are minor and reversed after 14-day treatment free period.
Histopathology Adequate battery: Yes	Mammary gland (feminization/acinar cell proliferation): Male: LD: 9/10 MD: 8/10 HD: 9/10 Female: Control: 6/10 LD: 10/10 MD: 10/10 HD: 10/10 Secretory activities of mammary gland Female: LD: 9/10 MD: 9/10 HD: 9/10 In recovery phage: Mammary gland (feminization/acinar cell proliferation) and Secretory activities: HD male: 3/5 HD female: 5/5
[Other evaluations]	None

Crl:WI = Charles River Wistar; HD = high dose; IV = intravenous; LD = low dose; MD = middle dose
-: indicates reduction in parameters compared to control.
*: [if the answer is “no” explain why the histopath battery is not adequate]
General toxicology; additional studies
Study: Amisulpride: Intravenous (Slow Bolus) Preliminary and 7-day Dose Range Finding Study in the Rat (Study # BGX0001).

In this dose range finding study, Crl:WI(Han) rats were divided into four separate arms. In the first arm, two males and two females were dosed with amisulpride for up to 3 days intravenously with an initial dose of 5 mg/kg/day, with subsequent doses of 3, 7.5, 10 and 25 mg/kg/day with a dose volume of 5 mL/kg. In the second arm (main study), five male and five female rats were dosed at 0 (placebo), 3, 5 and 7.5 mg/kg/day for 7 days. In the third (toxicokinetic) arm, six male and six female rats received a single IV dose of 1.5 mg/kg. In the fourth arm, three males and three females were added to the second arm (main study) and dosed with 10 and 25 mg/kg/day with a dose volume of 2.5 mL/kg.

Two males in the 25 mg/kg dose group (one at a 5 mL/kg dose volume, the other at a 2.5 mL/kg dose volume), convulsed and died immediately after the first dose. A third male in the 25 mg/kg at 5 mL/kg dose volume was sacrificed *in extremis* after one dose. Because of these deaths, other animals in these groups were not dosed as scheduled. When 10 mg/kg was given at a dose volume of 5 mL/kg, one female convulsed and died and the other three animals in the group were sacrificed for humane reasons on the first day of dosing. There were no deaths at lower dose levels. Amisulpride, when given by slow intravenous bolus administration, daily for 7 days, was tolerated in rats at doses of 3 to 7.5 mg/kg/day (5 mL/kg dose volume) and also at 10 mg/kg/day, when the dose volume was limited to 2.5 mL/kg body weight. Treatment related clinical signs included: breathing abnormalities, vocalizing and struggling at dosing, reddening of the pinnae, reduced activity and prostration. There were no treatment-related adverse effects on body weight, food intake or organ weights, and no treatment-related macroscopic pathology findings, when the test item was administered for 7 days over the 3 to 10 mg/kg/day dose range.

5.5.2. Genetic Toxicology

5.5.2.1. In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/number: Amisulpride: Bacterial Reverse Mutation Test (Study # BGX0013).

Key Study Findings:

- Amisulpride had no mutagenic potential in the Bacterial Reverse Mutation Assay.

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100, and *E Coli* WP2 *uvrA;* dose levels of amisulpride were 1.5, 5, 15, 50, 150, 500, 1500 or 5000 µg/plate; in the presence or absence of S9 mix.

Study is valid: Yes

5.5.2.2. In Vitro Assays in Mammalian Cells

Study title/number: Amisulpride: In vitro Mammalian Cell Cytogenetic Test in Human Lymphocytes (Study # BGX0014).

Key Study Findings:

- Amisulpride was negative for clastogenic effects in the in vitro cytogenetic assay using human lymphocytes in the presence or absence of S-9 mix.

GLP compliance: Yes

Test system: Human peripheral blood lymphocytes treated with amisulpride at dose levels of 0, 0.5, 50, 150 and 370 μg/mL in the presence or absence of S9 mix. For positive controls, Benzo(a)pyrene (10 and 14 μg/mL), Cyclophosphamide (10 μg/mL) and Mitomycin C (0.5 and 0.6 μg/mL) were used.

Study is valid: Yes

5.5.2.3. In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/number: Amisulpride: Oral (Gavage) Rat Micronucleus Test (Study # BGX0015).

Key Study Findings:

- Amisulpride was negative in the in vivo micronucleus assay in rats at oral doses up to 300 mg/kg/day.

GLP compliance: Yes

Test system: Amisulpride was administered orally to Crl:WI(Han) rats at doses of 0, 75, 150 and 300 mg/kg/day. Animals were dosed twice, approximately 24 hours apart. Animals were sacrificed approximately 24 hours after their second dose and bone marrow was harvested from the femur and bone marrow smears were prepared on glass slides. The stained slides were coded and 2000 polychromatic erythrocytes, including micronucleated polychromatic erythrocytes , were counted for each animal for the presence of micronuclei and the group frequencies were statistically analyzed.

Study is valid: Yes

Other Genetic Toxicity Studies

None

5.5.3. Carcinogenicity

Carcinogenicity studies of amisulpride were not conducted. Carcinogenicity studies are not required for this indication for which the drug will be administered as a single dose.

5.5.4. Reproductive and Developmental Toxicology

5.5.4.1. Fertility and Early Embryonic Development

Study title/number: Amisulpride: Oral (Gavage) Fertility and Early Embryonic Development Study in the Rat with Toxicokinetic Sampling/BGX0009.

Key Study Findings

- Oral administration of amisulpride resulted in a treatment-related effect on estrous cyclicity (diestrus), and majority of females (90% to 95%) failed to mate at all dose levels (60, 100 and 160 mg/kg/day). The effects on mating and fertility were reversed following 10 days of cessation of treatment.
- Necropsy revealed granular consistency of the mammary glands for some males (5/20) in the high dose group.
- There were no effects of treatment on the uterine/implantation data.

Conducting laboratory and location (b) (4)

GLP compliance: Yes

Table 6. Methods of Fertility and Early Embryonic Development Study in the Rat

Parameter	Details
Dose and frequency of dosing:	0, 60, 100 and 160 mg/kg/day. Amisulpride was administered daily for 14 days before and during pairing.
Route of administration:	Oral gavage
Formulation/Vehicle:	Amisulpride was formulated in citrate buffer (pH 5.0±0.1).
Species/Strain:	Crl:WI (Han) Rat
Number/Sex/Group:	20/sex/dose group
Satellite groups:	None
Study design:	Amisulpride was administered orally to male and female rats once a day for 14 days before and during pairing. Control animals received the vehicle only. Following 10 days of pairing, the majority of females treated with amisulpride failed to mate, and the dosing was stopped for both males and females. However, the animals remained in the pairing cages for up to 10 days without treatment until either mating occurred or 10 days had elapsed. Once mating was confirmed, mated females were treated with their appropriate dose of amisulpride until day 6 of gestation. A few females (N=2 to 4) that failed to mate in the 10-day off-dose period were paired with males from control group until mating occurred, or until 5 days had elapsed. Unmated females were not treated after the pairing period. Clinical signs, body weights and food consumption were recorded. Oestrous cycles were monitored 10 days prior to pairing and until mating was detected. The females were sacrificed on day 13 of gestation, the ovaries weighed and pregnancy parameters were assessed. The males were subjected to necropsy once pregnancy rates had been established. The testes and epididymis cauda were removed, weighed and sperm samples were evaluated for concentration, motility and morphology.
Deviation from study protocol affecting interpretation of results:	None

Table 7. Observations and Results of Fertility and Early Embryonic Development Study in the Rat

Parameters	Major findings
Mortality	None
Clinical Signs	No treatment-related clinical signs were observed.
Body Weights	Males in the medium- and high-dose groups showed reduced body weight gain (MD:1.5±4.8g; HD:2.7±3.9g vs. 7.3±3.3 gm in controls) during the first week of treatment when compared to controls ($p<0.001$ between days 1 and 4). On the third week of treatment, males in all dose groups showed reduced body weight gain (LD:8±4.6g; MD:6±5g; HD:7.3±4.2g vs. 12.1±4.4g in controls) compared to controls ($p<0.01$ to $p<0.001$). Females in all dose groups showed increased body weight gain (LD:25.1±5.3g; MD:22.6±6.5g; HD:27.4±15.3g vs. 13.1±4.6g in controls) during the first week of treatment ($p<0.001$), when compared with controls. During the first week of gestation period, a dose related reduction in body weight gain (LD:5.7±2.9g; MD:6.2±3.9g; HD:4.7±2.9g vs. 9.9±3.8g in controls) was noticed in all dose groups when compared with controls ($p<0.001$).
Necropsy findings [Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.] (continued below)	HD males: Glandular consistency of mammary gland in few animals (5/20). Amisulpride had no effects on the following pregnancy data. Mating/fertility index (%) CG: 100 LD: 85 MD: 90 HD: 95 Copulation index male (%) CG:100 LD: 80 MD: 80 HD: 90 Corpora lutea, number CG: 220±1.5 LD: 234±1.7 MD: 229±1.8 HD: 236±1.7 Implantations, number CG: 203±3.0 LD: 197±3.4 MD: 200±2.2 HD: 193±3.9 Pre-implantation lost (%) CG: 9.2 LD: 16.9 MD: 12.4 HD: 18

Parameters	Major findings
Necropsy findings [Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.] (continued)	Live embryos, number CG: 195±3.0 LD: 194±3.3 MD: 189±2.2 HD: 185±3.4 Post-implantation loss (%) CG: 3.6 LD: 1.3 MD: 5.3 HD: 3.4

CG = control group; Crl:WI = Charles River Wistar; HD = high dose; LD = low dose; MD = middle dose

5.5.4.2. Embryo-Fetal Development

Study title/number: Amisulpride: Oral (Gavage) Embryo-Fetal Development Study in the Rat (Study # BGX0012).

Key Study Findings

- Oral gavage administration of amisulpride to pregnant Crl:WI(Han) rats during organosis showed no test item-related macroscopic abnormalities at necropsy.
- Administration of amisulpride was not associated with any increase in fetal abnormalities.
- The NOAEL for maternal toxicity and embryo-fetal development was considered to be 160 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 8. Methods of Embryo-Fetal Development Study in the Rat

Parameter	Details
Dose and frequency of dosing:	0, 60, 100 and 160 mg/kg/day, once daily.
Route of administration:	Oral gavage
Formulation/Vehicle:	Amisulpride was formulated in citrate buffer (pH 5.0±0.1).
Species/Strain:	Crl:WI(Han) rats
Number/Sex/Group:	20 females/dose group
Satellite groups:	None
Study design:	Pregnant animals were dosed once daily by oral gavage, from gestation day 6 to gestation day 17. Females were observed daily from the start of treatment and their body weights recorded; food intake was also monitored. Females were sacrificed on day 20 of gestation and a necropsy conducted. Pregnancy and fetal parameters were assessed and external, visceral and skeletal examinations of the fetuses were conducted.
Deviation from study protocol affecting interpretation of results:	None

Table 9. Observations and Results of Embryo-Fetal Development Study in the Rat

Parameters	Major findings
Mortality	No mortality.
Clinical Signs	No clinical signs observed.
Body Weights	Animals in all dose groups showed statistically significant decrease in body weight gain (LD:60.9±12.9g; MD:60.9±12.3g; HD:55.4±10.8g vs. 68.3±10.6g in controls) on day 6 to 18 of gestation when compared to controls.
Necropsy findings Cesarean Section Data (continued below)	No treatment-related findings at necropsy in any female sacrificed on day 20 of gestation. Amisulpride had no effect on the pregnancy parameters at any dose levels. Corpora lutea, number CG: 240±1.5 LD: 250±1.4 MD: 247±1.3 HD: 251±1.3 Implantations, number CG: 220±2.5 LD: 224±1.6 MD: 222±2.4 HD: 224±2.7

Parameters	Major findings
Necropsy findings Cesarean Section Data (continued)	Pre-implantation loss (%) CG: 9.1 LD: 10.1 MD: 9.3 HD: 10.8 Post implantation loss (%) CG: 4.5 LD: 6.1 MD: 4.4 HD: 5.1
Necropsy findings Offspring malformations, variations, etc.	Amisulpride treatment was not associated with any increase in fetal abnormalities at any dose level. Only one major abnormality was noted in a single fetus after maternal treatment at 60 mg/kg/day (uni or bilateral rudimentary testis). A minor abnormality (14 ^{h} vestigial rib, uni or bilateral) with statistical significance ($p<0.05$) was noticed in fetuses (66.4%) from dams receiving the high dose.

CG = control group; LD = low dose; MD = mid dose; HD = high dose

Study title/number: Oral (Gavage) Embryo-Fetal Development Study in the Rabbit with Toxicokinetic Sampling (Study # BGX0011).

Key Study Findings

- Oral gavage administration of amisulpride to New Zealand White rabbits showed no test item-related macroscopic abnormalities at necropsy.
- Amisulpride had no effects on the pregnancy or fetal parameters at any dose levels.
- The NOAEL for maternal toxicity and embryo-fetal development was 210 mg/kg/day, the highest dose tested.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 10. Methods of Embryo-Fetal Development Study in the Rabbit

Parameter	Details
Dose and frequency of dosing:	0, 50, 100 and 210 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	Amisulpride was formulated in citrate buffer, pH 5.0±0.1.
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	22 females/dose group
Satellite groups:	None
Study design:	Pregnant females were dosed once daily by oral gavage, from gestation day 6 to gestation day 18. Females were observed daily and their body weights were recorded (daily from gestation day 5 to 19, and then on days 22, 25 and 28 of gestation) and food intake was monitored (daily over days 5 to 6 of gestation and every 2 days thereafter during gestation). Animals were sacrificed on day 28 of gestation and pregnancy parameters were determined. Gravid uterus and placenta weights were recorded. Fetuses were removed from the uterus, weighed, sexes determined and then examined for external, visceral and skeletal abnormities.
Deviation from study protocol affecting interpretation of results:	None.

Table 11. Observations and Results of Embryo-Fetal Development Study in the Rabbit

Parameters	Major findings
Mortality	No test article-related mortality.
Clinical Signs	No test article-related clinical signs were noticed.
Body Weights	There was a dose-related reduction in overall mean body weight gain (LD:0.185±0.097kg; MD:0.157±0.095kg; HD:0.074±0.126kg vs. 0.227±0.137kg in controls) during the treatment period (days 6 to 19 of gestation) compared with controls; statistically significant at 100 and 210 mg/kg/day ($p<0.05$). After the dosing was stopped, body weight gain was similar in all groups on day 28 of gestation.
Necropsy findings Cesarean Section Data (continued below)	No treatment-related findings at necropsy. Amisulpride had no effect on the pregnancy parameters at any dose levels. Corpora lutea, number CG: 229±1.4 LD: 192±1.8 MD: 214±2.0 HD: 208±1.9 Implantations, number CG: 206±1.4 LD: 173±1.8 MD: 202±2.0 HD: 181±1.5

Parameters	Major findings
Necropsy findings Cesarean Section Data (continued)	Pre-implantation loss (%) CG: 9.4 LD: 9.7 MD: 5.5 HD: 11.9 Post implantation loss (%) CG: 9.0 LD: 4.3 MD: 4.7 HD: 10.1
Necropsy findings Offspring malformations, variations, etc	Amisulpride treatment was not associated with any increase in fetal abnormalities at any dose level. Fetal abnormalities were noted in two fetuses from two litters in the control group (CG), one fetus in each of the LD and MD group and two fetuses from two litters in the HD group. They are: CG: One fetus with pelvic kidney and another fetus with adactyly – hind paw, absent 4th metatarsal and hind digits; microphthalmia. LD: One fetus with cystic dilatation of left cerebral hemisphere. MD: One fetus with cystic dilatation of left cerebral hemisphere. HD: One fetus with Malformed thoracic vertebral neural arches, malformed and fused thoracic vertebral, and another fetus with severely enlarged aortic arch. However, none of these findings were considered treatment-related because of isolated cases of these findings and the incidences are within historical control values.

CG: control group; LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Study title/number: Amisulpride: Oral (Gavage) Pre- and Post-Natal Development Study in the Rat (Study # BGX0006).

Key Study Findings

- Amisulpride had no effect on pregnancy parameters or litter survival and pup body weights.
- Maternal treatment of amisulpride had no effect on the F1 generation, including body weight gain, behavior, motor activity, sexual development, fertility and mating performance in either sex.
- The NOAEL for maternal toxicity and prenatal and postnatal development was considered to be 160 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 12. Methods of Prenatal and Postnatal Development Study in the Rat

Parameter	Details
Dose and frequency of dosing:	0, 60, 100 and 160 mg/kg/day; Once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	Amisulpride was formulated in citrate buffer at pH 5.0±0.1.
Species/Strain:	Crl:WI(Han) Rats
Number/Sex/Group:	22 females/dose group
Satellite groups:	None
Study design:	Animals were dosed orally once daily, from gestation day 6 to lactation day 20. Females were observed daily from the start of treatment and their body weights recorded; food intake was also monitored. The females were allowed to litter and rear their offspring to weaning on day 21 of lactation. Pups not selected for the F1 generation were sacrificed on day 21 of lactation together with all parental generation dams, and a necropsy examination was conducted. For the F1 generation, 20 males and 20 females per group were selected and were allowed to mature, untreated. The effects on growth, development, behaviour and reproductive performance were assessed.
Deviation from study protocol affecting interpretation of results:	None.

Table 13. Observations and Results of Prenatal and Postnatal Development Study in the Rat

Generation	Major Findings
F0 Dams	Three females from the 100 mg/kg/day dose group were sacrificed early. Animal #59 was sacrificed due to difficulties during parturition on day 22 of gestation; animal #54 was sacrificed following the death of all the pups in the litter; animal 64 was sacrificed due to poor clinical condition on day 14 of lactation. Early terminations of these females were not considered treatment-related, as there were no dose-related clinical observations. Females in the 160 mg/kg/day dose group showed lower body weight during gestation (14% less than controls), and the first week of lactation (6% less than controls). Slightly reduced food intake (about 9% less than control) was also noticed in this group during lactation. All F0 generation females did not show any effects of amisulpride treatment on the pregnancy parameters or litter survival at any dose level. Pup mortality, clinical signs, body weight and developmental observations were not affected by amisulpride administration to the F0 dams. There were no macroscopic abnormalities detected in F0 dams and pups.

Generation	Major Findings
F1 Generation	No unscheduled deaths or clinical signs were observed in either sex related to the test item. Body weight gain was unaffected in both sexes. There were no effects of maternal treatment on learning and memory, auditory function, motor activity, sexual development, fertility and mating performance in either sex at any dose levels. There were no effects of maternal treatment with amisulpride on the pregnancy parameters of the F1 generation. Necropsy findings revealed no macroscopic abnormalities related to maternal treatment with amisulpride in either sex.
F2 Generation	Not evaluated.

5.5.5. Other Toxicology Studies

Study: Evaluation of amisulpride for abuse potential using the self-administration (substitution) test in the rat (Study # 13.0123).

The abuse potential of amisulpride was assessed in male Sprague Dawley rats. In this study, cocaine was used as the positive control and citrate buffer at pH 5.0 was used as the negative control. The abuse potential of amisulpride (0.25 and 1 mg/kg/infusion) and cocaine (0.25/mg/kg/infusion) were evaluated using an IV self-administration paradigm in rats. Average number of infusions of cocaine were 34.8±2.8, 34.5±3.3, 38.2±3.7 and 37.9±3.4 per session. The rate of lever press response was stable during the course of the cocaine sessions (i.e., 0.113±0.051, 0.102±0.050, 0.093±0.028, and 0.135±0.069 responses per second). In contrast, the average number of infusions of amisulpride was 1.2±0.3, and 1.3±0.5 per session at dose levels of 0.25 and 1 mg/kg/infusion, respectively. Amisulpride at 0.25 and 1 mg/kg/infusion did not affect the rate of lever press response as compared to vehicle (0.002±0.001 and 0.003±0.001 responses per second, at 0.25 and 1 mg/kg/infusion, respectively). The result suggests that amisulpride has no abuse potential in humans.

6. Clinical Pharmacology

6.1. Executive Summary

In this original NDA, the Applicant proposes Barhemsys (amisulpride) injection for:

1) Prevention of PONV, either alone or in combination with an antiemetic of a different class

2) Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or who have not received prophylaxis

The proposed dosage and administration are as follows:

- Prevention of PONV: A single 5 mg IV infusion over 1 to 2 minutes at the time of induction of anesthesia
- Treatment of PONV: A single 10 mg IV infusion over 1 to 2 minutes in the event of nausea and/or vomiting after a surgical procedure

In support of the efficacy and safety of amisulpride for the proposed indications, the Applicant conducted one phase 2 dose-ranging trial, three phase 3 placebo-controlled trials for prevention of PONV with (Study DP10017) or without concomitant antiemetic (Studies DP10014 and DP10015), and two phase 3 trials for treatment of PONV with (Study DP10019) or without prophylactic antiemetic (Study DP10018). Majority of concomitant anti-emetics was 5-HT_3 antagonists of which ondansetron was most frequently used.

The clinical pharmacology program consists of a mass balance study, PK assessment in surgical patients in phase 3 trials as well as in vitro drug interaction studies. The effects of renal impairment on the PK of amisulpride were evaluated in a subset of surgical patients with or without renal impairment. The Applicant also conducted a thorough QT(tQT) study (Study DP10013) in which amisulpride prolonged the QT interval in a concentration-dependent manner. In the tQT study, amisulpride at the 5-mg dose proposed for the prevention of PONV did not have significant effect of amisulpride on the QT interval (ΔΔQTcF 90% CI upper bound: 7.1 ms). On the other hand, at a supra-therapeutic dose (40 mg infused over 8 min), a significant effect on the QT interval was observed with the largest ΔΔQTcF of 23.4 ms (90% CI upper bound: 25.5 ms). The effects of amisulpride 10 mg on the QT interval were not studied in the tQT study but were predicted to be 12.6 ms (90% upper CI: 14.1 ms) based on the concentration-QT relationship.

The key clinical pharmacology issues for this application are the appropriateness of amisulpride dosing regimen, and the dosing for patients with renal impairment. The potential drug interactions with concomitant drugs known to prolong QT interval and the risk mitigation strategy were also reviewed.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed this submission and found it acceptable for

the approval from a clinical pharmacology standpoint. The key review issues, and specific recommendations or comments are summarized below.

Table 14. Key Review Issues, Specific Recommendations, Comments

Review Issues	Proposed	Recommendations and Comments
General dosing instructions	Prevention of PONV: a single 5 mg IV infusion over 1 to 2 min	Acceptable
	Treatment of PONV: a single 10 mg IV infusion over 1 to 2 min (b) (4)	Acceptable The PK/PD modeling predicted the QTc prolongation at 10 mg with 1 min infusion to be ΔΔQTcF of 12.6 ms [90% upper CI: 14.1 ms]. The predicted effects at 10 mg infused over 1 minute are similar to the effects of moxifloxacin 400 mg, a positive control, on the QTc observed in the tQT study, i.e., ΔΔQTcF of 12.3 ms [90% upper CI: 14.6]. The risk of arrhythmias for drugs that prolong the mean QT/QTc interval by more than around 5 and less than 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk[4]. Refer to Section 8.4.5 for the cardiac safety of 10 mg amisulpride infused over 1 to 2 minutes in two clinical trials. We recommend that the label state the effects of amisulpride on the QT interval in Section 5 for Warning and Precaution Section and risk mitigation strategies such as avoid use in patients with congenital QT issue or with other QT prolongers should be stated in the label.
Dosing in patient subgroups (Renal impairment)	No dose adjustment is needed for patients with any degree of renal impairment	The proposed no dosage adjustment in patients with mild to moderate renal impairment is acceptable. However, we recommend “avoid use” in severe renal impairment because there is insufficient data to support the dosing in patients with severe renal impairment as safety data (N=8 in phase 2 and 3 trials) and PK (N=1) in patients with severe renal impairment are limited.
Dosing with ondansetron, a	Amisulpride 5 mg with ondansetron: no need of specific management	

[4] Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

commonly used antiemetic for PONV	(b) (4)	
		Per the ondansetron labeling, ECG monitoring is recommended in patients taking other medicinal products that lead to QT prolongation. As such, we recommend ECG monitoring when patients received ondansetron.

PD = pharmacodynamics; PK = pharmacokinetics; PONV = postoperative nausea and vomiting; ECG = electrocardiogram

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: amisulpride inhibits the dopamine D_2 receptor.

QT prolongation: amisulpride prolongs QT interval in a concentration-dependent manner. A thorough QT study was conducted at 5 mg infused over 1 to 2 min and at the supratherapeutic dose of 40 mg infused over 8 min. A dose- and concentration-dependent prolongation of QT interval was observed. At the 5-mg dose proposed for the prevention of PONV, no significant effect of amisulpride on the QT interval was observed with the largest ΔΔQTcF of 5.0 ms (90% CI upper bound: 7.1 ms). On the other hand, at a supra-therapeutic dose (40 mg infused over 8 min), a significant effect on the QT interval was observed with the largest ΔΔQTcF of 23.4 ms (90% CI upper bound: 25.5 ms). Because 10 mg was not studied in the tQT study, the QT prolongation at 10 mg was predicted based on the exposure-ΔΔQTcF relationship. Based on the IRT-QT's concentration-QTc analysis, at the highest recommended dose, i.e., 10 mg infused over 1 min, the largest mean (90% upper confidence bound) difference in QTcF from placebo after baseline-correction (ΔΔQTcF) is predicted to be 12.6 ms (90% upper CI: 14.1 ms).

Clinical Pharmacokinetics: After an intravenous infusion, the peak plasma concentration of amisulpride is achieved at the end of the infusion period and the plasma concentrations decrease about 50% of the peak value within about 15 minutes. The AUC_{inf} increases proportionally in the dose range from 5 mg to 40 mg amisulpride.

- Distribution: Following intravenous administration, the mean volume of distribution of amisulpride is estimated to be 127 to 144 L in surgical patients and 171 L in healthy subjects. Plasma protein binding is 25% to 30%.
- Elimination: The mean elimination half-life is approximately 4 to 5 hours. The plasma clearance of amisulpride is 20.6 L/h in surgical patients and 24.1 L/h in healthy subjects.

- Metabolism: No metabolite was detectable in plasma whereas four metabolites (C1, C2, C3, and C4) were identified in urine and feces. Each metabolite is accounted for <7% of dose. The metabolism of amisulpride is not mediated by major cytochrome P-450 enzymes.
- Excretion: amisulpride was excreted approximately 74% in urine (58% as unchanged) and 23% in feces (20% as unchanged). Renal clearance was estimated to be 20.5 L/h (342 mL/min) in healthy subjects suggesting that amisulpride undergoes active renal secretion.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed general dosing regimen of amisulpride is as follows:

- Prevention of PONV: 5 mg as a single intravenous injection infused over 1 to 2 minutes at the time of induction of anesthesia, either alone or in combination with other anti-emetics
- Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis: 10 mg as a single intravenous injection infused over 1 to 2 minutes in the event of nausea and/or vomiting after a surgical procedure

(b) (4), we recommend 1 to 2 min infusion for amisulpride 10 mg, which is consistent with how the clinical studies were conducted. Of note, in the proposed labeling submitted later (EDR 23, 4/23/2018), (b) (4) the infusion rate for amisulpride 10 mg to 1 to 2 min.

Table 15. Indication, Regimen, and Recommendation

Indication	Studied Regimen	Proposed Regimen	Recommendation
Prevention of PONV	5 mg over 1 to 2 min	5 mg over 1 to 2 min	5 mg over 1 to 2 min
Treatment of PONV	10 mg over 1 to 2 min	(b) (4) ((b) (4) 10 mg over 1 to 2 min)	10 mg over 1 to 2 min

Therapeutic Individualization

Specific Populations: Patients with Renal Impairment

The effects of renal impairment on PK of amisulpride was studied in surgical patients in phase 3 trials. In patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2), the mean AUC_{inf} of amisulpride was 1.3-fold higher than in patients with normal renal function. In phase 2 and 3 trials, only eight patients with severe renal impairment received amisulpride.

PK of amisulpride in severe renal impairment was only available in one patient (eGFR 8.2 mL/min/1.73 m^2), whose AUC_{inf} was 2.1-fold higher than those in patients with normal renal function. However, no clear trend in terms of the C_{max} was observed in patients with impaired renal function compared to with normal renal function. Therefore, no dose adjustment is necessary in patients with mild to moderate renal impairment. Administration to patients with

severe renal impairment should be avoided because limited data were available to evaluate the effect of severe renal impairment on PK.

Drug-Drug Interaction

Other Anti-Emetics that Prolong the QT Interval

Of 5-HT_3 antagonist approved for PONV, ondansetron was most frequently used with amisulpride as a prophylaxis agent or a rescue medication in the phase 3 trials. Both amisulpride and ondansetron prolong QTc interval in a concentration-dependent manner, and co-administration may lead to an additive effect on hERG inhibition.

Given that amisulpride 5 mg has no risk for QT prolongation, amisulpride 5 mg (for prevention of PONV) and ondansetron 4 mg can be simultaneously or sequentially co-administered (b) (4) (b) (4) However, in order to minimize the risk of QTc prolongation which is expected at amisulpride 10 mg (for treatment of PONV), we recommend that amisulpride 10 mg be given at least 30 min before or 10 min after the end of ondansetron infusion (at the approved 4-mg dose for PONV). In the clinical trial, a 30-min interval was instructed for the assessment of treatment effect of amisulpride 10 mg.

The Other Drugs Prolong the QT Interval

For patients taking other drugs known to prolong QT interval, close ECG monitoring is recommended.

Other Anti-Emetics in the Same Class (i.e., D_2 antagonist)

For management of PONV, concomitant use of anti-emetics in the same class is not typically recommended because of the synergistic effects between anti-emetics having different mechanisms. Of note, there are other D_2 antagonists which are available as antiemetics in the US such as droperidol, metoclopramide, and prochlorperazine. In DP10017 for the prevention of PONV with add-on therapy to other anti-emetics with amisulpride, other D_2 antagonists were excluded aside from amisulpride. In DP10018/DP10019 for the treatment of PONV, some patients received other D_2 antagonists for prophylaxis or as a rescue medication, but the proposed indication does not include the treatment of PONV for patients who have received antiemetic prophylaxis with D_2 antagonist. Safety of concomitant use with amisulpride and other D_2 antagonist was not evaluated in this submission but pharmacologic drug interaction between amisulpride and other D_2 antagonists is possible. Unwanted pharmacologic response might be caused by greater D_2 antagonism. Of D_2 antagonist approved for PONV, droperidol has been reported to cause significant QT prolongation and Torsades de Pointes at recommended doses or at even lower doses. Therefore, amisulpride should be avoided in patients taking droperidol.

Levodopa

The Applicant proposed to avoid using levodopa with amisulpride because reciprocal antagonism of effects occurs between levodopa and amisulpride given that levodopa is decarboxylated to dopamine in extracerebral tissues. Even though this submission did not explain this drug interaction with the clinical data or published literature, it is pharmacologically plausible.

Outstanding Issues

The effect of severe renal impairment on PK of amisulpride

Amisulpride is primarily excreted in urine so the systemic exposure to amisulpride can be increased in patients with renal impairment. In surgical patients with renal impairment, AUC was higher in patients with mild to moderate renal impairment up to 1.3-fold compared to patients with normal renal function. However, the extent of effect in severe renal impairment could not be adequately addressed due to the limited data. The only available PK result for severe renal impairment came from one patient and showed 2.1-fold higher AUC compared to patients with normal renal function.

Table 16. Recommended Study to Address the Outstanding Issue

Key Issue(s) to be addressed	Effect of severe renal impairment on PK of amisulpride. Insufficient data are available to label the product for patients with severe renal impairment.
Rationale	PK in patients with severe renal impairment were not adequately characterized; PK data in severe renal impairment were available in only one patient and safety data in patients with severe renal impairment are limited to eight patients in phase 2 and 3 trials.
Recommended study to address the deficiency	PK study following a single dose of amisulpride in patients with severe renal impairment and end-stage renal disease (eGFR <30 mL/min/1.73 m^2) and healthy subjects as a control group. ECG assessments should be included.

ECG = electrocardiogram; eGFR = estimated glome rular filtration rate; PK = pharmacokinetics

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 17. Summary of the General Pharmacology and PK of Amisulpride

Pharmacology	
Mechanism of Action	Dopamine D_2 receptor antagonist Dopamine D_2 receptors are in the chemoreceptor trigger zone (CTZ) and respond to the dopamine released from the nerve endings. Activation of CTZ relays stimuli to the vomiting center which is involved in emesis.
Active moieties	Amisulpride
QT prolongation	Amisulpride prolongs QTc in concentration-dependent manner. The estimated maximum ΔΔQTcF for various doses is as follows: - 5 mg/2 min IV infusion: 5.0 ms (90% upper CI: 7.1 ms) - 40 mg/8 min IV infusion (4-fold of the maximum recommended dose, i.e., 10 mg): 23.4 ms (90% upper CI: 25.5 ms) In addition, the concentration-ΔΔQTc model predicted the largest ΔΔQTcF as 12.6 ms (90% upper CI: 14.1 ms) at 10 mg infused over 1 min (the maximum proposed dose).
Bioanalysis	Racemic amisulpride was measured using adequately validated LC-MS/MS methods. When R- and S-amisulpride was measured separately, concentrations of two isomers were virtually the same in human plasma.
Healthy Volunteers vs. Patients	Population PK analysis estimated the plasma clearance of 20.6 L/h in surgical patients, which is 15% lower than 24.1 L/h in healthy subjects.
Dose Proportionality	Mean AUC_{inf} increased dose proportionally after single 5-mg and 40-mg doses in healthy subjects. AUC_{inf} and C_{max} increased dose-proportionally after single 5-mg and 10-mg doses infused over 1 to 2 min in surgical patients.
PK variability	After a 5 or 10 mg single IV administration in surgical patients, CV% for C_{max}: 55 to 156% and AUC_{inf}: 37 to 46%.
PK model	A three-compartment linear model with first-order elimination following IV administration adequately described the PK of amisulpride.
Stereoisomer	Amisulpride is a racemic drug containing 50% each of R- and S-amisulpride. The PK profiles of two enantiomers are similar in healthy subjects.
Distribution	Volume of distribution: 127 to 171 L which indicates amisulpride distributes into tissues. Plasma protein binding: 25 to 30% at 37 to 1850 ng/mL of amisulpride Blood to plasma ratio: 0.9 to 1.1
Elimination	Half-life: 4 to 5 hours in healthy subjects and surgical patients Clearance: 20.6 L/hr in surgical patients, slightly lower than 24.1 L/hr in healthy subjects
Metabolism	No metabolites were detectable in plasma while four minor metabolites, formed by oxygenation, N-dealkylation, dehydrogenation or methylation, were identified in urine and feces. In vitro study suggests that the metabolism of amisulpride is not mediated by major cytochrome P-450 enzymes.
Excretion	Following administration of a radiolabeled amisulpride, approximately 74% of amisulpride was excreted in urine (58% as unchanged) and 23% in feces (20% as unchanged). Renal clearance was estimated to be 20.5 L/hr (342 mL/min) in healthy subjects, suggesting that amisulpride undergoes active renal secretion. Active renal secretion may be mediated by MATE1 and/or MATE2-K, for which amisulpride is a substrate in in vitro study.

Pharmacology	
Inhibition/Induction	In vitro, amisulpride does not inhibit or induce CYP enzymes at concentrations higher than plasma concentrations observed in humans. In vitro, amisulpride inhibits MATE1 and MATE2-K at concentrations higher than plasma concentrations observed in humans, but not other transporters.

AUC = area under the curve; CV = coefficient of variation; CYP = cytochrome P; IV = intravenous; LC-MS/MS = liquid chromatography-coupled tandem mass spectrometry; MATE = multidrug and toxin extrusion protein; PK = pharmacokinetics

ADME in healthy volunteers (mass balance study, DP10020)

Elimination predominantly occurred via kidney as the 56% of the dose was excreted unchanged amisulpride in urine. In a mass balance study, 97% of the administered dose was excreted in urine and feces over 144 hours (74% of the dose was recovered in urine and 23% was recovered in feces). The 85.6% of the dose was excreted within 48 hours. The 15% and 6.1% of the dose was recovered as metabolites in urine and feces over 48 hours, respectively (Table 18).

Table 18. Proportion (%) of Dose Excreted in Urine and Feces Following 10 mg Infused over 4 Minutes

Compound	**Urine (0 to 48 h)**	**Feces (0 to 96 h)**
Amisulpride (parent)	57.5	20.6
C1 (Oxygenation)	4.9	2.1
C2 (N-Dealkylation)	3.6	2.0
C3 (Oxygenation + di-dehydrogenation or methylation + dehydrogenation)	1.5	Not detected
C4 (Oxygenation + dehydrogenation)	5.0	2.0
Total	72.5	26.7

Source: 5.3.3.1. DP10020 Study Report

Pharmacokinetics in Healthy Subjects and Surgical Patients

Following single dose intravenous administration of amisulpride, the systemic exposure increased dose-proportionally in the dose range from 5 to 40 mg of amisulpride in healthy subjects and surgical patients. Table 19 shows the summary of PK parameters from clinical studies.

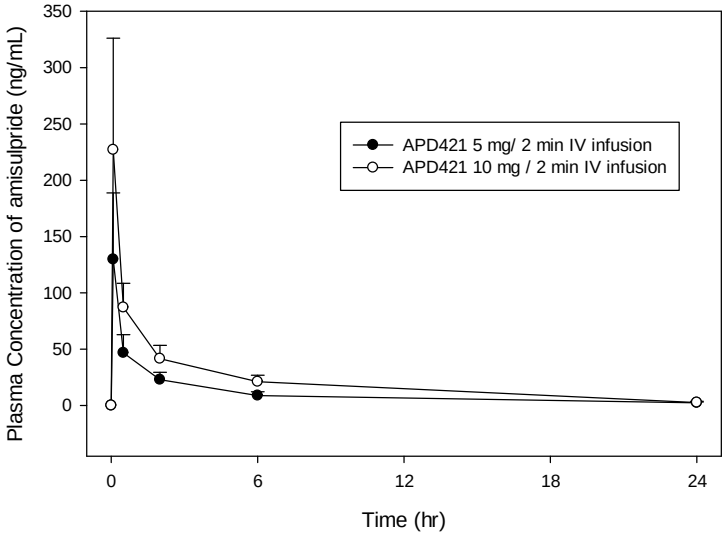
Table 19. Summary of Key PK Parameters from Clinical Studies of Amisulpride

Population	**Study**	**N**	**Dose (mg)**	**Infusion (min)**	**Mean (SD)**				
					C_{max} (ng/mL)	**AUC_{inf} (ng*h/mL)**	**$T_{1/2}$ (h)**	**CL (L/h)**	**V_{ss} (L)**
Healthy	DP10013	39	5	2	200 (139)	154 (30)	4.1 (0.8)	26.0 (3.8)*	218 (54)*
	DP10013	39	40	8	1305 (329)	1374 (239)	5.0 (0.7)	27.8 (4.6)*	128 (24)*
	DP10020	6	10	4	357 (149)	228 (19)	3.7 (0.5)	43.5 (3.2)	171 (26)
Surgical Patients	DP10014	26	5	~1	161 (58)	260 (65)	4.9 (1.0)	20.4 (4.9)	131 (38)
	DP10018/	22	5	~2	127 (64)	204 (94)	4.6 (2.3)	28.6 (10.7)	144 (76)
	DP10019	29	10	~2	285 (446)	401 (149)	3.8 (1.6)	28.0 (9.5)	127 (45)

*The value is from reviewer's analysis because the Applicant did not provide.
AUC = area under the curve; CL = clearance; PK = pharmacokinetics; SD = standard deviation; NA = not available
Source: 2.7.2. Summary of Clinical Pharmacology, Table 2.7.2-20.

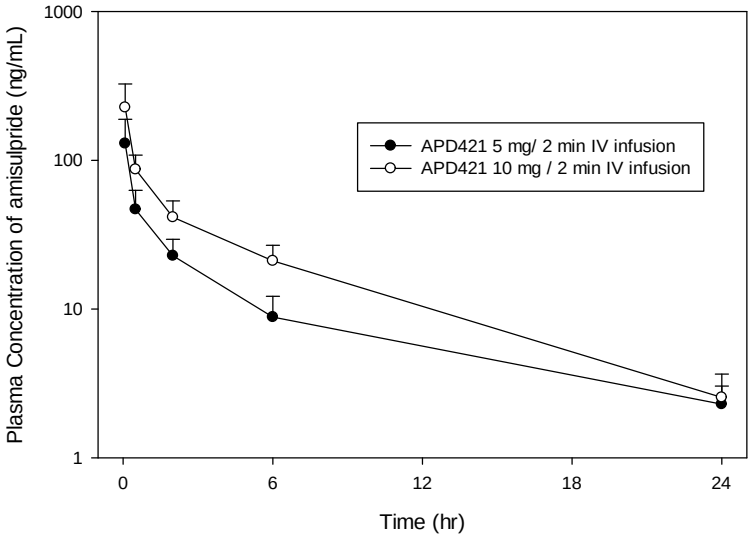
After an intravenous infusion, the peak plasma concentration of amisulpride is achieved at the end of the infusion period. The plasma concentration declines in a multiphasic manner with distribution phase and elimination phase. The plasma concentrations declined rapidly to about 50% of the peak value within about 15 minutes after dosing (Figure 3, Figure 4).

Figure 3. Linear Plot of Amisulpride Plasma Concentration Versus Time in Study DP10018 & DP10019 (Pooled)



Markers show arithmetic mean concentration; error bars show standard deviation.
Source: Reviewer's plot. Study DP10018/DP10019 PK Report, Figure 1.

Figure 4. Log-linear Plot of Amisulpride Plasma Concentration Versus Time in Study DP10018 & DP10019 (Pooled)



(Reviewer's plot)

Amisulpride for PONV Versus Oral Amisulpride as an Antipsychotic

Amisulpride in oral or intramuscular formulation has been used as an anti-psychotic in a range of 50 to 1200 mg/day outside of the US. The Applicant submitted safety data from other regulatory authority post-marketing databases, and literature for oral amisulpride as supportive safety information. Based on a cross-study comparison, the systemic exposure to amisulpride for the proposed highest dose, i.e., 10 mg, is generally lower than that of 200 mg oral amisulpride single dose.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

The efficacy of 5 mg amisulpride for prevention and 10 mg amisulpride for treatment of PONV was supported by three placebo-controlled phase 3 trials (i.e., DP10014, DP10015, and DP10017) and two placebo-controlled phase 3 trials (i.e., DP10018 and DP10019), respectively. See Section 8 for evaluation and details of the study design and results of the phase 3 trials.

6.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for which the Indication Is Being Sought?

Yes, the proposed doses, 5 and 10 mg, are appropriate for prevention of PONV and treatment of PONV, respectively. The proposed infusion duration of 1 to 2 min is consistent with the infusion duration studied in the clinical trials.

QT prolongation at amisulpride 10 mg infused over 1 min predicted by the IRT-QT's concentration-QTc analysis is ΔΔQTcF 12.6 ms (90% upper CI: 14.1) which is similar to that of moxifloxacin 400 mg. The labeling will indicate the QT prolongation by amisulpride. The close ECG monitoring for patients should be recommended. The management of the risk for QT prolongation at 10 mg is deferred to the clinical review.

6.3.2.2.1. Dosing rationale

The proposed dose was selected based on the complete response rate in a dose-ranging study (DP10006) at 1 mg to 20 mg for prevention of PONV and two phase 3 trials (DP10018 and DP10019) comparing 5 mg and 10 mg for treatment of PONV. The complete response is defined as no episodes of vomiting/retching and no use of anti-emetic rescue medication in the first 24 hours.

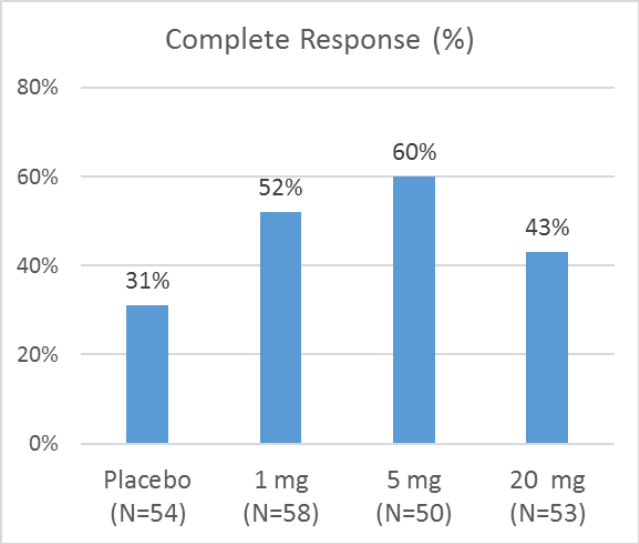
Prevention of PONV

In Study DP10006, a total of 215 adult patients with a moderate-to-high risk of PONV were randomly assigned to a single IV dose of amisulpride 1 mg, 5 mg, 20 mg or matching placebo at induction of general inhalational anesthesia.

Between 1 mg and 5 mg, the complete response rate increased but the response rate at 20 mg was lower than those at 1 mg or 5 mg (Figure 5). Lower efficacy at higher doses in preventing nausea

and vomiting (so-called 'bell-shaped' dose-response relationship) was consistently observed in nonclinical studies in ferrets with apomorphine or cisplatin-induced emesis. Based on the results of this dose-ranging trial, subsequent phase 3 trials (DP10014, DP10015, and DP10017) for prevention of PONV were studied at 5 mg.

Figure 5. The Proportion of Patients with Complete Response in the 24-hour Postoperative Period (mITT Population) in DP10006



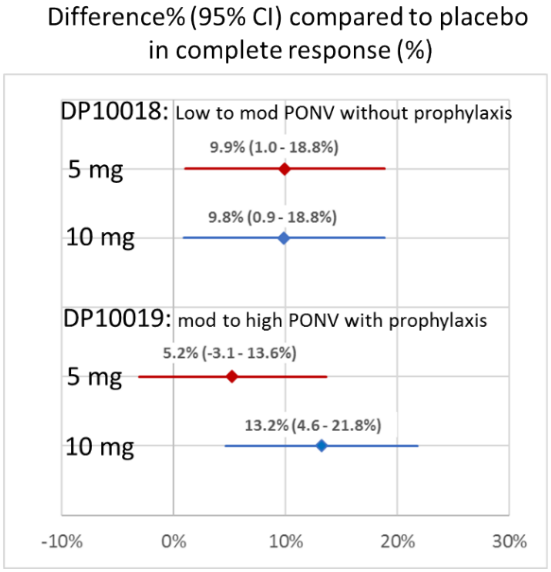
Source: 2.7.3. Summary of Clinical Efficacy, Page 9

Treatment of PONV

Studies DP10018 and DP10019 were both randomized, double-blind comparison of two doses of amisulpride (5 mg and 10 mg) and placebo with 1:1:1 ratio as treatment for established PONV in patients who had undergone surgery under general anesthesia. In DP10018 study, patients enrolled were at low-to-moderate risk of PONV and received no PONV prophylaxis, whereas in DP10019, patients were at moderate-to-high risk and had received anti-emetic prophylaxis.

The complete response rates for the 10-mg dose were significantly higher compared to placebo in both prophylaxis failure patients with moderate-to-high risk of PONV and prophylaxis-naïve patients with low-to-moderate risk of PONV (P=0.016, 0.003, respectively), whereas the 5-mg dose did not show a statistically significant benefit in prophylaxis failure patients with moderate to high risk of PONV (P=0.109) (Figure 6). As such, the 10-mg dose was proposed for the treatment of PONV.

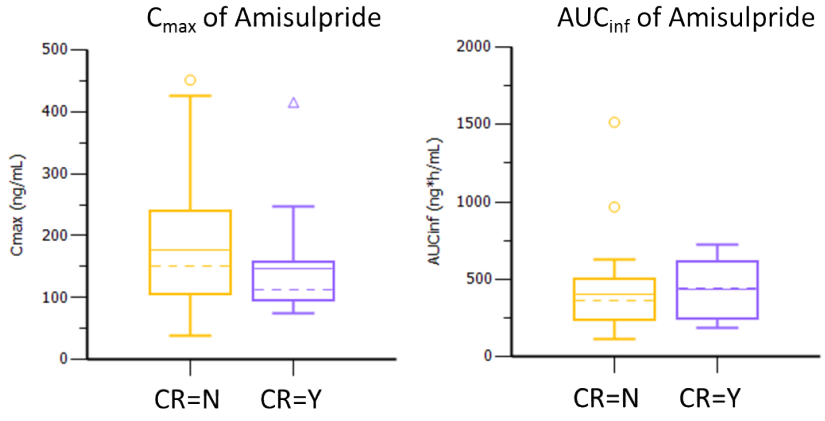
Figure 6. Difference Compared to Placebo in Complete Response in the 24-hour Postoperative Period (mITT Population) in DP10018 and DP10019



Source: 2.7.3. Summary of Clinical Efficacy, Table 2.7.3-6

Of note, an exposure-response relationship was not clear in the subset of patients in DP10018 and DP10019 whose PK samples were available (N=45). The logistic regression analysis conducted by the Applicant suggested that a relationship between the exposure (C_{max} or AUC_{inf}) and the complete response was not evident regardless of patient populations (i.e., with versus without prophylaxis treatment or low-to-moderate risk versus moderate-to-high risk). Despite acknowledging small sample size (N=45), we confirmed that no significant differences in exposure between patients who showed complete response and those who didn't (Figure 7) in this PK subset population of DP10018 and DP10019. Therefore, failure to respond at 5 mg for treatment of PONV in DP10019 is less likely caused by insufficient dose but more likely to relate to other PONV-related intrinsic or extrinsic factors.

Figure 7. Comparison of Exposure Between Patients who Showed Complete Response and Those who Didn't in the PK Subset Population of DP10018 and DP10019



(Reviewer's plot)
CR = complete response; N = non-responders; Y = responders

6.3.2.2.2. Dose-related adverse events

Dose-dependent increase in AEs was not apparent except for infusion site pain and QT prolongation that was observed in tQT study. Infusion site pain occurred in 6% of patients who received 10 mg amisulpride, compared to 3.7% for amisulpride at 5 mg and 4.1% for placebo. Also, infusion site pain occurred in most of the healthy subjects who received 10 and 40 mg amisulpride infusions in DP10013 and DP10020. The concentration-QTc relationship is discussed more detail in the following section. Of note, multiple post-marketing safety surveillance and published literature have reported that acute overdoses of oral amisulpride, ranging from 4,000 mg to 80,000 mg, have been associated with the development of Torsades de Pointes. For the review of safety assessment including post-marketing data, see Section 8.

6.3.2.2.3. QT prolongation

Amisulpride prolongs the QT interval in a concentration-dependent manner. In the thorough QT study of amisulpride (DP10013), the largest ΔΔQTcF was 23.4 ms (90% CI upper bound: 25.5 ms) at a supra-therapeutic dose (40 mg infused over 8 min) and 5.0 ms (90% CI upper bound: 7.1 ms) at the lower proposed dose of 5 mg IV over 2 min (Table 20).

Table 20. The Largest ΔΔQTcF and 90% CI by Treatment

Treatment	Time (hour)	ΔΔQTcF (ms) (90% CI)
Amisulpride 5 mg infused over 2 min	0.133	5.0 (2.8, 7.1)
Amisulpride 40 mg infused over 8 min	0.133	23.4 (21.3, 25.5)
Moxifloxacin 400 mg	4	12.3 (10.1, 14.6)

Source: 5.3.4.1. DP10013 Study Report, Table 12
CI = confidence interval

Since the tQT study did not include the highest proposed dose, i.e., amisulpride 10 mg, the concentration-QTc model was used to project the QTc effect at 10 mg. (b) (4)

(b) (4)

Nonetheless, when the largest ΔΔQTcF was predicted at simulated C_{max} according to various infusion rate based on the concentration-QTc model established by the IRT-QT (Table 4), the potential risk of QT prolongation at 10 mg was similar between 4 min and 1 min infusion, i.e., the 90% upper CI of the largest ΔΔQTcF, 12.7 ms and 14.1 ms, respectively.

Table 21. Predicted ΔΔQTcF with Various Infusion Rate in a Simulated Patient Population

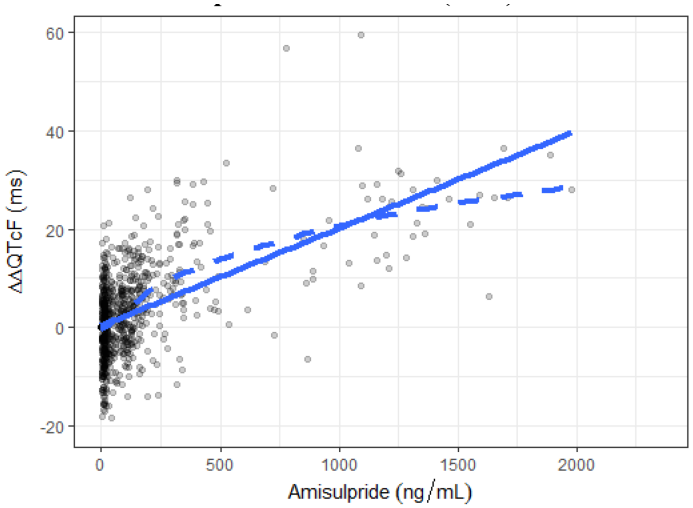
Dosing regimen	Simulated C_{max} (ng/mL)[1)] Median (90% PI)	Predicted ΔΔQTcF [2)](ms) Mean (90% CI)
Amisulpride 10 mg/1 min infusion	390 (192, 732)	12.6 (11.0, 14.1)
Amisulpride 10 mg/2 min infusion	378 (188, 699)	12.3 (10.8, 13.8)
Amisulpride 10 mg/4 min infusion	331 (170, 626)	11.3 (9.8, 12.7)

Source: Brief PK Simulation Report in SDN 23 dated 4/23/2018
[1] Predicted values using the concentration-QTc model established by the IRT-QT
PI = prediction interval; CI = confidence interval

The magnitude of QT prolongation for amisulpride 10 mg with both infusion rates is predicted to be greater than the threshold of risk identified in ICH guideline E14 (10 ms) and be similar to that of moxifloxacin 400 mg. However, the QT interval is predicted to return <5 ms within 30 min after 10-mg dose. Based on our analysis with the concentration-QTc model established by the IRT-QT and the applicant's population PK model, a mean plasma amisulpride concentration of 116 ng/mL in 30 min after dosing 10 mg over 1 min which is predicted to lead to a ΔΔQTcF of 4.5 ms (90% upper CI: 5.3).

The predicted values for the largest ΔΔQTcF at 10 mg were different between the Applicant's analysis and the IRT-QT's analysis. As the linear model used by the Applicant was deemed inappropriate by the IRT-QT' review, the IRT-QT alternatively used E_{max} model to describe the observed concentration-QTc relationship for amisulpride (Figure 8).

Figure 8. Evaluation of the Relationship Between Amisulpride and ΔΔQTcF



The blue line represents a linear fit (solid line that the Applicant proposed) and a loess fit (dashed line that IRT-QT analyzed)
Source: the IRT-QT review in DARRTS dated January 12, 2018, by Lars Johannsen, PhD et al.

6.3.2.3. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

Yes, as amisulpride is primarily cleared by the kidney, and renal impairment affects systemic exposure. While no dosage adjustment is necessary in patients with mild to moderate renal impairment because of the small increase in exposure, we recommend that use in patient with severe renal impairment be avoided because the extent of effect of severe renal impairment on PK was not adequately assessed in this application due to limited data available in one patient. Safety data in patients with severe renal impairment was also limited given the fact that eight patients with severe renal impairment received amisulpride across phase 2 and phase 3 trials.

Meanwhile, no clinically significant differences in the PK of amisulpride were observed based on age, sex, and race based on population PK analysis.

6.3.2.3.1. Renal Impairment

A dedicated renal impairment study for amisulpride was not conducted. The effect of renal impairment on PK was investigated in a subset of patients from three phase 3 studies, DP10014, DP10018 and DP10019. In study DP10014, 15 of the 26 subjects with a full PK profile had renal impairment, and in studies DP10018 and DP10019, 12 out of 21 patients in the 5-mg dose group and 13 out of 27 in the 10-mg group had impaired renal function which was estimated by glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) Study equation.

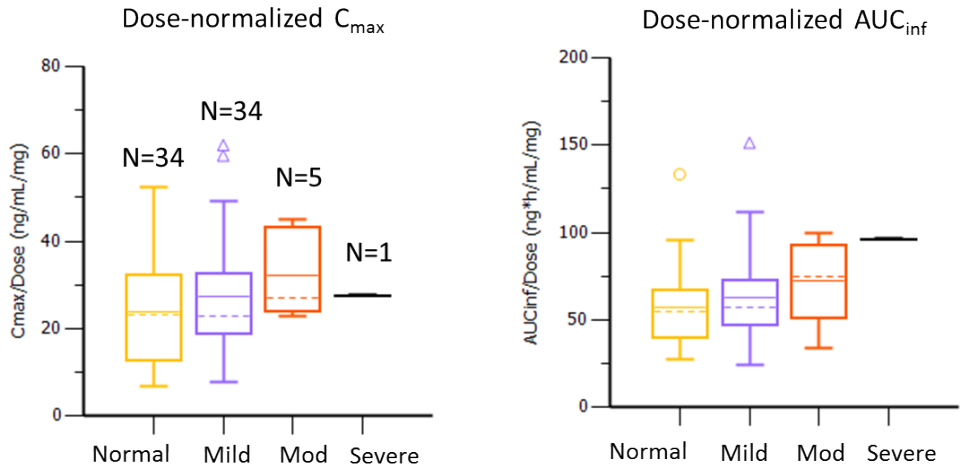
Patients with mild to moderate renal impairment showed higher AUC_{inf} up to around 1.3-fold, and one patient with severe renal impairment (eGFR 8.2 mL/min/1.73 m^2) showed 2.1-fold higher AUC_{inf} compared to patients with normal renal function (Table 22, Figure 9). However, no clear trend in terms of differences in C_{max} was observed in patients with impaired renal function compared to with normal renal function.

Table 22. Mean (SD) PK Parameters for Amisulpride by Degree of Renal Impairment

Renal Impairment	DP10014			DP10018/DP10019						Pooled		
	5 mg			5 mg			10 mg					
	N	C_{max}	AUC_{inf}	N	C_{max}	AUC_{inf}	N	C_{max}	AUC_{inf}	N	C_{max}/Dose	AUC_{inf}/Dose
Normal	11	145 (30)	259 (68)	9	134 (78)	189 (73)	14	357 (639)	365 (86)	34	31 (41)	41 (14)
Mild	12	177 (76)	254 (65)	10	114 (57)	211 (111)	12	232 (95)	411 (169)	34	27 (13)	45 (17)
Moderate	3	154 (61)	286 (77)	2	172 (52)	252 (154)	-	-	-	5	32 (10)	54 (19)
Severe	-	-	-	-	-	-	1	275	781	1	28	78

C_{max} in ng/mL; AUC_{inf} in ng*h/mL; AUC = area under the curve; SD = standard deviation
Normal function: eGFR ≥90 mL/min/1.73 m^2
Mild impairment: eGFR =60 to 89 mL/min/1.73 m^2
Moderate impairment: eGFR =30 to 59 mL/min/1.73 m^2
Severe impairment: eGFR =15 to 29 mL/min/1.73 m^2
Source: Response to information request, SDN 28 dated 5/25/2018

Figure 9. Comparison of Dose-Normalized C_{max} and AUC_{inf} by Degree of Renal Impairment from Pooled PK Subset of DP10014, DP10018, and DP10019 (Reviewer's Plot)



Based on the PK results and the safety profiles in patients with renal impairment, the Applicant proposed no dose adjustment for any degree of renal impairment, which is acceptable for mild to moderate renal impairment. The extent of effect of severe renal impairment on PK could not be adequately assessed because the data were limited to a single subject. Beyond PK, clinical safety data were available for eight patients with severe renal impairment, which is insufficient to address the need for dose adjustment. Clinical safety data for higher systemic exposures is available in patients who received 20 mg (DP10006, N=53) and in healthy subjects who received 40 mg (DP10013, N=40), although it was deemed insufficient by clinical reviewers to address the safety at higher exposure which might be caused by severe renal impairment. The potential for significant increase in exposure (i.e., >2-fold) by severe renal impairment cannot be excluded. Therefore, use of amisulpride in patients with severe renal impairment should be avoided until the effect of severe renal impairment on PK is adequately evaluated. See Section 8 for the review of safety in patients with renal impairment and high doses such as 20 mg (DP10006) and 40 mg (DP10013).

6.3.2.3.2. Hepatic Impairment

The effect of hepatic impairment was not studied. Given that approximately 80% of amisulpride administered is excreted in unchanged form and CYP enzymes are unlikely to involve in metabolism of amisulpride based on results of in-vitro studies, hepatic impairment is not expected to affect systemic exposure significantly. Thus, no dosage adjustment is necessary in patients with hepatic impairment.

6.3.2.3.3. Other intrinsic factors

Based on population PK analyses, no clinically relevant effects of age, sex, or race on the systemic exposure of amisulpride were observed that would require a dose adjustment; age (median: 43, range: 19 to 80), sex (106 female and 37 male patients) and race (116 white, 18 Asians, 5 blacks, and 4 patients with other race) were not significant covariates in the population

PK model. Amisulpride clearance in surgical patients was estimated to be 15% lower than that of healthy volunteers, i.e., 20.6 L/h versus 24.1 L/h.

The effect of body weight was incorporated into the clearance and the volume of distribution in the final population PK model with an allometric exponent fixed to 0.75. For a population with a range of body weights between 45 kg and 160 kg, this means that compared to the median weight of 70 kg, subjects with the lowest body weight were projected to have 28% lower clearance, while subjects at the highest body weight were projected to have 86% higher clearance. However, this effect was not sufficient to recommend dose adjustment because body weight only accounted for a small portion of between-subject variability (e.g., 7% out of 28% variability in the systemic clearance). Refer to the Pharmacometrics assessment in the Appendix 16.2.2 for more details.

6.3.2.4. Are There Clinically Relevant Drug-Drug Interactions, and What Is the Appropriate Management Strategy?

Yes, given that amisulpride prolongs the QTc interval concentration-dependently, caution needs to be exercised when amisulpride with other medications known to cause significant QT prolongation is concomitantly used. In particular, amisulpride will be used concomitantly with other antiemetics per the proposed indication; concomitant use with QT-prolonging antiemetics such as ondansetron is a concern.

Given a minimal risk of QT prolongation at amisulpride 5 mg, amisulpride 5 mg for prevention of PONV can be simultaneously administered with ondansetron 4 mg. However, as QT prolongation is anticipated at amisulpride 10 mg, when amisulpride 10 mg for treatment of PONV is concomitantly used with ondansetron 4 mg, (b) (4) (b) (4) we recommend a 30-min interval (b) (4) when ondansetron is administered after amisulpride 10 mg (b) (4)

6.3.2.4.1. Pharmacodynamic Drug Interaction Between Amisulpride and Ondansetron

During the phase 3 trial of amisulpride, ondansetron was the most frequently (about 50% of patients) used concomitant antiemetic as a prophylaxis of PONV as well as a rescue medication. The approved adult dosing regimen of ondansetron for PONV is a single IV dose of 4 mg over >30 sec, preferably 2 to 5 min, at induction of anesthesia, or after surgery if the patient did not receive prophylactic antiemetics and experiences PONV.

Per the labeling of ondansetron, ondansetron 8 mg infused over 15 min has no effect on QT interval (i.e., the largest ΔΔQTcF (90% upper CI) was 5.6 ms (7.4 ms)) whereas 32 mg infused over 15 min significantly prolongs QTc interval (ΔΔQTcF was 19.5 ms (21.8 ms)). Thus, the ondansetron labeling recommends ECG monitoring in patients taking other medication that lead to QT prolongation in Section 5, Warning and Precaution. On the other hand, based on data from

Zuo et al, 2014 and the ondansetron label, ondansetron 4 mg infused over 30 sec to 5 min, the approved dose for PONV, is unlikely to cause a QTc interval increase ≥10 ms. Also, the QT increase will fall below 5 ms within a short time (10 min).

As both ondansetron and amisulpride prolong QT interval in a concentration-dependent manner, pharmacodynamic interaction in terms of QTc prolongation is possible with additive effect. Both amisulpride and ondansetron inhibit hERG potassium ion channel (IC_{50} =68 µM and 1.3 µM, respectively) and two or more hERG potassium ion channel blockers are usually believed to have an additive effect. In addition, in the in vitro patch clamp study (Study ACAC-001), the combination of amisulpride 2.82 µM and ondansetron 135 µM which was treated either simultaneously or sequentially caused at most an additive effect on hERG blockade (15% to 26% inhibition) compared to each alone (i.e., 5% inhibition with amisulpride 2.82 µM alone; 18% inhibition with ondansetron 135 µM alone). See Section 5.3.3 Safety Pharmacology for details of Study ACAC-001 review. Meanwhile, pharmacokinetic interaction between amisulpride and ondansetron is unlikely.

Based on the proposed indication of amisulpride, possible situations of concomitant use of amisulpride and ondansetron are listed in Table 23.

Table 23. Conditions of Concomitant Use with Amisulpride and Ondansetron

Indication	Scenario (pertinent clinical trials)	Prophylaxis	Treatment	Further rescue
Prophylaxis: amisulpride 5 mg	Scenario 1 (DP10006/ DP10014/ DP10015)	Amisulpride 5 mg		Ondansetron 4 mg
	Scenario 2 (DP10017)	Ondansetron 4 mg + amisulpride 5 mg (simultaneously)		Ondansetron 4 mg
Treatment: amisulpride 10 mg	Scenario 3 (DP10018/ DP10019)	Ondansetron 4 mg	Amisulpride 10 mg	
			Amisulpride 10 mg	Ondansetron 4 mg

Source: Reviewer's analysis

1. Amisulpride 5 mg and Ondansetron 4 mg (Scenario 1 and Scenario 2)

(b) (4)

(b) (4) In DP10017, a phase 3 trial for prevention of PONV with combination with other antiemetics, 285 out of 572 patients (49.8%) received ondansetron 4 mg with amisulpride 5 mg simultaneously like Scenario 2 (Table 23). Only 1 individual in the treatment arm (572 patients) was reported as having a prolonged QT interval. Ondansetron was administered to this patient 3 hours after the amisulpride dose and the QT prolongation was reported on the following day. Thus, the safety data of DP10017 in those patients would primarily support this simultaneous and sequential administration for 5 mg amisulpride and 4 mg ondansetron. See Section 8 for detail of safety evaluation of DP10017.

Amisulpride 10 mg and Ondansetron 4 mg (Scenario 3)

The Applicant postulated that the QT prolongation associated with an amisulpride 10-mg dose would fall below 5 ms within 8 min subsequently proposing to administer amisulpride 10 mg and ondansetron 4 mg with a 10-min interval in between. However, given the difference between the Applicant's amisulpride concentration-QT model and the QT-IRT's model, we recommend having at least a 30-min interval between two drugs when ondansetron is administered after amisulpride dosing (b) (4) (b) (4)

While no clinical QT studies were performed with 10 mg amisulpride and 4 mg ondansetron in combination and alone to evaluate whether the effect of the combination is additive, synergistic, or antagonistic, it is anticipated that each drug will cause a certain degree of QT prolongation.

For ondansetron, following ondansetron 16 mg infused over 15 min followed by two doses of 8 mg over 30 sec, the C_{max} was predicted as 203.8 ng/mL (Zuo et al. 2014), so ondansetron 4 mg infused over 30 sec might lead to C_{max} around 100 ng/mL assuming dose-proportional C_{max} increase. On the other hand, per the ondansetron labeling, ondansetron 4 mg infused over 5 min resulted in C_{max}, 42.9 ng/mL. The concentration-QTc analysis of ondansetron by Zuo et al (2014), the largest ΔΔQTcF values at C_{max} 90 ng/mL and 141 ng/mL were 4.1 ms (90% upper CI: 6.0) and 6.5 ms (8.3), respectively. Also, in the same publication, the length of time that the 90% CI of ΔΔQTcF was above >10 ms was short (<2 min) following ondansetron 8 mg with 30 sec infusion which prolonged QTc up to 10.8 ms (13.4). As such, based on data from Zuo et al, 2014 and the ondansetron label, ondansetron 4 mg infused over 30 sec to 5 min (C_{max} 42.9 to around 100 ng/mL), which is approved dose for PONV, is unlikely to cause a QTc interval increase $\geq$10 ms. Also, the QT increase will fall below 5 ms within a short time (10 min).

For amisulpride 10 mg infused over 1 min, the mean C_{max} is predicted to be 390 ng/mL by the Applicant's population PK model simulations. The 390 ng/mL translates to a ΔΔQTcF of 12.6 ms (90% upper CI: 14.1) based on the QT-IRT's concentration-QTc model (Table 21). Further analysis using the Applicant's population PK model for amisulpride yields a mean plasma amisulpride concentration of 116 ng/mL in 30 min after dosing 10 mg over 1 min. This translates to a ΔΔQTcF of 4.5 ms (90% upper CI: 5.3). Thus, we recommend waiting at least 30 min after a 10-mg dose of amisulpride to administer ondansetron in light of the QT effects of both ondansetron and amisulpride.

In addition, in DP10018 and DP10019, phase 3 trials for treatment of PONV, ondansetron was used as either prophylaxis (DP10019 only) or further rescue medication in about 50% of the patient population. In those two trials, further rescue medication was planned to be given at least in 30 min after amisulpride, so the majority of patients who received further rescue took ondansetron in >30 min after amisulpride dosing. However, some patients received ondansetron as either prophylaxis or further rescue medication within 5 to 30 min before or after amisulpride 5 or 10 mg dosing. The safety review for DP10018 and DP10019 particularly in patients who used both amisulpride 10 mg and ondansetron is deferred to the clinical review. See Section 8 for detail of safety evaluation of DP10018 and DP10019.

6.3.2.5. Pharmacodynamic Drug Interaction Between Amisulpride and Other Medication that Causes QT Prolongation

In addition to ondansetron, droperidol is an antiemetic on the US market known to significantly prolong QT. Since droperidol is a D_2 antagonist as the same as the mechanism of action of amisulpride, droperidol would not be appropriate for combination use with amisulpride not only per the proposed indication but also the safety reason. Other than that, caution should be exercised when co-administering amisulpride with other medications known to cause significant QT prolongation with close ECG monitoring.

Pharmacokinetic Drug-Drug Interactions

No in vivo drug-drug interaction (DDI) was conducted for amisulpride. In vitro DDI studies indicate that amisulpride is a substrate of transporters such as MATE-1 and MATE2-K and inhibits MATE-1 and MATE-2K at therapeutic concentration. However, clinically significant DDI with substrates or inhibitors of MATEs is not expected because amisulpride is given as a single dose treatment.

Transporters related DDI

The in vitro study (Study CYP1369 R4) indicated that amisulpride is a substrate for P-gp, BCRP, OCT1, MATE1 and MATE2-K, but not for OATP1B1, OATP1B3, OAT1, OAT3 and OCT2. Given that amisulpride undergoes active renal secretion, MATE1 and/or MATE2-K may contribute to active renal secretion.

In vitro, amisulpride inhibited MATE1 (IC_{50} 2.62µM) and MATE2-K (IC_{50} 10.1µM), in vivo inhibition of MATE1 and MATE2-K cannot be rule out based on $[I]/IC_{50}$; MATE1 $[I]_{max}/IC_{50}$ =0.83; MATE2-K $[I]_{max}/IC_{50}$ =0.14, ≥0.02). But, in vitro amisulpride does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2 at therapeutic concentration.

CYP related DDI

The in vitro study (Study CYP1369 R4) indicated little or no CYP-mediated metabolism of amisulpride (i.e., CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). Amisulpride was not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4, or an inducer of CYP1A2, CYP2B6, or CYP3A4.

7. Sources of Clinical Data and Review Strategy

The development program for Barhemsys (amisulpride injection) addressed the indications of:

- Prophylaxis Against PONV
- Treatment of PONV

The development program included five clinical trials; of which, three (Studies DP10014, DP10015 and DP10017) were for prophylaxis, and two (Studies DP10018 and DP10019) were for the treatment indications.

Table 24 provides a summary of all trials pertinent to the evaluation of the efficacy and safety of Barhemsys (amisulpride).

Table 24. Brief Description of the Phase 3 Efficacy Studies

Trial Identity	Study Design	Regimen/ schedule/ route	Study End-points	Treatment Duration/ Follow Up	No. of Subjects	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
DP10014	Prophylaxis Randomized 1:1, double-blind, multi-center, placebo-controlled, phase 3	5 mg IV Placebo IV	PONV	from 31 July 2013 to 17 January 2014	Enrolled 368 Treated 347 (amisulpride 5 mg:169, Placebo: 178)	Females and males age ≥18 at moderate to high risk of PONV and were undergoing elective surgery under general anesthesia, for elective surgery that required overnight admission to hospital, and was scheduled to last at least 1 hour from induction of anesthesia	France (4 sites) and Germany (6 sites)
DP10015	Prophylaxis Randomized 1:1, double-blind, multi-center, placebo-controlled, phase 3	5 mg IV Placebo IV	PONV	between 8 and 22 days from 13 August 2013 to 28 January 2014	Enrolled 364 Treated 342 (amisulpride 5 mg:176, Placebo: 166)	Females and males age ≥18 at risk of PONV undergoing elective, in-patient surgery using an open or laparoscopic surgical technique, under general anesthesia scheduled to last at least one hour from induction of anesthesia and requiring at least one overnight stay in hospital	United States (9 sites)
DP10017	Prophylaxis Randomized 1:1, double-blind, multi-center, placebo-controlled, phase3b	5 mg IV Placebo IV Both (Given in combination with a standard anti-emetic that was not a dopamine D_2 Antagonist)	PONV	from 12 February 2015 to 28 September 2015	Enrolled 1297 Treated 1204 (amisulpride 5 mg:572, Placebo: 575)	Females and males age ≥18 at risk of PONV undergoing elective, in-patient surgery using an open or laparoscopic surgical technique, under general anesthesia scheduled to last at least one hour from induction of anesthesia and requiring at least one overnight stay in hospital	Germany (7 sites), France (7 sites) and United States (15 sites)

Trial Identity	Study Design	Regimen/ schedule/ route	Study End-points	Treatment Duration/ Follow Up	No. of Subjects	Study Population	No. of Centers and Countries
DP10018	Treatment Randomized 1:1:1, double-blind, multi-center, placebo-controlled, phase 3	5 mg IV 10 mg IV Placebo IV	PONV	from 09 August 2015 to 18 July 2016	Enrolled 1988 Treated 560 (amisulpride 10 mg: 188, amisulpride 5 mg: 191, Placebo: 181)	Females and males age ≥18 at low to moderate risk for PONV who were undergoing elective ambulatory (day-case) or in-patient surgery under general inhalational anesthesia and had received no prior PONV prophylaxis	Germany (5 sites), France (2 sites), Canada (3 sites) and United States (10 sites)
DP10019	Treatment Randomized 1:1:1, double-blind, multi-center, placebo-controlled, phase 3	5 mg IV 10 mg IV Placebo IV	PONV	From 20 January 2017 to 31 March 2017	Enrolled 2285 Treated 702 (amisulpride 10 mg: 230, amisulpride 5 mg: 237, Placebo: 235)	Females and males age ≥18 surgical patients with moderate-to-high risk of PONV who had received prior prophylaxis with an agent of a different class from amisulpride (i.e., not a dopamine antagonist)	Germany (5 sites), France (2 sites), Canada (3 sites) and United States (13 sites)

7.1. Review Strategy

The sponsor has submitted a total of five phase 3, randomized, double-blind, placebo-controlled studies for review. Of the five clinical trials, three are for the indication of “Prevention of Post-Operative Nausea and Vomiting” and two are for the indication of “Treatment of Post-Operative Nausea and Vomiting”. Based on the sponsor’s and the statistical reviewer’s assessments (after replicating and confirming the sponsor’s results), Study DP10014 did not show the superiority of amisulpride to placebo, and therefore, in this review, we will not discuss this study. It should be noted, despite the fact that it did not demonstrate the superiority at the 2-sided significance level of 0,05 with a P-value of 0.09, Study DP10014 is supportive of amisulpride, showing a difference of 9.6% (amisulpride - Placebo) with a 95% Confidence Interval (CI) of (-0.9%, 20.1%).

We will focus solely on the two prophylaxis of PONV Studies (DP10015 and DP10017) and the two treatment of PONV Studies (DP10018 and DP10019).

According to the sponsor’s Statistical Analysis Plan (SAP), dated April 2014, Page 23 of 64, all secondary efficacy endpoints are planned to be exploratory. Therefore, we will not present the results of the secondary endpoints in this review.

Since this NDA consists of two different indications, in this review, each indication will be evaluated individually. Studies DP10015 and DP10017 for the *prevention* of PONV indication will be reviewed first and then we will proceed to studies DP10018 and DP10019 for the *treatment* of PONV indication.

In addition, since the studies under review were conducted using different designs, we shall not conduct analysis of the pooled data.

In this review, we will present both the reviewers' results as well as the sponsor's results, which are confirmed by the reviewers.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Data Sources

The statistical reviewer reviewed the Applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The NDA was submitted in eCTD format and was entirely electronic. Both SDTM and ADaM datasets were submitted. The applicant supplied all data electronically as SAS transport files which can be found in the CDER electronic document room (EDR): \\CDSESUB1\evsprod\NDA209510\209510.enx

The primary and secondary endpoints for each study were included in the ADaM datasets. The statistical reviewer used datasets PONV.xpt and ADEFF.xpt that contain the primary and secondary endpoints for each study.

Data and Analysis Quality

We found the quality of the submitted data acceptable for the efficacy analyses.

8.2. Indication 1: Prophylaxis Against PONV

8.2.1. Study DP10015

This was a randomized, double-blind, placebo-controlled, phase 3 study of amisulpride 5 mg as prophylaxis against PONV. The study was conducted in the United States at nine sites. The study period was from 13-Aug-2013 to 28-Jan-2014.

8.2.1.1. Primary and Secondary Objectives

The primary of objective of study DP10015 was to compare the efficacy of an experimental 5-mg dose of amisulpride to placebo in the prevention of PONV in adult patients at moderate to high risk of PONV.

The secondary objective of the study was to assess the safety and tolerability of amisulpride in terms of the nature and frequency of AEs and laboratory and ECG abnormalities associated with amisulpride injection in patients at risk of PONV.

8.2.1.2. Study Design

Study DP10015 was a multi-center, double-blind, randomized, placebo-controlled study with 2 treatment groups of patients. This study was performed in adult patients (≥18 years), at moderate to high risk of PONV, who were undergoing elective surgery under general anesthesia scheduled to last at least one hour from induction of anesthesia and expected to require at least one overnight stay in hospital.

The study planned to randomize a total of 340 patients on a 1:1 basis to treatment with 5 mg amisulpride injection and matched Placebo. The total duration of the study for each patient was between 8 and 22 days.

A centralized schedule of randomised treatment assignments was computer-generated (b) (4) (b) (4), stratified by country, and then stratified by number of PONV risk factors (2 vs 3 vs 4). The randomized treatment assignment was allocated from the schedule, sequentially to patients in the order in which they were enrolled and communicated to the enrolling center via an interactive web response system (IWRS). Sealed randomization codes were readily available in each center to the investigator/delegate and were only to be used in the event of an emergency. The investigator or designee entered the patient number allocated by the IWRS in the appropriate place on each patient's case report form (CRF).

Using the simplified scoring system, patients were defined as at risk of PONV if they had at least 2 of the following risk factors (each bullet counted as 1 risk factor):

- Past history of PONV or motion sickness
- Habitual non-smoking status
- Female sex
- Planned postoperative opioid use for analgesia

Patients were screened up to 14 days before the planned date of their operation and admitted to hospital on the day before (day -1) or morning of (day 0) their operation. Study medication was given at induction of anesthesia. Assessments were conducted during the 24 hours following study drug administration. Patients were discharged 24 hours after the end of their operation. Patients who had met the criteria for experiencing PONV could have been discharged any time from 16 hours after completion of surgery, at the discretion of the investigator, provided that scheduled 24-hour procedures were completed prior to discharge. Patients who did not fail prophylaxis could also have been discharged any time from 16 hours after completion of surgery, if they had completed an overnight stay, they had not suffered any significant nausea or vomiting since waking on day 1 and scheduled 24-hour procedures were completed prior to discharge. Patients who had not failed prophylaxis at the time of discharge were given a diary card to complete at home. Patients were followed up at 72 hours, by telephone if they had been discharged. Telephone follow-up was conducted 7 days after the operation.

8.2.1.3. Primary Efficacy Endpoint

The primary efficacy variable was the incidence of CR, defined as no episodes of vomiting or retching, and with no use of anti-emetic medication, during the first 24 hours after completion of surgery.

8.2.1.4. Analysis Population

The primary efficacy analysis population was the intent-to-treat (ITT) population. The ITT population included all patients were randomized into the study and received study medication.

With the exception of the 34 patients who received anti-emetic medication incorrectly, none of the other protocol deviations prevented the inclusion of patients in the per protocol (PP) population.

8.2.1.5. Determination of Sample Size

The Sponsor asserts that the results from the previous phase 2 study of amisulpride injection, supported by published evidence, suggested that approximately 40% of a moderate/high risk population would experience no PONV in the 24-hour postoperative period, in the absence of active prophylaxis, and that an effective anti-emetic would deliver an increase of at least 20 percentage points on that rate.

With a sample size of 340, a randomization ratio of 1:1, and a 2-sided type I error rate of 0.05, the sponsor estimated that a Pearson chi-square test with continuity correction would have a 95% power to detect a difference between a 60% rate of protection from PONV in the amisulpride injection group and a 40% rate in the placebo group.

8.2.1.6. Primary Efficacy Analysis

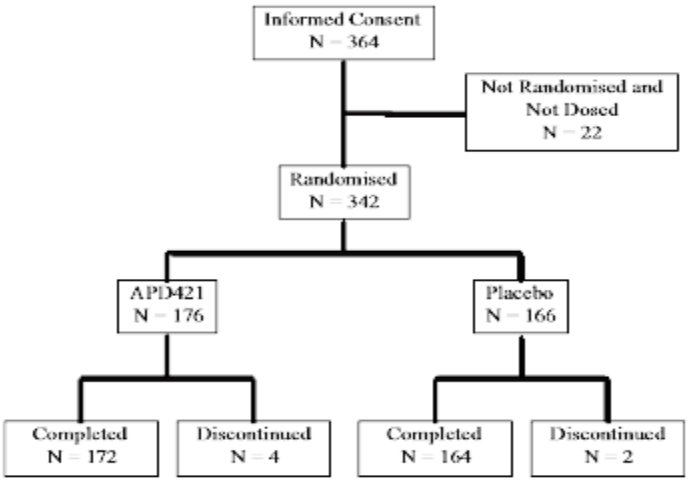
For the primary analysis, the Sponsor used a Pearson chi-square (χ^2) test with Yates's continuity correction at a two-sided significance level of 5%. To confirm the sponsor's results, in this review, we used a simple χ^2 test and a Cochran-Mantel-Haenszel (CMH) test to assess the robustness of the results.

8.2.1.7. Disposition of Subjects

A total of 364 patients were enrolled in the study, of which 22 were not randomized and not dosed. Of these, 4 withdrew their consent, 3 did not comply with the protocol procedures and 15 were not dosed for other unspecified reasons.

Figure 10 and Table 25 show the dispositon of subjects.

Figure 10. Disposition of Subjects – Study DP10015



Source: Sponsor's Study Report Page 35 of 696

Table 25. Disposition of Subjects by Treatment Arm - Study DP10015

	PLACEBO (N=166) n (%)	5mg APD421 (N=176) n (%)	NOT DOSED (N=22) n (%)	OVERALL (N=364) n (%)
Informed Consent	166 (100)	176 (100)	22 (100)	364 (100)
Not Randomised (Not Dosed)	0	0	22 (100)	22 (6.0)
Randomised (Dosed)	166 (100)	176 (100)	0	342 (94.0)
Completed	164 (98.8)	172 (97.7)	0	336 (92.3)
Discontinued (After Randomisation)	2 (1.2)	4 (2.3)	0	6 (1.6)
WITHDRAWAL OF CONSENT	0	1 (0.6)	4 (18.2)	5 (1.4)
PROTOCOL NON-COMPLIANCE	0	0	3 (13.6)	3 (0.8)
LOST TO FOLLOW-UP	2 (1.2)	1 (0.6)	0	3 (0.8)
OTHER	0	2 (1.1)	15 (68.2)	17 (4.7)

Source: Sponsor's Study Report Page 63 of 696

A total of 342 patients were randomized and dosed, comprising 176 randomized to amisulpride injection and 166 to placebo. Of these, four patients from the amisulpride injection group and two patients from the placebo group discontinued prematurely after randomization. Reasons for premature discontinuation were: Lost to follow-up for one patient from the amisulpride injection group and two from the placebo group, withdrawal of consent for one patient from the amisulpride injection group, and other unspecified reasons for two patients from the amisulpride injection group. A total of 172 (98%) patients randomized to amisulpride injection and 164 (99%) randomized to placebo completed the Study.

8.2.1.8. Subjects with Major Protocol Deviations

A total of 16 patients in the amisulpride injection group and 18 patients in the placebo group received antiemetic medications that were either incorrect or given at the wrong time in relation to the surgical procedure. The main incorrect medication was diphenhydramine given postoperatively, which occurred for nine patients in the amisulpride injection group and nine in the placebo group.

8.2.1.9. Populations Analyzed

Table 26 shows the analysis populations for each treatment arm.

Table 26. Population Analyzed by Treatment Arm - Study DP10015

Population	Not Randomised (N = 21) n (%)	APD421 (N = 176) n (%)	Placebo (N = 166) n (%)	Total (N = 364) n (%)
All Patients	22 (100)	176 (100)	166 (100)	364 (100)
Safety	0	176 (100)	166 (100)	342 (94.0)
ITT	0	176 (100)	166 (100)	342 (94.0)
Per Protocol	0	160 (90.9)	148 (89.2)	308 (84.6)
Opiates	0	127 (72.2)	117 (70.5)	244 (67.0)

Source: Sponsor's Study Report Page 36 of 696

All randomized patients were included in the ITT population, which was considered the primary efficacy analysis population. All of them underwent an operation and received study medication. The PP population include a total of 308 subjects.

8.2.1.10. Demographics and Baseline Characteristics

Table 27 and Table 28 show the demographic and baseline characteristics of subjects in Study DP10015 by treatment arm.

Table 27. Demographic in ITT Population - Study DP10015

		APD421 (N = 176)	Placebo (N = 166)	Total (N = 342)
Age (years)	Mean (range)	54.5 (23–88)	53.0 (21–86)	53.8 (21–88)
Body mass index (kg/m^2)	Mean (range)	32.6 (16–62)	33.2 (17–66)	32.9 (16–66)
Race	White/Caucasian n (%) Other n (%)	157 (89.2) 19 (10.8)	140 (84.3) 26 (15.7)	297 (86.8) 45 (13.2)
Sex	Male n (%) Female n (%)	62 (35.2) 114 (64.8)	56 (33.7) 110 (66.3)	118 (34.5) 224 (65.5)

Source: Sponsor's Study Report Page 37 of 696

The majority of the subjects were female. The demographic characteristics between the two arms were similar.

Table 28. Baseline Characteristics in ITT Population - Study DP10015

		PLACEBO (N=166) n (%)	5mg APD421 (N=176) n (%)	OVERALL (N=342) n (%)
History of PONV	YES	47 (28.3)	58 (33.0)	105 (30.7)
	NO	119 (71.7)	118 (67.0)	237 (69.3)
History of motion sickness	YES	42 (25.3)	55 (31.3)	97 (28.4)
	NO	124 (74.7)	121 (68.8)	245 (71.6)
Smoking history	NEVER	115 (69.3)	106 (60.2)	221 (64.6)
	EX-SMOKER	33 (19.9)	50 (28.4)	83 (24.3)
	CURRENT	18 (10.8)	20 (11.4)	38 (11.1)
Expected to need post-op opioids	YES	166 (100)	176 (100)	342 (100)
Number of risk factors	2	49 (29.5)	55 (31.3)	104 (30.4)
	3	81 (48.8)	79 (44.9)	160 (46.8)
	4	36 (21.7)	42 (23.9)	78 (22.8)

Source: Sponsor's Study Report Page 87 of 696

Subjects in the amisulpride injection arm had a higher number of subjects with history of PONV (33% versus 28% in Placebo), motion sickness (31% in amisulpride injection versus 25% in Placebo), and subjects who never smoked (60% for amisulpride injection versus 69% in Placebo).

8.2.1.11. Analysis and Results of the Primary Efficacy Endpoint

The primary efficacy endpoint, CR, was the defined as absence of any episode of emesis or use of rescue medication with the first 24 hours, postoperatively. In the primary analysis, subjects who received rescue medication were considered as non-responders.

Table 29 and Table 30 show the results based on the sponsor's analysis based on the Pearson χ^2 test with Yates's continuity correction as well as the statistical reviewer's analysis based on the Pearson χ^2 test, respectively.

Table 29. Analysis of the Primary Efficacy Endpoint (ITT) – Study DP10015

Treatment	Occurrence of Event (0-24 h)	N	%	95% Confidence Limits Lower %	Upper %
PLACEBO (N=166)	YES	112	67.47	59.78	74.53
	NO	54	32.53	25.47	40.22
5mg APD421 (N=176)	YES	98	55.68	48.02	63.15
	NO	78	44.32	36.85	51.98

Source: Sponsor's Study Report Page 210 of 696

In the ITT population, CR occurred in 78 patients (44.3%, 95% CI (36.9%, 52.0%)) in the amisulpride injection group and 54 patients (32.5%; 95% CI (25.5%, 40.2%)) in the placebo group. The difference in rates of CR (amisulpride injection – Placebo) was 11.8% with a 95% CI of (1.6, 22.0%), which was statistically significant in favor of amisulpride (p=0.03).

The statistical reviewer wasable to replicate the sponsor's findings and concurs with their results. Table 30 shows the results of the analyses of the primary efficacy endpoint by the reviewer for the ITT as well as PP populations, using chi-square test. The results are consistent with the sponsor's findings.

Table 30. Analysis of the Primary Efficacy Endpoint – Study DP10015

Populations Analyzed	amisulpride 5 mg	Placebo	P-Value Difference (95% CI)
ITT	78/176 (44.3%)	54/166 (32.5%)	0.03 11.8% (1.6%, 22.0%)
PP	75/160 (46.9%)	50/148 (33.8%)	0.02 13.1% (2.2%, 24.0%)

Source: Reviewer, using a Chi Square test

Results from the Cochran–Mantel–Haenszel (CMH) test conducted in the ITT population are consistent with the primary analysis results.

We also summarized the data by gender and past history of PONV/Motion Sickness in Table 31 and Table 33.

Table 31. Response Rates by Gender (ITT) – Study DP10015

Gender	amisulpride 5 mg	Placebo
Female (N=224)	42/114 (36.8%)	27/110 (24.6%)
Male (N=118)	36/62 (58.1%)	27/56 (48.2%)

Source: Reviewer
ITT = intent-to-treat

The majority of the subjects were female. As shown in Table 31 numerically, males had a higher response rate in both arms than the females.

Table 32. Response Rates by History of PONV and Motion Sickness (ITT) – Study DP10015

Risk Factor	amisulpride 5 mg IV	Placebo IV
History of Motion Sickness		
Yes	18/55 (32.7%)	10/42 (23.8%)
No	60/121 (49.6%)	44/124 (35.5%)
History of PONV		
Yes	18/58 (31.0%)	13/47 (27.7%)
No	60/118 (50.9%)	41/119 (34.5%)

Risk Factor	amisulpride 5 mg IV	Placebo IV
Smoking		
Yes	10/25 (40.0%)	10/24 (41.7%)
No	68/151 (45.0%)	44/142 (31.0%)
Opioid		
Yes	78/176 (44.3%)	54/166 (32.5%)
No	-	-

Source: Reviewer, using Cochran-Mantel-Haenszel Test
ITT = intent-to-treat; IV = intravenous; PONV = postoperative nausea and vomiting

Table 32 shows that in general, numerically, in both treatment arms, subjects with no history of motion sickness or PONV did better than the subjects with history of motion sickness. More than 85% of the subjects were non-smokers and almost all the subjects were on opioids.

This study was conducted only in United States. Therefore, no analysis by country was performed.

8.2.2. Study DP10017

This was a multi-center, double-blind, randomized, placebo-controlled, phase 3b study with two treatment groups. The Study was conducted in Germany (7 sites), France (7 sites), and United States (15 sites). The study period was from 12-Feb-2015 to 28-Sept-2015.

8.2.2.1. Primary and Secondary Objectives

The primary objective of study DP10017 was to assess the efficacy of amisulpride injection at 5 mg in combination with a standard anti-emetic in the prevention of PONV in adult, surgical patients at high risk of PONV.

The secondary objectives of the study were:

- To assess the safety and tolerability of 5 mg amisulpride injection, given in combination with a standard anti-emetic, in terms of the nature and frequency of AEs and laboratory abnormalities associated with amisulpride injection in patients at risk of PONV.
- To evaluate the overall cost of care with combination amisulpride injection plus standard anti-emetic therapy and compare with that of standard anti-emetic monotherapy.

8.2.2.2. Study Design

The study plan was to randomize a total of around 1,200 patients on a 1:1 basis to receive one of two IV treatment regimens, to provide a minimum of 550 evaluable patients in each group. The treatment regimens were as follows:

- amisulpride injection at 5 mg plus a standard anti-emetic that is not a dopamine D_2-antagonist (e.g., ondansetron IV at 4 mg, granisetron IV at 1 mg, dexamethasone IV at 4 mg)

- amisulpride injection placebo plus a standard anti-emetic that is not a dopamine D_2-antagonist.

The study consisted of screening from days –28 to 0 (day of operation); a primary study period, which was the period beginning with the first dose of prophylactic anti-emetic therapy and ending 24 hours after completion of surgery, and a safety follow-up that continued up to day 7.

Admission of patients to the hospital/clinic or ambulatory surgery center was to follow normal institutional practice. Patients were screened up to 28 days before or on the planned date of their operation and admitted to hospital on the day before (day -1) or morning of (day 0) their operation. Preoperatively, premedication could be given according to the choice and usual practice of the treating physicians, with the exception that anti-emetic drugs were not to be administered.

The choice of anesthetic technique and drugs administered was at the discretion of the investigator, with the exception that anti-emetic drugs, other than the study drugs, were not to be administered as prophylaxis; additionally, the use of total intravenous anesthesia (TIVA) with propofol was not permitted. Induction with a single, standard dose of propofol was permitted, but further doses of propofol for maintenance were not permitted. Study medication (amisulpride injection /Placebo) was given by slow IV push over one minute at induction of anesthesia. The standard anti-emetic was to be given as per normal institutional practice.

8.2.2.3. Primary Efficacy Endpoint

The primary efficacy variable was the same as in study DP10015.

8.2.2.4. Analysis Population

The primary analysis used the mITT population. All patients who signed the informed consent form (ICF), were randomized into the study and received a dose of either amisulpride or placebo were included in the mITT analysis population.

The PP analysis population included all patients who received study medication, had an efficacy assessment documented at the nominal 24-hour time point (or had an episode of PONV, as per the primary efficacy variable definition, documented during the 24- hour postoperative period) and were adherent to the protocol with no major protocol violations.

8.2.2.5. Determination of Sample Size

Based on a one-sided type I error rate of 0.025, the sponsor estimated that the sample size of 1,100 patients (550 per group) gives a power of 90.6% of detecting a difference of 10 percentage points in CR rate between the combination group (60%) and the monotherapy group (50%). The assumptions were made based on the results of previous studies of amisulpride injection, supported by evidence in the literature.

8.2.2.6. Primary Efficacy Analysis

The primary efficacy analysis was a comparison of the incidence of CR in the 0 to 24-hour period after surgery between the group who received amisulpride injection in combination with a standard anti-emetic and the group who received placebo in combination with a standard anti-emetic. The sponsor used Pearson's χ^2 test with Yates's continuity correction at a one-sided significance level of 2.5%. The statistical reviewer analyzed the data considering a two-sided significance level of 5% using a χ^2 test first, and then reanalyzing the data by the CMH test.

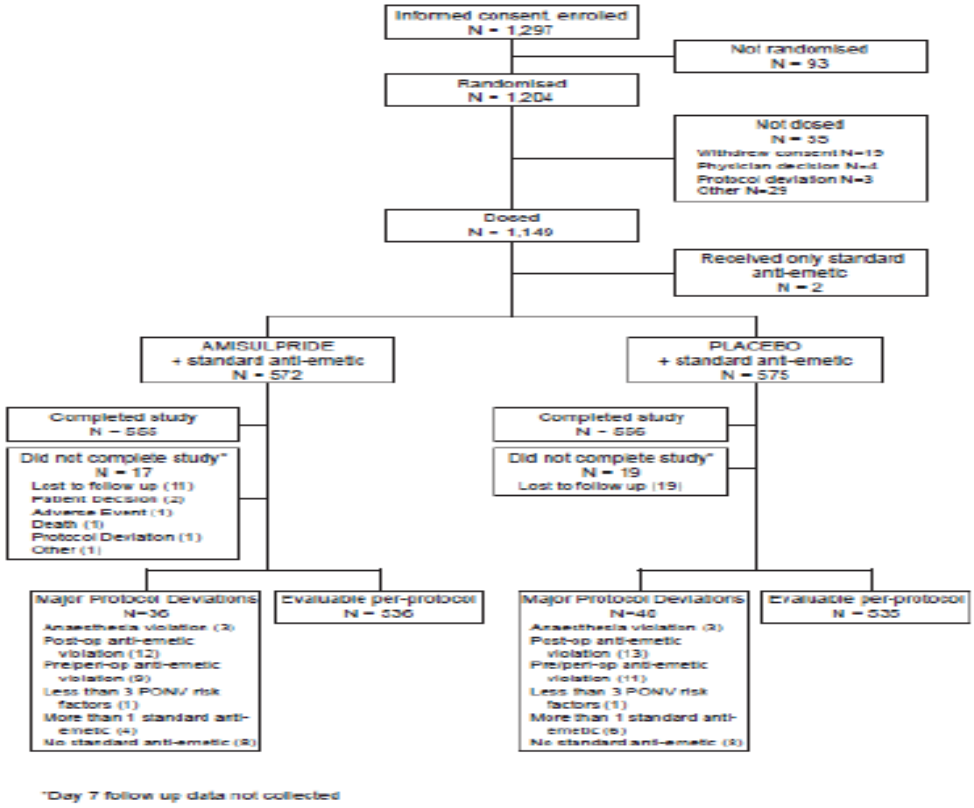
8.2.2.7. Disposition of Subjects

Informed consent was signed by 1,297 patients in the study, 1,149 of whom were included in the safety analysis population, which was defined as all patients who had received any study medication (amisulpride injection, placebo or the combination standard antiemetic).

Two of the 1,149 patients in the safety analysis population ((b) (6)) received only the standard anti-emetic drug and did not receive amisulpride injection or placebo and were therefore excluded from the mITT analysis population (N=1,147). A further 76 patients were excluded from the per-protocol analysis population (N=1,071). A subgroup of patients who received opioids for analgesia postoperatively included 788 patients.

Figure 11 shows the disposition of the subjects.

Figure 11. Disposition of Subjects – Study DP10017



Source: Sponsor's Study Report Page 42 of 705

A total of 555 patients in the amisulpride group and 556 patients in the placebo group completed the study. Seventeen patients in the amisulpride group and 19 patients in the placebo group received treatment and discontinued the study prematurely. Eleven of the 17 patients in the amisulpride group and all 19 patients in the placebo group who discontinued prematurely were lost to follow-up. The remaining six patients in the amisulpride group discontinued prematurely for the following reasons: AE (one patient), death (one patient), patient withdrawal (two patients), protocol deviation (one patient), and other, unspecified, reason (one patient).

8.2.2.8. Populations Analyzed

The primary analysis population was mITT. A total of 76 patients were excluded from the per-protocol (PP) analysis population, 36 in the amisulpride injection group, and 40 in the placebo group. The most common reason for protocol deviation was "antiemetic violation post-operatively – not intended for PONV rescue" (12 patients in the amisulpride injection group and 13 patients in the placebo group), followed by "anti-emetic violation pre/peri operatively" (nine and 11 patients in the amisulpride injection group and placebo group, respectively) and "no combination anti-emetic administered" (eight patients in each group). The number and type of protocol deviation was similar in the two groups. Table 33 shows the populations analyzed by treatment group.

Table 33. Populations Analyzed by Treatment Arm - Study DP10017

Population	APD421 + anti-emetic (N = 572) n (%)	Placebo + anti-emetic (N = 575) n (%)	Total (N = 1,204) n (%)
Safety	572 (100)	575 (100)	1,149* (95.4)
mITT	572 (100)	575 (100)	1,147 (95.3)
Per Protocol	536 (93.7)	535 (93.0)	1,071 (89.0)
Received opioids	388 (67.8)	400 (69.6)	788 (65.4)

Source: Sponsor's Study Report Page 43 of 705

8.2.2.9. Demographic and Other Baseline Characteristics

The demographics of the mITT population are summarized in Table 34.

Table 34. Demographic in mITT Population - Study DP10017

		APD421 + anti-emetic (N = 572)	Placebo + anti-emetic (N = 575)	Total (N = 1,147)
Age (years)	Mean (range)	48.8 (18–91)	48.3 (18–86)	48.5 (18–91)
Sex	Female n (%) Male n (%)	552 (96.5) 20 (3.5)	557 (96.9) 18 (3.1)	1109 (96.7) 38 (3.3)
Race*	White/Caucasian n (%) Black n (%)	438 (76.6) 48 (8.4)	425 (73.9) 58 (10.1)	863 (75.2) 106 (9.2)
Body mass index (kg/m^2)	Mean (range)	30.55 (16.4–80.2)	29.97 (12.6–62.2)	30.26 (12.6–80.2)

Source: Sponsor's Study Report Page 44 of 705

The majority of the subjects in Study 17 were female (97%). The mean age of the patients was 48.5 years (range 18 to 91 years). The demographic characteristics of the two treatment groups were similar in the mITT population and there were no notable differences in demographics between the mITT population and the PP population.

A total of 39.4% of patients had a history of PONV (39.7% of the amisulpride group and 39.1% of the placebo group). Three risk factors were reported for 56.4% of patients overall, four risk factors for 43.4% of patients and two risk factors for 0.2% of patients. Nearly all patients were expected to require postoperative opioids (99.4%). History of motion sickness was reported for 35.0% of patients and 10.2% of patients were smokers.

8.2.2.10. Analysis and Results of the Primary Efficacy Endpoint

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Table 35 and Table 36 show the results of primary analysis based on the Pearson χ^2 test with Yates's continuity correction as well as the statistical reviewer's analysis based on the Pearson χ^2 test, respectively.

Table 35. Analysis of the Primary Efficacy Endpoint - Study DP10017

	Placebo IV + Standard Anti-emetic (N=575) n (%)	APD421 5mg IV + Standard Anti-emetic (N=572) n (%)
n	575	572
Yes (%)	268 (46.6)	330 (57.7)
95% CI	(42.53, 50.69)	(53.64, 61.74)
No (%)	307 (53.4)	242 (42.3)
Difference (APD421 5mg IV - Placebo IV)		11.08
SE		2.93
95% CI		(5.34, 16.83)
One-sided p-value		<0.001

Source: Sponsor's Table 14.2.1.1.1, Page 398 of 705 of Study Report

Table 36. Analysis of the Primary Efficacy Endpoint - Study DP10017

Populations Analyzed	amisulpride 5 mg IV + Standard Anti-emetic	Placebo IV + Standard Anti-emetic	P-Value Difference 95% CI
mITT	330/573 (57.6%)	268/574 (46.7%)	<0.001 10.9% (5.2%, 16.7%)
PP	319/537 (59.4%)	258/534 (48.3%)	<0.001 11.1% (5.2%, 17.0%)

Source: Reviewer,using a χ2 test
CI = confidence interval; IV = intravenous; mITT = modified intent-to-treat; PP = per protocol

Our results were similar to that of the Sponsor's. In the mITT population, CR occurred in 330 patients (57.6%; 95% confidence interval [CI] 53.64, 61.74%) in the amisulpride injection group and 268 patients (46.6%; 95% CI 42.5, 50.7%) in the placebo group. The difference in rate of CR (amisulpride injection - placebo) was 10.9% (95% CI 5.2, 16.7%), which was statistically significant in favor of amisulpride injection ($p<0.001$).

In the PP population, CR was reported in 319 patients (59.5%; 95% CI 55.4, 63.7%) in the amisulpride injection group and 258 patients (48.2%; 95% CI 44.0, 52.5%) in the placebo group. The difference between groups (amisulpride injection - placebo) was statistically significant in favor of the active treatment: 11.1% (95% CI 5.2, 17.0%; $p<0.001$).

We re-analyzed the data using CMH test and the results are consistent with the primary analysis result.

Table 37, Table 38 and Table 39 show the results of subgroup analysis of the primary efficacy endpoint by the standard anti-emetic drugs, risk factors and country by treatment arm, respectively.

Table 37. Response Rates by standard anti-emetic subset - Study DP10017

	amisulpride 5 mg IV + Standard Anti-emetic	Placebo IV + Standard Anti-emetic
Betamethasone	12/12 (100%)	15/21 (71.4%)
Dexamethasone	168/267 (62.9%)	119/251 (47.4%)
Ondansetron	147/285 (51.6%)	131/294 (44.6)

Source: Reviewer's analysis

Majority of the subjects were on dexamethasone or ondansetron. Table 38 shows that, numerically, subjects who took betamethasone in addition to the study drug did better and had a higher response rates (in both amisulpride injection (12/12=100%) and in the Placebo arm (15/21=71.4%) than the other two standard anti-emetic drugs. However, we should note that the number of subjects in these groups were very small.

Table 38. Response Rates by Risk Factors - Study DP10017

Risk Factor	amisulpride 5 mg IV + Standard Anti-emetic	Placebo IV + Standard Anti-emetic
History of Motion Sickness		
Yes	102/202 (50.5%)	86/199 (43.2%)
No	228/371 (61.5%)	182/375 (48.5%)
History of PONV		
Yes	115/228 (50.4%)	84/224 (37.5%)
No	215/345 (62.3%)	184/350 (52.6%)

Source: Reviewer

In general, in both groups, numerically, Subjects with no motion sickness or history of PONV responded better.

Table 39. Analysis by Country - Study DP10017

Country	amisulpride 5 mg IV + Standard Anti-emetic	Placebo IV + Standard Anti-emetic
Germany	97/141 (68.8%)	72/138 (52.2%)
France	67/79 (84.8%)	48/85 (56.5%)
United States	166/353 (47.0%)	148/351 (42.2%)

Source: Reviewer

As seen in Table 39 observed difference in response rate in France was numerically higher than in Germany and the United States. In fact, although the U.S. population constituted the majority of the mITT study population (more 350 patients per arm), the difference between the two arms in US was relatively low (4.9%). Since country of France showed a much higher response rate than the other two countries, we conducted exploratory analysis by removing France from the dataset. The results showed a statistically significant difference of 8.3% ($p<0.009$) between the two arms and a 95% CI of (2.0%, 14.5%). Since the study was not designed to demonstrate statistical significance based on sub-group analyses, it should be noted that these analyses are

exploratory.

In addition, we looked at the individual sites in France. A total of seven sites participated in France. Table 40shows the response rates for all the sites in France. Although, response rates varied substantially from site to site, for all sites except one the response rates were in favor of amisulpride injection 5 mg IV arm compared to pacebo.

Table 40. Analysis by Site in France

Site #	amisulpride 5 mg IV + Standard Anti-emetic	Placebo IV + Standard Anti-emetic
701	10/14 (71.4%)	4/14 (28.6%)
702	8/12 (66.7%)	7/13 (53.9%)
703	8/10 (80.0%)	8/9 (88.9%)
704	6/7 (85.7%)	1/6 (16.7%)
705	2/2 (100.0%)	4/5 (80.0%)
706	5/6 (83.3%)	1/6 (16.7%)
707	28/28 (100.0%)	23/32 (71.9%)

Source: Reviewer

8.3. Indication 2: Treatment of PONV

8.3.1. Study DP10018

Study DP10018 is a multi-center, randomized, double-blind, placebo-controlled study with three parallel groups and was conducted in 20 centers in Germany, France, Canada and the United States. The study period was from 09 August 2015 to 18 July 2016.

8.3.1.1. Primary and Secondary Objectives

The primary objective of the study was to compare the efficacy of 5 mg and 10 mg amisulpride injection to Placebo for established PONV in adult surgical patients who have not had prior PONV prophylaxis.

The secondary objectives of the study were:

• To assess the safety and tolerability of single-dose amisulpride injection given as treatment for PONV in terms of the nature and frequency of AEs and laboratory abnormalities.

• To assess the exposure-response relationship of amisulpride injection as treatment for PONV in a subset of patients.

8.3.1.2. Study Design

This was a multi-center, randomized, double-blind, placebo-controlled, phase 3 study with three

parallel treatment groups in patients who had no prior prophylaxis for PONV.

This study included adult patients 18 and older at low-to-moderate risk of suffering PONV (as judged by the investigator) who were undergoing elective ambulatory (day-case) or in-patient surgery under general inhalational anesthesia for an expected duration of at least one hour from induction of anesthesia to extubating who experienced PONV in the 24-hour period after surgery and had received no prior PONV prophylaxis. In judging whether the patient was at low-to-moderate risk of experiencing PONV, and therefore not suitable for PONV prophylaxis, the investigator paid attention to risk factors such as:

- History of PONV and/or motion sickness
- Habitual non-smoking status
- Female
- Likely use of opioid analgesia postoperatively

Estimated recruitment was to be 580, to give at least 558 evaluable patients, thereby providing an average of 186 evaluable patients in each of the three treatment groups. Subjects were randomized on a 1:1:1 basis to receive one of three single-dose IV treatment regimens:

- Placebo
- Amisulpride injection at 5 mg
- Amisulpride injection at 10 mg

Study medication (amisulpride injection or Placebo) was given by slow IV push over about two minutes. The study consisted of screening from days –28 to 0 (day of operation); a primary study period, which was the period beginning with the first episode of PONV (emesis and/or a request by the patient for anti-emetic medication to treat nausea) and ending 24 hours after administration of study medication, and a safety follow-up that continued up to day 7.

A centralized schedule of randomized treatment assignments was computer-generated (b) (4) (b) (4) where it was incorporated into double-blind labelling and packaging. Randomization was stratified according to study center.

To be randomized into the study after surgery, the patient must have met all four of the following criteria:

- Undergone a non-excluded surgical procedure
- Not received any pre- or peri-operative anti-emetic agent as prophylaxis against PONV
- Experienced in the period 0 to 24 hours after the end of surgery a first episode of PONV, defined as one or more episodes of emesis (vomiting/retching) and/or a request by the patient for anti-emetic medication to treat nausea
- Not already received any anti-emetic treatment for the episode of PONV

The primary study period commenced as soon as a patient experienced a first episode of PONV, defined as an episode of emesis and/or request by the patient for anti-emetic medication to treat nausea. Nausea was recorded based on an 11-point verbal rating scale.

8.3.1.3. Primary Efficacy Endpoint

The primary efficacy variable was the success or failure of initial PONV treatment, where success, also called CR, is defined as no emetic episodes (vomiting or retching) from 30 minutes (to allow the study medication to work) to 24 hours after administration of study medication and no administration of anti-emetic rescue medication at any time in the 24-hour period after administration of study medication.

8.3.1.4. Analysis Populations

The primary analysis population was mITT, which was defined as all patients who signed the ICF, were randomized into the study and received a dose of the study medication.

The PP analysis population included all patients who received study medication, had an efficacy assessment documented at the nominal 24-hour time point (or had failed initial PONV treatment prior to the nominal 24-hour time point) and were adherent to the protocol with no major protocol deviations.

8.3.1.5. Determination of Sample Size

Based on sponsor's estimation, a sample size of 558 subjects (average 186 per arm) provides a power of 90% at an overall one-sided type I error rate of 0.0125 of detecting a difference in response rate of 17.5% (47.5% vs. 30%) between a amisulpride dose group and placebo group. A Bonferroni type correction was used to adjust for multiplicity from making two pairwise comparisons with placebo. Treatment arms were compared using Pearson's χ^2 test.

8.3.1.6. Primary Efficacy Analysis

The primary efficacy analysis was a comparison of the incidence of the primary efficacy variable between the two groups (amisulpride injection versus Placebo), using a Pearson's χ^2 test at a one-sided significance level of 1.25%. The statistical reviewer. used a CMH test to assess the robustness of the results.

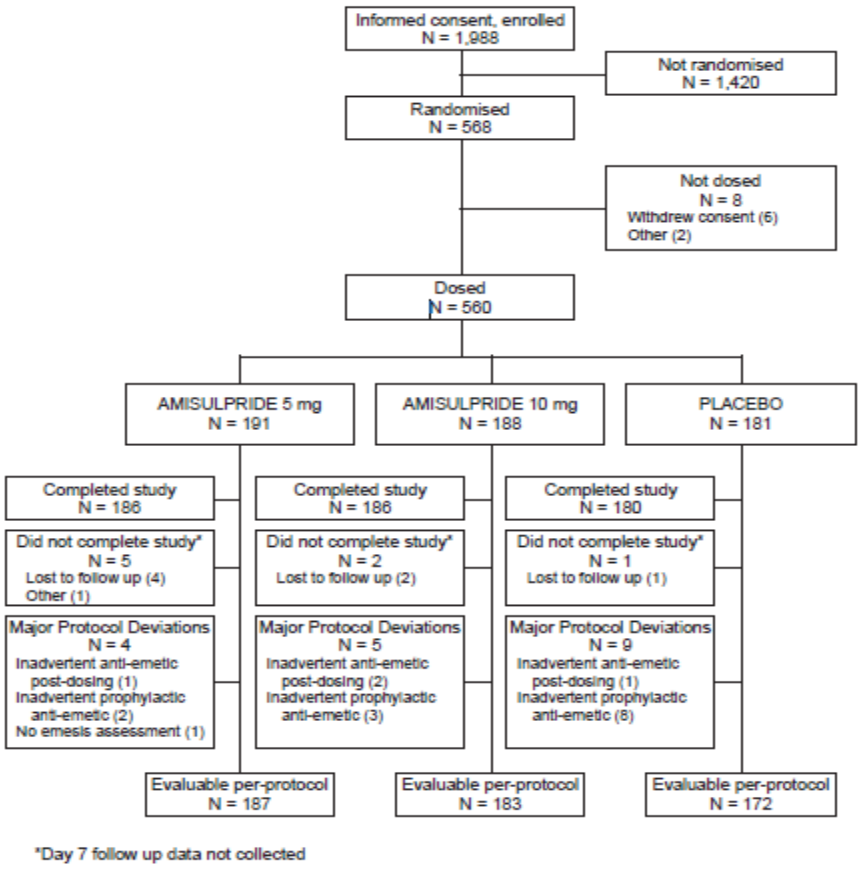
8.3.1.7. Multiple Comparison/Multiplicity

In the statistical analysis plan, the sponsor pre-specified Bonferroni procedure to adjust for multiplicity from making two pairwise comparisons with placebo. However, in the clinical study report, the sponsor applied a more powerful Hommel's procedure.

8.3.1.8. Disposition of Subjects

A total of 1,988 patients signed informed consent and were enrolled in the study. A total of 560 patients were randomized and received treatment: 191 patients in the amisulpride injection 5 mg group; 188 in the amisulpride injection 10 mg group, and 181 in the placebo group. The disposition of patients is shown in Figure 12.

Figure 12. Disposition of Patients – Study DP10018



Source: Sponsor's Study Report Page 53 of 91

A total of 188 subjects completed the Study in the 10 mg treatment arm, 186 in the 5 mg arm and 181 subjects completed the study in the Protocol arm.

8.3.1.9. Populations Analyzed

There were 18 major protocol deviations, 17 of which were inappropriate anti-emetic use (coded as "inadvertent anti-emetic post dosing" or "inadvertent prophylaxis anti-emetic"). The other major protocol deviation (patient [redacted] (b) (6)) comprised no emesis (efficacy) assessment after drug administration. All 18 patients who had major protocol deviations were excluded from the PP analysis population. Table 41 shows the number of

subjects in each analysis population by treatment arm.

Table 41. Populations Analyzed – Study DP10018

Population	APD421 5 mg (N = 194) n (%)	APD421 10 mg (N = 191) n (%)	Placebo (N = 183) n (%)	Total (N = 568) n (%)*
Safety	191 (98.5)	188 (98.4)	181 (98.9)	560 (98.6)
mITT	191 (98.5)	188 (98.4)	181 (98.9)	560 (98.6)
Per Protocol	187 (96.4)	183 (95.8)	172 (94.0)	542 (95.4)

Source: Sponsor's Study Report Page 54 of 91

8.3.1.10. Demographic and Other Baseline Characteristics

The mean age of the patients was 46.1 years (range 18 to 82 years) and the majority of the patients were female (76.3%). Table 42 shows the demographic characteristics of subjects for Study DP10018.

Table 42. Demographic Characteristics (mITT Population) – Study DP10018

		APD421 5 mg (N = 191)	APD421 10 mg (N = 188)	Placebo (N = 181)	Total (N = 560)
Age (years)	Mean (range)	44.3 (18–76)	47.4 (19–82)	46.5 (19–79)	46.1 (18–82)
Sex	Female n (%) Male n (%)	146 (76.4) 45 (23.6)	145 (77.1) 43 (22.9)	136 (75.1) 45 (24.9)	427 (76.3) 133 (23.8)
Race*	White n (%) Black n (%) Asian n (%) American Indian/Alaska native n (%)	153 (80.1) 14 (7.3) 7 (3.7) 1 (0.5)	152 (80.9) 17 (9.0) 4 (2.1) 0	151 (83.4) 13 (7.2) 3 (1.7) 0	456 (81.4) 44 (7.9) 14 (2.5) 1 (0.2)

Source: Sponsor's Study Report Page 55 of 91

The demographic characteristics of subjects were balanced among the three treatment arms.

The presence of risk factors for PONV in the mITT population at screening was similar between the treatment groups. A total of 5.5% of patients in the mITT population had a history of PONV (5.2% of the amisulpride injection 5 mg group, 3.7% of the amisulpride injection 10 mg group and 7.7% of the placebo group).

There were no differences in demographics and baseline characteristics between the mITT population and the PP population.

8.3.1.11. Analysis and Results of the Primary Efficacy Endpoint

In the mITT population, CR occurred in 60 patients (31.4%; 95% CI 24.83%, 38.0%) in the amisulpride injection 5 mg group, 59 patients (31.4%; 95% CI 24.75%, 38.02%) in the amisulpride 10 mg group and 39 patients (21.5%; 95% CI 15.56%, 27.54%) in the placebo group (Table 43).

Table 43. Analysis of the Primary Efficacy Endpoint (mITT) – Study DP10018

Time Interval	APD421 5 mg (N = 191)			APD421 10 mg (N = 188)			Placebo (N = 181)	
	No n (%)	Yes n (%)	p*	No n (%)	Yes n (%)	p*	No n (%)	Yes n (%)
0-24 hours§	131 (68.6)	60 (31.4)	0.015 0.016†	129 (68.6)	59 (31.4)	0.016 0.016†	142 (78.5)	39 (21.5)
0-2 hours	79 (41.4)	112 (58.6)	0.002	83 (44.1)	105(55.9)	0.009	102 (56.4)	79 (43.6)
2-24 hours	91 (47.6)	100 (52.4)	0.552	79 (42.0)	109 (58.0)	0.170	85 (47.0)	96 (53.0)

Source: Sponsor's Study Report Page 57 of 91
* one-sided p value for comparison with placebo group
† p value adjusted for multiplicity using Hommel's procedure
§ primary endpoint of study

The difference in CR rate (amisulpride injection - Placebo) for the amisulpride injection 5 mg group was 9.87% with a 95% CI (0.9%, 18.77%) and nominal one-sided p-value of 0.015. The difference in the CR rate for the amisulpride injection 10 mg group and Placebo was 9.84% with a 95% CI (0.9%, 18.8%) with one-sided p-value of 0.016.

Based on the pre-specified Bonferroni procedure, neither p-values is statistically significant at one-sided 0.0125 level. In the clinical study report, the sponsor indicates that based on Hommel's procedure (which is a post-hoc analysis), both treatment comparisons achieved statistical significance.

The statistical reviewer analyzed the data for the primary efficacy endpoint for CR in both ITT and PP populations and confirmed sponsor's results. Table 44 shows these results.

Table 44. Analysis of the Primary Efficacy Endpoint (mITT) - Study DP10018

Populations Analyzed	amisulpride 10 mg IV	amisulpride 5 mg IV	Placebo IV	P-Value* Difference (95% CI)
ITT	59/188 (31.4%)	60/191 (31.4%)	39/181 (21.6%)	amisulpride 10 mg - Pl: 0.03 9.8% (0.9%, 18.8%) amisulpride 5 mg - Pl: 0.03 9.9% (1.0%, 18.8%)
PP	59/183 (32.2%)	60/187 (32.1%)	35/172 (20.4%)	amisulpride 10 mg - Pl: 0.01 11.9% (2.8%, 21.0%) amisulpride 5 mg - Pl: 0.01 11.7% (2.7%, 20.7%)

Source: Reviewer, using χ^2 test
*Tests conducted at 0.025 two-sided significance levels based on Bonferroni correction
CI = confidence interval; ITT = intent-to-treat; IV = intravenous; mITT = modified intent-to-treat; PP = per protocol

As a supportive analysis, we conducted an analysis using CMH test. These analyses results are consistent with the primary analysis result.

We analyzed the data by gender, risk factors and by country. Table 45, Table 46 and Table 47 show these results.

Table 45. Response Rates by Gender - Study DP10018

Gender	amisulpride 10 mg IV	amisulpride 5 mg IV	Placebo IV
Female	45/145 (31.0%)	40/146 (27.4%)	26/136 (19.1%)
Male	14/43 (32.6%)	20/45 (44.4%)	13/45 (28.9%)

Source: Reviewer

As shown in Table 45, numerically, the male sub-population had higher response rates than the females in all the treatment arms.

Table 46. Response Rates by Risk Factors - Study DP10018

Risk Factor	amisulpride 10 mg IV	amisulpride 5 mg IV	Placebo IV
History of Motion Sickness			
Yes	1/7 (14.3%)	0	1/2 (50.0%)
No	58/181 (32.0%)	60/181 (33.2%)	38/179 (21.2%)
History of PONV			
Yes	2/7 (28.6%)	1/10 (10.0%)	3/14 (21.4%)
No	57/181 (31.5%)	59/181 (32.6%)	36/167 (21.6%)
Opioid			
Yes	57/175 (32.6%)	55/175 (31.4%)	37/171 (21.6%)
No	2/13 (15.4%)	5/16 (31.3%)	2/10 (20.0%)

Source: Reviewer

The majority of the subjects had no history of motion sickness or history of PONV; and their response rates ranged from 31.5% to 33.2%, as shown in Table 46. For the Placebo arm the response rates ranged from 20% to 21.6%. For subjects with opioid use, the response rate for the10 mg was 32.6% and for the 5 mg was 31.4%); and the Placebo arm had a response rate of 21.6% for the subjects who used opioids.

Table 47. Response Rates by Country - Study DP10018

Country	amisulpride 10 mg IV	amisulpride 5 mg IV	Placebo IV
Canada	8/31 (25.8%)	13/32 (40.6%)	4/32 (12.5%)
Germany	20/60 (33.3%)	17/60 (28.3%)	12/63 (19.1%)
France	4/7 (57.1%)	1/4 (25.0%)	2/5 (40.0%)
United States	27/90 (30.0%)	29/95 (30.5%)	21/81 (25.9%)

Source: Reviewer

As shown in Table 47 the response rate by country was mixed. Subjects in Germany and France, had a higher response rate with the 10 mg IV treatment groups. Canada and the US showed a higher response to the 5 mg treatment arm.

8.3.2. Study DP10019

This is a phase 3, multi-center, randomized, double-blind, placebo-controlled study of amisulpride injection (amisulpride for IV injection) as treatment of established postoperative nausea and vomiting, in patients who have had prior prophylaxis. Study start date was March 2016 and study completion date was January 2017. This study was conducted in 23 centers in Germany, France, Canada and the United States.

8.3.2.1. Primary and Secondary Objectives

Primary:

To compare the efficacy of 5 mg and 10 mg amisulpride to placebo as treatment for established PONV in adult, surgical patients who had received prior PONV prophylaxis.

Secondary:

• To assess the safety and tolerability of single-dose amisulpride injection given as treatment for PONV in terms of the nature and frequency of AEs and laboratory abnormalities.

• To assess the exposure-response relationship of amisulpride injection as treatment for PONV in a subset of patients.

8.3.2.2. Study Design

Adult patients (aged at least 18 years) at moderate-to-high risk of suffering PONV (as judged by the investigator), undergoing elective, ambulatory (day-case) or in-patient surgery under general anesthesia expected to last at least one hour and having had prior PONV prophylaxis that did not involve a dopamine-antagonist anti-emetic.

To be randomized into the study after surgery, the patient must have met all four of the following criteria:

• Undergone a non-excluded surgical procedure

• Have received pre- or peri-operative PONV prophylaxis, which was not with a dopamine-antagonist anti-emetic

• Experienced a first episode of PONV, defined as one or more episodes of emesis (vomiting/retching) and/or a request by the patient for anti-emetic medication to treat nausea, not more than 24 hours after the end of their operation (wound closure) and prior to discharge from hospital ("qualifying PONV episode"), for which they have not already received any anti-emetic treatment

• Not received any dopamine-antagonist agent likely to prevent or treat nausea or vomiting (given as prophylaxis or otherwise) in the period from 24 hours prior to the start of their operation up to the time of the qualifying PONV episode Test Product.

Dose and Mode of Administration were: amisulpride injection at 5 mg or 10 mg administered as a single, slow, intravenous (IV) push over about two minutes.

8.3.2.3. Changes to the Planned Analyses

- To evaluate how the nausea evolves during the first 3 hours after study drug administration, the evolution score of nausea is derived as the AUC of nausea scores in the periods 0 to 60 min, 0 to 120 min and 0 to 180 min. Similar analysis to maximum severity of nausea is implemented.
- Categorical analyses of absolute and relative reduction in nausea from baseline to posttreatment are included.
- Sensitivity analyses which include emesis and nausea events occurring in the first 30 minutes after study drug administration are added.
- On discussion between the study director and the senior investigators involved in study design, it was unanimously agreed that treating all potential anti-emetics as rescue medication, even when given for a different indication to a subject who had clear evidence of a response to treatment, was an unreasonably conservative approach. A modified rule, whereby an anti-emetic given for an indication other than PONV rescue is not treated as rescue medication if the subject meets clearly defined criteria indicative of a response to study drug treatment, was therefore instituted prior to database lock.

8.3.2.4. Primary Efficacy Endpoint

The primary efficacy endpoint is the same as in study DP10018.

8.3.2.5. Analysis Populations

The intention-to-treat (ITT) analysis population will include all evaluable patients, i.e., all patients who have signed the informed consent form, been randomized into the study and received a dose of either amisulpride injection or placebo study medication. Patients will be classified by their actual received treatment. All efficacy endpoints will be analyzed using the ITT analysis population.

Per-protocol (PP) analysis population will include only those ITT patients who have no major protocol violation and have at least one efficacy (i.e., emesis) assessment documented at the nominal 24-hour time point (or have failed initial PONV treatment prior to the nominal 24-hour time point). Analysis of primary and secondary efficacy endpoints will be repeated on the PP analysis population to test for robustness of results.

8.3.2.6. Determination of Sample Size

A sample size of 558 subjects (average 186 per arm) provides a power of 90% at an overall one-sided α of 0.0125 of detecting a difference of 0.175 between the response rate in the placebo group, assumed to be 0.30, and the response rate in either amisulpride dose group, assumed to be 0.475, using the Bonferroni correction to adjust for multiplicity from making two pairwise comparisons with placebo. Treatment arms are compared using Pearson's $\chi 2$ test.

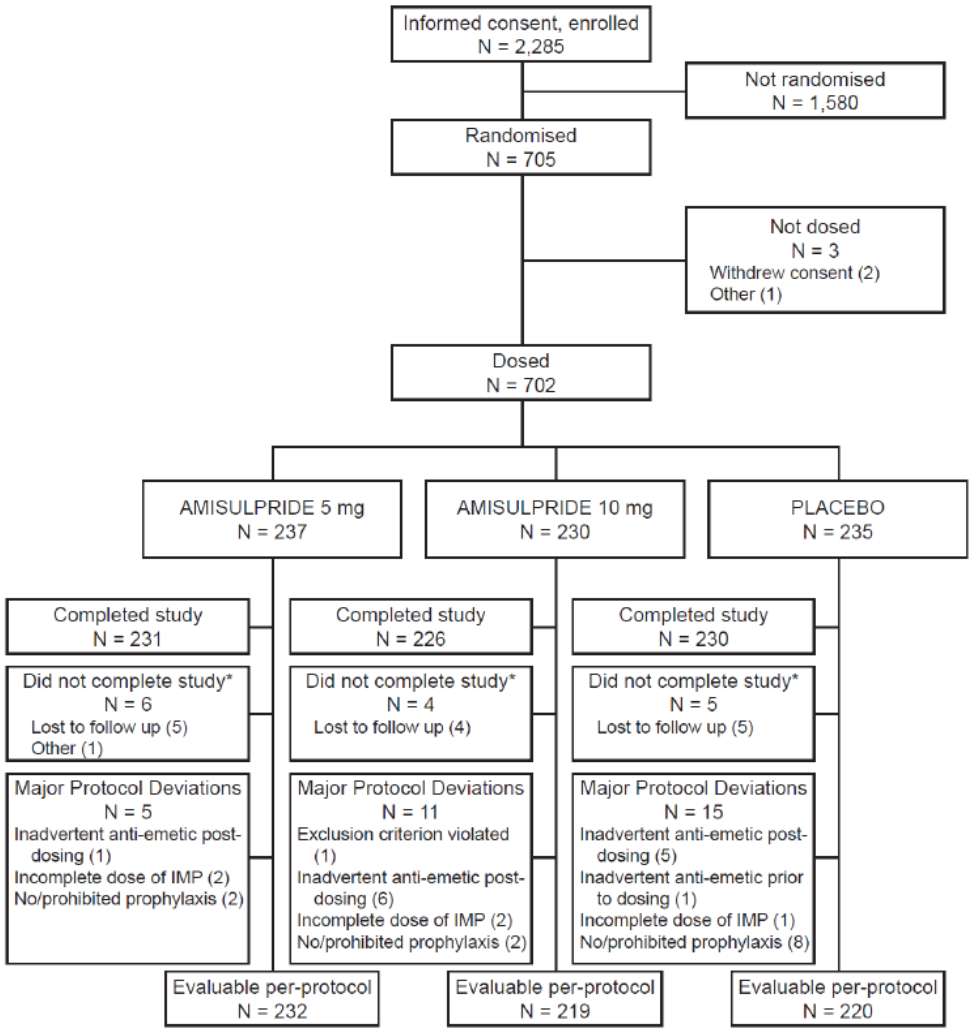
8.3.2.7. Primary Efficacy Analysis

The primary efficacy analysis was a comparison of the incidence of CR between the a amisulpride injection group and the placebo group using Pearson's χ^2 test.

8.3.2.8. Disposition of Subjects

A total of 2,285 patients signed informed consent and were enrolled in the study. The number of patients enrolled per country was as follows: Germany, 657; France, 81; Canada, 521; and the United States, 1,026. A total of 705 of the enrolled patients were randomized. The number of randomized patients per country was as follows: Germany, 160; France, 28; Canada, 142 and the United States, 375. Figure 13 and Table 48 show the disposition of the subjects.

Figure 13. Disposition of Subjects – Study DP10019



Source: Sponsor's Study Report, Page 54 of 99

Out of 705 randomized subjects, a total of 226 subjects in the 10 mg treatment arm, 231 in the 5 mg arm and 230 subjects in the Placebo group completed the study. Moreover, a total of 219 subjects in the 10 mg arm, 232 in the 5 mg group and 220 in the Placebo arm were evaluable for the per-protocol analyses.

Table 48. Disposition of Subjects by Treatment Arm – Study DP10019

	Placebo IV (N=236) n (%)	APD421 5mg IV (N=237) n (%)	APD421 10mg IV (N=232) n (%)	Overall (N=705) n (%)
Patients Enrolled [a]				2285
Patients who were randomised and received treatment	235 (99.6)	237 (100)	230 (99.1)	702 (99.6)
Patients who did not receive treatment and discontinued the study	1 (0.4)	0	2 (0.9)	3 (0.4)
Adverse Event [b]	0	0	0	0
Death [b]	0	0	0	0
Withdrawal by Subject [b]	1 (100)	0	1 (50.0)	2 (66.7)
Physician Decision [b]	0	0	0	0
Protocol Deviation [b]	0	0	0	0
Lost to Follow-up [b]	0	0	0	0
Other [b]	0	0	1 (50.0)	1 (33.3)
UNKNOWN [b]	0	0	0	0
Patients who received treatment and completed the study	230 (97.5)	231 (97.5)	226 (97.4)	687 (97.4)
Patients who received the treatment and discontinued the study	5 (2.1)	6 (2.5)	4 (1.7)	15 (2.1)
Adverse Event	0	0	0	0
Death	0	0	0	0
Withdrawal by Subject	0	0	0	0
Physician Decision	0	0	0	0
Protocol Deviation	0	0	0	0
Lost to Follow-up	5 (2.1)	5 (2.1)	4 (1.7)	14 (2.0)
Other	0	1 (0.4)	0	1 (0.1)

Source: Sponsor's Tables and Figures, Page 1 of 451

As shown in Table 48, a total of 230 subjects in the amisulpride, 10 mg arm, 237 subjects in the 5 mg arm and 235 subjects in the Placebo arm were randomized and received treatment and they were included in the mITT population for the primary analyses.

8.3.2.9. Populations Analyzed

Five randomized patients (0.7%) in the mITT population did not receive a complete dose of study medication, two patients in the amisulpride injection 5 mg group (b) (6)), two patients in the amisulpride injection 10 mg group (b) (6) and one patient in the placebo group (b) (6). The reasons for incomplete dosing were: burning sensation or pain at the site of administration (one patient in each treatment group); and forgotten dose/administration error (one patient in each of the amisulpride groups). Table 49 shows the different analysis populations used in this study.

Table 49. Populations Analyzed – Study DP10019

Population	APD421 5 mg (N = 237) n (%)	APD421 10 mg (N = 232) n (%)	Placebo (N = 236) n (%)	Total (N = 705) n (%)*
Safety	237 (100)	230 (99.1)	235 (99.6)	702 (99.6)
mITT	237 (100)	230 (99.1)	235 (99.6)	702 (99.6)
Per Protocol	232 (97.9)	219 (94.4)	220 (93.2)	671 (95.2)

Source: Sponsor's Study Report, Page 56 of 99

All patients in the PP population received a complete dose of study medication.

8.3.2.10. Demographic and Other Baseline Characteristics

The mean age of the patients was 46.3 years (range 18 to 85 years) and the majority of the patients were female (90.2%). The presence of risk factors for PONV in the mITT population at screening was similar between the treatment groups.

Demographic and baseline characteristics are presented in Table 50 and Table 51.

Table 50. Demographic Characteristics (mITT Population) – Study DP10019

		APD421 5 mg (N = 237)	APD421 10 mg (N = 230)	Placebo (N = 235)	Total (N = 702)
Age (years)*	Mean (range)	45.8 (18–84)	46.9 (18–85)	46.0 (18–81)	46.3 (18–85)
Sex	Female n (%)	213 (89.9)	208 (90.4)	212 (90.2)	633 (90.2)
	Male n (%)	24 (10.1)	22 (9.6)	23 (9.8)	69 (9.8)
Race†	White n (%)	196 (82.7)	189 (82.2)	193 (82.1)	578 (82.3)
	Black n (%)	19 (8.0)	21 (9.1)	22 (9.4)	62 (8.8)
	Asian n (%)	5 (2.1)	6 (2.6)	8 (3.4)	19 (2.7)
	American Indian/Alaska native n (%)	1 (0.4)	0	0	1 (0.1)
	Native Hawaiian or Other Pacific Islander n (%)	1 (0.4)	0	0	1 (0.1)
	Missing	6 (2.5)	4 (1.7)	3 (1.3)	13 (1.9)
	Not Reported‡	9 (3.8)	10 (4.3)	9 (3.8)	28 (4.0)

Source: Sponsor's Study Report, Page 57 of 99

The demographic characteristics of the three treatment groups were similar in the mITT population, and there were no notable differences in demographics between the mITT population and the PP population.

Table 51. Baseline Characteristics of Subjects – Study DP10019

	Placebo IV (N=235) n (%)	APD421 5mg IV (N=237) n (%)	APD421 10mg IV (N=230) n (%)	Overall (N=702) n (%)
Sex				
Female	212 (90.2)	213 (89.9)	208 (90.4)	633 (90.2)
Male	23 (9.8)	24 (10.1)	22 (9.6)	69 (9.8)
History of PONV				
YES	121 (51.5)	123 (51.9)	110 (47.8)	354 (50.4)
NO	114 (48.5)	114 (48.1)	120 (52.2)	348 (49.6)
History of motion sickness				
YES	91 (38.7)	83 (35.0)	77 (33.5)	251 (35.8)
NO	144 (61.3)	154 (65.0)	153 (66.5)	451 (64.2)
Smoking history				
Current smoker	27 (11.5)	22 (9.3)	26 (11.3)	75 (10.7)
Former smoker	42 (17.9)	32 (13.5)	43 (18.7)	117 (16.7)
Non-smoker	166 (70.6)	183 (77.2)	161 (70.0)	510 (72.6)
Expected to need post-operative opioids				
YES	228 (97.0)	231 (97.5)	224 (97.4)	683 (97.3)
NO	7 (3.0)	6 (2.5)	6 (2.6)	19 (2.7)
Number of Risk factors				
1	2 (0.9)	1 (0.4)	1 (0.4)	4 (0.6)
2	7 (3.0)	17 (7.2)	10 (4.3)	34 (4.8)
3	105 (44.7)	90 (38.0)	108 (47.0)	303 (43.2)
4	121 (51.5)	129 (54.4)	111 (48.3)	361 (51.4)

Source: Sponsor's Tables and Figures, Page 51 of 451

A total of 50.4% of patients in the mITT population had a history of PONV (51.9% of the amisulpride injection 5 mg group, 47.8% of the amisulpride 10 mg group and 51.5% of the placebo group). History of motion sickness was lower (35.8% overall; 35.0%, 33.5% and 38.7% of the amisulpride injection 5 mg, amisulpride injection 10 mg and placebo groups, respectively). One risk factor was reported for 0.6% of patients, two risk factors for 4.8% of patients, three risk factors for 43.2% of patients, and four risk factors for 51.4% of patients. There were no patients with zero risk factors. Most patients were expected to require postoperative opioids (97.3%) and 72.6% of patients were non-smokers.

8.3.2.11. Statistical Analysis and Results of the Primary Efficacy Endpoint

For efficacy variables, the sponsor conducted all statistical tests at a one-sided significance level of 2.5% unless otherwise specified. The adjusted p-values based on the Bonferroni correction were reported in the primary analysis.

Table 52 and Table 53 show the results of the primary efficacy analyses by the sponsor and the reviewer, respectively.

Table 52. Analysis of the Primary Efficacy Endpoint mITT – Study DP10019

Time interval	APD421 5 mg (N = 237)			APD421 10 mg (N = 230)			Placebo (N = 235)	
	No n (%)	Yes n (%)	p*	No n (%)	Yes n (%)	p*	No n (%)	Yes n (%)
0-24 hours‡	157 (66.2)	80 (33.8)	0.109 0.109†	134 (58.3)	96 (41.7)	0.001 0.003†	168 (71.5)	67 (28.5)
0–2 hours	103 (43.5)	134 (56.5)	0.059	70 (30.4)	160 (69.6)	<0.001	119 (50.6)	116 (49.4)
0–4 hours	132 (55.7)	105 (44.3)	0.053	94 (40.9)	136 (59.1)	<0.001	148 (63.0)	87 (37.0)
0–6 hours	138 (58.2)	99 (41.8)	0.021	109 (47.4)	121 (52.6)	<0.001	158 (67.2)	77 (32.8)

Source: Sponsor's Study Report, Page 60 of 99

Table 53. Analysis of the Primary Efficacy Endpoint by Analysis Populations – Study DP10019

Populations Analyzed	amisulpride 10 mg IV	amisulpride 5 mg IV	Placebo IV	P-Value Difference (95% CI)
mITT	96/230 (41.7%)	80/237 (33.8%)	67/235 (28.5%)	amisulpride 10 mg - Placebo 0.003 13.2% (4.6%, 21.8%) amisulpride 5 mg - Placebo 0.22 5.2% (-3.1%, 13.6%)
PP	90/219 (41.1%)	78/232 (33.6%)	63/220 (28.6%)	amisulpride 10 mg - Placebo 0.006 12.5% (3.6%, 21.3%) amisulpride 5 mg - Placebo 0.25 5.0% (-3.5%, 13.5%)

Source: Reviewer

In the mITT population, CR occurred in 80 patients (33.8%; 95% CI 27.73 to 39.78) in the amisulpride injection 5 mg group, 96 patients (41.7%; 95% CI 35.37 to 48.11) in the amisulpride injection 10 mg group and 67 patients (28.5%; 95% CI 22.74 to 34.28) in the placebo group.

The difference in rate of CR for the amisulpride injection 10 mg group versus Placebo was 13.23% (95% CI 4.63 to 21.83) and was statistically significant (nominal p=0.003). The difference in rate of CR for amisulpride injection 5 mg versus placebo group was 5.24 percentage points (95% CI 3.10 to 13.59), which was not statistically significant (p=0.22).

In the PP population, CR occurred in 78 patients with a difference of 33.6% and a 95% CI (27.54, 39.70) in the amisulpride injection 5 mg group, 90 patients (41.1%; 95% CI 34.58 to 47.61) in the amisulpride injection 10 mg group and 63 patients (28.6%; 95% CI 22.66 to 34.61) in the placebo group.

Results from the exploratory analysis using CMH test in the mITT population are consistent with the primary analysis result.

Table 54. Response Rates by Gender - Study 19

Gender	amisulpride 10 mg IV	amisulpride 5 mg IV	Placebo IV
Female	84/208 (40.4%)	65/213 (30.5%)	61/212 (28.8%)
Male	12/22 (54.6%)	15/24 (62.5%)	6/23 (26.1%)

Source: Reviewer

As shown in Table 55 most subjects in the study were female. Numerically, females had a higher response rates (40.4%) in the 10-mg arm compared to the 5 mg and Placebo arms. The male subpopulation showed a higher response rate (62.5%) in the 5-mg treatment group than the other treatment arms.

Table 55. Response Rates by Country - Study 19

Country	amisulpride 10 mg IV	amisulpride 5 mg IV	Placebo IV
Canada	20/48 (41.7%)	19/47 (40.4%)	13/47 (27.7%)
Germany	18/48 (37.5%)	17/55 (30.9%)	15/55 (27.3%)
France	5/10 (50.0%)	2/9 (22.2%)	4/9 (44.4%)
United States	53/124 (42.7%)	42/126 (33.3%)	35/124 (28.2%)

Source: Reviewer

As shown in Table 56, all countries showed a numerically higher response rate in the 10 mg treatment arm than the 5 mg group.

Table 56. Response Rates by Risk Factors - Study 19

Risk Factor	amisulpride 10 mg IV	amisulpride 5 mg IV	Placebo IV
History of Motion Sickness			
Yes	34/77 (44.2%)	25/83 (30.1%)	25/91 (27.5%)
No	62/153 (40.5%)	55/154 (35.7%)	42/144 (29.2%)
History of PONV			
Yes	43/110 (39.1%)	39/123 (31.7%)	35/121 (28.9%)
No	53/120 (44.2%)	41/114 (36.0%)	32/114 (28.1%)
Smoking			
Yes	14/26 (53.9%)	7/22 (31.8%)	9/27 (33.3%)
No	82/204 (40.2%)	73/215 (34.0%)	58/208 (27.9%)
Opioid			
Yes	93/224 (41.5%)	78/231 (33.8%)	65/228 (28.5%)
No	3/6 (50.0%)	2/6 (33.3%)	2/7 (28.6%)

Source: Reviewer

In general, subjects in the 10 mg treatment arm had a higher response rate than the 5 mg among all the risk groups.

Table 57. Summary of the "Prophylaxes" Studies (Response Rates)

	amisulpride 5 mg	Placebo	P-Value Difference (95% CI)
Study DP10015	78/176 (44.3%)	54/166 (32.5%)	0.03 11.8% (1.6%, 22.0%)
Study DP10017*	330/573 (57.6%)	268/574 (46.7%)	0.001 10.9% (5.2%, 16.7%)

Both arms in Study DP10017 took standard anti-emetic drugs in addition to their assigned Study Drug.

Table 58. Summary of the "Treatment" Studies (Response Rates)

	amisulpride 10 mg	amisulpride 5 mg	Placebo	P-Value Difference (95% CI)
Study DP10018	59/188 (31.4%)	60/191 (31.4%)	39/181 (21.6%)	amisulpride 10 mg - Placebo 0.03 9.8% (0.9%, 18.8%) amisulpride 5 mg - Placebo: 0.03 9.9% (1.0%, 18.8%)
Study DP10019	96/230 (41.7%)	80/237 (33.8%)	67/235 (28.5%)	amisulpride 10 mg - Placebo 0.003 13.2% (4.6%, 21.8%) amisulpride 5 mg - Placebo 0.22 5.2% (-3.1%, 13.6%)

8.4. Review of Safety

8.4.1. Safety Review Approach

The primary review of safety of amisulpride for the prevention/treatment of PONV focused on the evaluation of pooled data from trials DP10017, DP10015, DP10014, DP10006, DP10018, and DP10019 evaluating the two proposed doses of amisulpride (5 mg and10 mg)[5]. It is appropriate to include Study DP10006 (phase 2 dose ranging study) and Study DP10014 (failed prevention efficacy trial) in the pooled analyses since both of these studies had similar study designs as the other four. All six studies were double-blind, placebo-controlled, multi-center studies of amisulpride in patients undergoing general anesthesia and elective surgery. All studies, in support of the prevention of PONV compared a 5-mg dose of amisulpride to placebo; study

[5] The efficacy review focused on the four pivotal trials DP10017 DP10015, DP10018 and DP10019 (two for prevention and two for treatment)

DP10006 also included comparisons of two other doses, 1 mg and 20 mg. The studies in support of amisulpride as a treatment of (b) (4) PONV compared amisulpride at 5-mg and 10-mg doses to placebo. All trials were similar with regard to design, study population, dosing regimen and key primary and secondary endpoints.

The safety review will also include more details of the following Adverse Events of Special Interest:

- QT prolongation
- Severe or serious cardiac adverse events
- Extrapyramidal symptoms (EPS)
- Neuroleptic malignant syndrome

8.4.2. Review of the Safety Database

Overall Exposure

Individual patient data for patients undergoing surgery (DP10017, DP10015, DP10014, DP10006, DP10018, and DP10019) who took any study medications (amisulpride, Placebo, or the combination standard anti-emetic) were pooled to evaluate the safety profile of amisulpride, whether prematurely withdrawn from the study or not. The inclusion of these six studies in a safety pooled analysis was an appropriate pooling strategy, discussed at the pre-NDA meeting and agreed to by FDA.

The clinical safety program for amisulpride includes six randomized, double-blind, placebo-controlled, multi-center studies of 3313 patients undergoing general anesthesia for elective surgery, four in the prevention of PONV (studies DP10017, DP10015, DP10014, and DP0006) and two in the treatment of established PONV (studies DP10018 and DP0019). The clinical studies with amisulpride evaluated a single dose and patient follow-up was short-term. The studies in support of amisulpride for the prevention of PONV all compared a 5-mg dose of amisulpride to placebo; study DP10006 also included comparisons of two other doses, 1 mg and 20 mg. The studies in support of amisulpride as a treatment of (b) (4) PONV compared amisulpride at 5-mg and 10-mg doses to placebo. These six studies provided the primary safety data database for this clinical review.[6]

In total, 3313 patients were exposed to study medication (placebo or amisulpride), with 1924 patients exposed to amisulpride and 1389 patients receiving placebo. Amisulpride was

[6] In addition, the general safety of a thorough QT (TQT) study (study DP10013) of 45 healthy, adult volunteers who received 5 mg and 40 mg of amisulpride was reviewed separately. Thirty-nine received amisulpride and thirty-eight subjects received all four treatments (amisulpride 5 mg, amisulpride 40 mg, moxifloxacin 400 mg and placebo) separated by a washout of ≥7 days. See Section 6.2.2.3 for full details of this study

administered once at a 5-mg dose to 1395 patients, of whom 572 also received a standard anti-emetic concomitantly (mostly either ondansetron or dexamethasone with a few patients receiving betamethasone); and as a single 10-mg dose to 418 patients. A small number of patients received a single 1-mg (N=58) or 20-mg (N=53) dose. Of the 1389 patients who received placebo, 575 also received a standard anti-emetic concomitantly. See Table 59 below for further details. Certain areas of the safety review will focus only on the data from the four pivotal trials.

Table 59. Summary of Clinical Studies Included in the Pooled Safety Population

Study	Study Design	Study Population	Treatment	No. of Patients Enrolled/Safety	Safety Assessments
Prevention of PONV					
DP10017	Phase III, randomised, double-blind, placebo-controlled study with two parallel groups	Adult patients (≥18 years) at high risk of PONV, undergoing elective surgery under general anaesthesia	5 mg APD421 or placebo administered once as a slow, IV push over 1 minute at the time of induction of anaesthesia; given in combination with standard anti-emetic	1297/1149 (APD421, 572; placebo, 575; anti-emetic only, 2)	AEs, vital signs, laboratory parameters (haematology, clinical chemistry) and ECGs
DP10014	Phase III, randomised, double-blind, placebo-controlled study with two parallel groups	Adult patients (≥18 years) at moderate-to-high risk of PONV, undergoing elective surgery under general anaesthesia	5 mg APD421 or placebo administered once as a slow, IV push over 1 to 2 minutes at the time of induction of anaesthesia	368/347 (APD421 169, placebo 178)	AEs, vital signs, laboratory parameters (haematology, clinical chemistry) and ECGs
DP10015	Phase III, randomised, double-blind, placebo-controlled study with two parallel groups	Adult patients (≥18 years) at moderate-to-high risk of PONV, undergoing elective surgery under general anaesthesia	5 mg APD421 or placebo administered once as a slow, IV push over 1 to 2 minutes at the time of induction of anaesthesia	364/342 (APD421 176, placebo 166)	AEs, vital signs, laboratory parameters (haematology, clinical chemistry) and ECGs
DP10006	Phase II, dose-ranging randomised, double-blind, placebo-controlled study	Adult patients (≥18 years) at moderate-to-high risk of PONV, undergoing elective surgery under general anaesthesia	1 mg, 5 mg or 20 mg APD421 or placebo administered once as a slow, IV push over 1 to 2 minutes at the time of induction of anaesthesia	223/215 (APD421 161, placebo 54)	AEs, vital signs, laboratory parameters (haematology, clinical chemistry) and ECGs
Treatment of PONV					
DP10018	Phase III, double-blind, randomised, parallel-group, placebo-controlled study with three parallel groups	Adult patients (≥18 years) at low-to-moderate risk of PONV, undergoing elective surgery under general anaesthesia, not receiving prior prophylaxis	5 mg or 10 mg APD421 or placebo administered once as a single, slow, IV push over ~ 2 minutes	1988[a]/560 (APD421, 379; placebo, 181)	AEs, laboratory parameters (haematology, clinical chemistry)
DP10019	Phase III, double-blind, randomised, parallel-group, placebo-controlled study	Adult patients (≥18 years) at moderate-to-high risk of PONV, undergoing elective surgery under general anaesthesia, receiving prior prophylaxis	5 mg or 10 mg APD421 or placebo administered once as a single, slow, IV push over ~ 2 minutes	2285[b]/702 (APD421, 467; placebo, 235)	AEs, laboratory parameters (haematology, clinical chemistry)

Integrated Summary of Safety Table 1, pg. 7

Relevant Characteristics of the Safety Population:

Demographic characteristics of the subject population in the amisulpride development program are presented below in Table 60 and in greater detail in the efficacy section of this review. A brief summary of demographic information relevant to the evaluation of safety will be presented here. Since the clinical studies evaluated a single dose (either 5 mg or 10 mg), the efficacy, and safety populations for the proposed doses were similar. There is some safety data available for lower/higher doses from Study DP10006[7] (1 mg; N=58 and 20 mg; N=53); however, the number of patients exposed to these doses is limited. Thus, it is difficult to draw definite

[7] Dose ranging study not included as a pivotal trial (or part of efficacy analyses)

conclusions, in addition, these are not the proposed doses. In addition, a specific QT study was done which included an amisulpride dose of 40 mg (4x-8x proposed dose), see Section 8.4.4 QT study.

The clinical studies included predominantly a female population (81% to 97%), and the majority of patients were white (74% to 82%). See Table 60 below for further details. Since it was important to enroll subjects who had a moderate/high risk for PONV, and being female itself was a risk factor, for the proposed indication of PONV, it was reasonable to enroll a disproportionate number of females in the clinical studies. However, studies were reasonably well balanced in sex by treatment group. Safety for a single dose D_2 receptor antagonist is not expected to be different between the sexes.[8]

[8] FDA has accepted other clinical development programs for PONV wherein pivotal clinical trials are predominantly female.

Table 60. Summary of Demographic Characteristics by Treatment (Safety Population)

	Placebo		APD421		
	Placebo – SA[a] N=814	Placebo + SA[b] N=575	5 mg – SA[a] N=823	5 mg + SA[b] N=572	10 mg N=418
Age (years)					
n	814	575	823	572	418
Mean±SD	49.0±14.25	48.3±13.98	48.8±14.76	48.8±14.24	47.1±13.64
Range	18 to 86	18 to 86	18 to 88	18 to 91	18 to 85
<65 (n [%])	696 (85.5)	501 (87.1)	682 (82.9)	487 (85.1)	374 (89.5)
≥65 (n [%])	118 (14.5)	74 (12.9)	141 (17.1)	85 (14.9)	44 (10.5)
Sex (n [%])					
n	814	575	823	572	418
Male	155 (19.0)	18 (3.1)	155 (18.8)	20 (3.5)	65 (15.6)
Female	659 (81.0)	557 (96.9)	668 (81.2)	552 (96.5)	353 (84.4)
Race (n [%])					
n	733	490	740	493	389
White	659 (81.0)	425 (73.9)	670 (81.4)	438 (76.6)	341 (81.6)
Non-white	74 (9.1)	65 (11.3)	70 (8.5)	55 (9.6)	48 (11.5)
American Indian or Alaska native	0	0	3 (0.4)	4 (0.7)	0
Asian	12 (1.5)	7 (1.2)	14 (1.7)	2 (0.3)	10 (2.4)
Black or African American	60 (7.4)	58 (10.1)	49 (6.0)	48 (8.4)	38 (9.1)
Native Hawaiian or other Pacific Islander	0	0	1 (0.1)	1 (0.2)	0
Ethnicity (n [%])					
n	371	351	397	353	214
Hispanic or Latino	48 (5.9)	57 (9.9)	54 (6.6)	66 (11.5)	36 (8.6)
Not Hispanic or Latino	323 (39.7)	294 (51.1)	343 (41.7)	287 (50.2)	178 (42.6)
BMI (kg/m^2)					
n	398	575	395	572	-
Mean±SD	29.14±7.843	29.97±8.333	28.88±7.538	30.55±8.762	-
Range	16.6 to 66.2	12.6 to 62.2	16.2 to 62.1	16.4 to 80.2	-
<30 (n [%])	258 (31.7)	341 (59.3)	252 (30.6)	321 (56.1)	-
≥30 (n [%])	140 (17.2)	234 (40.7)	143 (17.4)	251 (43.9)	-

BMI=body mass index; SA=standard anti-emetic; SD=standard deviation; - =Not recorded.
a Placebo and 5 mg APD421 groups from studies DP10006, DP10014, DP10015, DP10018 and DP10019.
b Placebo and 5 mg APD421 groups from study DP10017.
Source: Table 1.2.2 and Table 1.2.5.
Percentages are of Safety population.

Summary of Clinical SafetyTable 2.7.4-1 Pg 10

As described above in Section 2.1 an important demographic characteristic in defining risk for PONV is the number of risk factors a patient has.

The following tables, Table 61 to Table 64, depict the number and percentages of patients by Treatment Group and Number of Risk Factors for each of the pivotal studies. For the most part, treatment groups for the proposed doses were equally balanced by number of risk factors.

Table 61. Study 15: Number and Percentages of Patients by Treatment Group and Number of Risk Factors

	Treatment Group		
No. of Risk Factors	APD421 5 mg	Placebo	Total
0	0% (0/176)	0% (0/166)	0% (0/342)
1	0% (0/176)	0% (0/166)	0% (0/342)
2	31.3% (55/176)	29.5% (49/166)	30.4% (104/342)
3	44.9% (79/176)	48.8% (81/166)	46.8% (160/342)
≥ 4	23.9% (42/176)	21.7% (36/166)	22.8% (78/342)
Total	100% (176/176)	100% (166/166)	100% (342/342)

From Sponsor Response to IR received February 22, 2018

Table 62. Study 17: Number and Percentages of Patients by Treatment Group and Number of Risk Factors

	Treatment Group		
No. of Risk Factors	APD421 5 mg	Placebo	Total
0	0% (0/572)	0% (0/575)	0% (0/1147)
1	0% (0/572)	0% (0/575)	0% (0/1147)
2	0.2% (1/572)	0.2% (1/575)	0.2% (2/1147)
3	56.1% (321/572)	56.7% (326/575)	56.4% (647/1147)
≥ 4	43.7% (250/572)	43.1% (248/575)	43.4% (498/1147)
Total	100% (572/572)	100% (575/575)	100% (1147/1147)

From Sponsor Response to IR received February 22, 2018

Table 63. Study 18: Number and Percentages of Patients by Treatment Group and Number of Risk Factors

	Treatment Group			
No. of Risk Factors	APD421 5 mg	APD421 10 mg	Placebo	Total
0	0% (0/191)	0% (0/188)	0.6% (1/181)	0.2% (1/560)
1	5.2% (10/191)	5.3% (10/188)	8.3% (15/181)	6.3% (35/560)
2	36.6% (70/191)	35.1% (66/188)	36.5% (66/181)	36.1% (202/560)
3	51.8% (99/191)	55.9% (105/188)	49.7% (90/181)	52.5% (294/560)
≥ 4	6.3% (12/191)	3.7% (7/188)	5.0% (9/181)	5.0% (28/560)
Total	100% (191/191)	100% (188/188)	100% (181/181)	100% (560/560)

From Sponsor Response to IR received February 22, 2018

Table 64. Study 19: Number and Percentages of Patients by Treatment Group and Number of Risk Factors

	Treatment Group			
No. of Risk Factors	APD421 5 mg	APD421 10 mg	Placebo	Total
0	0% (0/237)	0% (0/230)	0% (0/235)	0% (0/702)
1	0.4% (1/237)	0.4% (1/230)	0.9% (2/235)	0.6% (4/702)
2	7.2% (17/237)	4.3% (10/230)	3.0% (7/235)	4.8% (34/702)
3	38.0% (90/237)	47.0% (108/230)	44.7% (105/235)	43.2% (303/702)
≥ 4	54.4% (129/237)	48.3% (111/230)	51.5% (121/235)	51.4% (361/702)
Total	100% (237/237)	100% (230/230)	100% (235/235)	100% (702/702)

From Sponsor Response to IR received February 22, 2018

Adequacy of the Safety Database:

The total subject exposure to 5 mg amisulpride for prevention of PONV and 10 mg amisulpride for treatment of PONV provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database presented by the applicant is sufficient to characterize the safety profile of amisulpride (5 mg) for the prevention of PONV and (10 mg) for the treatment of PONV.

8.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no concerns about data quality and integrity. Narrative summaries for individual subjects with SAEs and AEs of special interest were reviewed.

Categorization of Adverse Events

Treatment-emergent adverse events were defined as AEs that were not present before study treatment administration or that worsened in intensity during the study evaluation period.

A serious AE was defined as any event that was fatal or life-threatening, required in-patient hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect in the offspring of a patient who received drug, or was deemed medically significant or required intervention to prevent one or other of the aforementioned outcomes. This reviewer considers these definitions acceptable.

As nausea and vomiting in the 24-hour period after end of surgery (prophylaxis studies) or study drug treatment (treatment studies) were recorded as part of the efficacy assessment, they are specifically not included in the analysis as TEAEs as they have already been taken into account in efficacy assessments.

All AEs from individual studies were coded from verbatim text to preferred terms (PTs) and grouped by system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1.

Treatment-emergent AEs of special interest (including cardiovascular, neurological, psychiatric) were determined using Standardized MedDRA Queries (SMQs) in the relevant areas, with a broad search applied to all SMQs apart from neuroleptic malignant syndrome, for which both a broad and narrow search were applied.

Routine Clinical Tests

Clinically relevant tests were collected at appropriate time intervals (baseline and postoperatively) including laboratory tests (chemistry, hematology, urinalysis, prolactin), vital signs, weight and height and 12 lead ECGs. However, ECGs were performed in the prophylaxis studies and were not performed in the treatment studies (despite FDA advice to perform them). ECG evaluation during the clinical trials that included amisulpride doses of 10 mg might have been informative.

Of note, some variation in certain laboratory tests would be expected in patients when pre-op values are compared to post-op values. Drops in hemoglobin, elevations in WBC, and changes in electrolytes (including glucose) can typically be seen in this clinical setting.

These safety assessment methods and time intervals were reasonable for the studied population and indications that were investigated.

8.4.4. Safety Results

Deaths

There was one death in the treatment group of the amisulpride clinical trials. The patient ([redacted]) was 65 years old female with past medical history of diabetes, morbid obesity and hypertension, was randomized to amisulpride and combination anti-emetic (ondansetron) and had an open exploratory laparotomy, with a colon resection and extensive lysis of adhesions. Post-operative course was complicated by systemic inflammatory response syndrome (SIRS), acute renal failure requiring dialysis, metabolic acidosis, hyperglycemia, hypocalcemia, and tachycardia. Three days after receiving study medication she had ventricular fibrillation, CPR was required, and she died. This death was assessed by investigators as not related.

This patient had multiple comorbidities; she had a complex open abdominal surgery followed by a complicated post-operative course. This death does not seem attributable to the study treatment which the patient received 3 days prior, especially given the short half-life of amisulpride (4 to 5 hours).

Serious Adverse Events

All serious TEAEs reported in the six trials, irrespective of causality, are presented by MedDRA SOC and by treatment group in right salpingo-oophorectomy and was noted to have a prolonged QT interval on EKG 19 hours after amisulpride treatment. The QT prolongation although ongoing, was reportedly resolving, and the patient was discharged home to follow-up with

cardiology. Of note, this patient also received prophylaxis with ondansetron and two additional doses of ondansetron doses as treatment (see Table 66 for further details).

Table 65. Included in the Table are 1-mg and 20-mg doses of amisulpride, which represent much smaller subgroups (and doses not being proposed) thus it is difficult to make any definitive safety conclusions. When amisulpride 5 mg and 10 mg are compared to their respective placebo groups (e.g., amisulpride 5 mg + Standard Anti-emetic (SA) and Placebo + SA), the total percentages are similar. For individual SOCs, most were similar, although event numbers were small, so again it is difficult to make any definitive safety conclusions. For the SOC INFECTIONS AND INFESTATIONS, the amisulpride 5 mg + SA treatment group appears to have a larger percentage of events than the Placebo + SA treatment group. Upon review of the PTs, in the amisulpride 5 mg + SA group there were two patients with peritonitis, two patients had post-operative wound infections, and one patient each with pneumonia/sepsis and viral gastroenteritis. The Placebo + SA treatment group had one case of pneumonia, one urinary tract infection and one staph infection. Despite a small imbalance, all of these SAEs could occur as a complication of surgery thus could typically be seen in any post-op patient population. All of the SAEs that occurred in any amisulpride treatment group are listed by PT/verbatim term below in Table 66. Review of the narrative summaries did not reveal any specific safety signals. There were six patients with cardiac SAEs, which included patient (b) (6) already described above. See Section 0

Statistical and Clinical and Evaluation for further details.

One patient ((b) (6)) was an 80-year-old female who had open abdominal surgery for suspected ovarian cancer. She had an intra-abdominal hemorrhage and a subsequent reoperation, where she had hypokalemia, tachycardia, and angina. However, these events occurred 3½ days after amisulpride treatment, thus it is doubtful that amisulpride was the cause of them.

There were two patients (amisulpride10 mg) with events that occurred 3 days (tachyarrhythmia) and 5 days (acute MI) after amisulpride treatment. Once again, given the time course of events and the short half-life of the drug, it is unlikely that amisulpride was the cause of these events.

Patient (b) (6) was 65 years old female with a past medical history significant for diabetes mellitus and hypertension. She had an acute myocardial infarction (MI) 18 hours after amisulpride treatment. Given the patient's baseline risk factors, it is unlikely that amisulpride was the cause of her acute MI.

The last patient (b) (6)) was a 45-year-old female who underwent laparoscopic right salpingo-oophorectomy and was noted to have a prolonged QT interval on EKG 19 hours after amisulpride treatment. The QT prolongation although ongoing, was reportedly resolving, and the patient was discharged home to follow-up with cardiology. Of note, this patient also received prophylaxis with ondansetron and two additional doses of ondansetron doses as treatment (see Table 66 for further details).

Table 65. Serious Adverse Events by System Organ Class and Treatment

			Amisulpride				
SOC	Placebo N=814	Placebo+ SA N=575	1 mg N=58	5 mg N=823	5 mg+SA N=572	10 mg N=418	20 mg N=53
TOTAL	**21 (2.6%)**	**18 (3.1%)**	**1 (1.7%)**	**20 (2.4%)**	**20 (3.5%)**	**7 (1.7%)**	**2 (3.8%)**
Injury, poisoning and procedural complications	9 (1.1%)	4 (0.7%)	1 (1.7%)	7 (0.9%)	5 (0.9%)	3 (0.7%)	2 (3.8%)
Gastrointestinal disorders	7 (0.9%)	3 (0.5%)	0	3 (0.4%)	2 (0.3%)	1 (0.2%)	0
Infections and infestations	2 (0.2%)	3 (0.5%)	0	2 (0.2%)	6 (1%)	1 (0.2%)	0
Cardiac disorders*	1 (0.1%)	1 (0.2%)	0	1 (0.1%)	3 (0.5%)	2 (0.5%)	0
Renal and urinary disorders	1 (0.1%)	3 (0.5%)	0	1 (0.1%)	1 (0.2%)	0	0
Hepatobiliary disorders	0	1 (0.2%)	0	1 (0.1%)	2 (0.3%)	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	1 (0.1%)	1 (0.2%)	0	1 (0.1%)	2 (0.3%)	0	0
Vascular disorders	1 (0.1%)	2 (0.3%)	0	0	2 (0.3%)	0	0
Nervous system disorders	2 (0.2%)	1 (0.2%)	0	1 (0.1%)	0	0	0
General disorders and administration site conditions	0	1 (0.2%)	0	1 (0.1%)	1 (0.2%)	0	0

			Amisulpride				
SOC	Placebo N=814	Placebo+ SA N=575	1 mg N=58	5 mg N=823	5 mg+SA N=572	10 mg N=418	20 mg N=53
Metabolism and nutrition disorders	0	1 (0.2%)	0	1 (0.1%)	1 (0.2%)	0	0
Reproductive system and breast disorders	0	2 (0.3%)	0	1 (0.1%)	0	0	0
Blood and lymphatic system disorders	1 (0.1%)	1 (0.2%)	0	0	0	0	0
Investigations	0	0	0	1 (0.1%)	1 (0.2%)	0	0
Eye disorders	0	0	0	1 (0.1%)	0	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	0	0	1 (0.1%)	0	0	0
Psychiatric disorders	0	0	0	0	0	1 (0.2%)	0
Skin and subcutaneous tissue disorders	0	0	0	0	1 (0.2%)	0	0

Reviewers Table Adapted from ISS Pg 706-712 Table 2.14.1

Table 66. SAEs Occurring in Any Amisulpride Treatment Group

Study	Pt ID	Sex	Treatment date/time	Verbatim term	Preferred term	AE onset	Time to onset*	AE end
	(b) (6)		(b) (6)			(b) (6)		(b) (6)
1 mg APD421								
DP10006	(b) (6)	F		Post operative abdominal wall haematoma	Post procedural haematoma		3d 19h 10m	
5 mg APD421								
DP10018	(b) (6)	F		Phlegmonous type collection	Abdominal abscess		3d	
DP10017		F		Acute kidney injury	Acute kidney injury		2d	
DP10015		F		Non-ST segment elevation myocardial infarction	Acute myocardial infarction		0d 18h 4m	
DP10017		F		Acute on chronic respiratory failure	Acute respiratory failure		1d 2h 57m	
DP10017		F		Acute respiratory failure	Acute respiratory failure		0d 17h 51m	
DP10014		F		Adenocarcinoma recurrence	Adenocarcinoma		7d	
DP10015		F		Postoperative anemia	Anaemia postoperative		0d 22h 12m	
DP10014		M		Pouch insufficiency	Anastomotic leak		7d	
DP10017		F		Angina pectoris	Angina pectoris		3d 12h 44m	
DP10019		F		Postoperative rise in creatinine	Blood creatinine increased		1d	
DP10015		F		Dehydration	Dehydration		10d	
DP10017		F		Wosening dyspnea	Dyspnoea		1d 2h 57m	
DP10017		F		Prolonged QT interval	Electrocardiogram QT prolonged		0d 19h 18m	
DP10018		F		Stage4 endometriosis : extension of disease to the left ureter that requires unexpected procedure	Endometriosis		1d	
DP10017		F		Viral gastroenteritis	Gastroenteritis viral		1d 14h 28m	
DP10017		F		Large haematoma	Haematoma		1d 21h 18m	
DP10015		M		Hematuria	Haematuria		1d	

Acacia Pharma

Study	Pt ID	Sex	Treatment date/time	Verbatim term	Preferred term	AE onset	Time to onset*	AE end
DP10017	(b) (6)	F	(b) (6)	Liver cytolysis	Hepatocellular injury	(b) (6)	5d 2h 31m	(b) (6)
DP10019		F		Numbness in leg	Hypoaesthesia		3d	
DP10017		F		Worsening of electrolyte imbalance (potassium 2.6mmol/l)	Hypokalaemia		2d 21h 50m	
DP10015		M		Ileus	Ileus		3d 0h 39m	
DP10017		F		Diffuse abdominal bleeding	Intra-abdominal haemorrhage		0d 12h 50m	
DP10017		F		Shock liver	Ischaemic hepatitis		3d 4h 16m	
DP10017		F		Leak prior eroded band site	Medical device complication		0d 4h 35m	
DP10019		F		Abscess presacral	Pelvic abscess		5d	
DP10017		F		Rectum vaginal injury	Pelvic organ injury		0d 2h 7m	
DP10019		F		Fatty tissue prolapse at the tempral lobe	Periorbital fat herniation		5d	
DP10017		F		Peritonitis	Peritonitis		0d 4h 54m	
DP10017		F		Peritonitis	Peritonitis		6d 6h 56m	
DP10017		F		Pneumonia	Pneumonia		4d 1h 34m	
DP10017		F		Pneumothorax	Pneumothorax		-15d -6h -17m	
DP10014		F		Thrombosis of the portal vein	Portal vein thrombosis		3d	
DP10019		F		Post cholecystectomy bile leak	Post procedural bile leak		2d	
DP10018		M		Enlarging hematoma post-op	Post procedural haematoma		1d	
DP10017		F		Postoperative bleeding	Post procedural haemorrhage		0d 21h 3m	
DP10017		F		Postoperative bleeding	Post procedural haemorrhage		0d 5h 43m	
DP10019		F		Postoperative hemorrhage	Post procedural haemorrhage		3d	
DP10018		F		Post-operative ileus	Postoperative ileus		4d	
DP10017		F		Surgical site infection (umbilical infection)	Postoperative wound infection		6d 18h 4m	
DP10017		F		Post operative surgical site infection	Postoperative wound infection		2d 2h 16m	
DP10017		F		Unknown post operative pain	Procedural pain		0d 7h 50m	
DP10018		F		Postoperative surgical pain	Procedural pain		1d	
DP10018		F		Pulmonary embolism	Pulmonary embolism		2d	
DP10015		F		Fever, unknown origin	Pyrexia		3d 12h 49m	
DP10017		F		Sepsis	Sepsis		6d 6h 56m	
DP10017		F		Shock	Shock		4d	
DP10015		M		Small bowel obstruction	Small intestinal obstruction		10d 6h 29m	
DP10017		F		Small bowel obstruction	Small intestinal obstruction		5d 3h 22m	
DP10017		F		Tachycardia	Tachycardia		3d 12h 44m	
DP10017		F		Large periumbilical haematoma	Umbilical haematoma		4d 20h 6m	
DP10017		F		Pulseless ventricular tachycardia	Ventricular fibrillation		2d 13h 30m	
DP10015		F		Vomiting	Vomiting		10d	
DP10017		F		Continous secretion breast wound	Wound secretion		1d 21h 18m	
10 mg APD421								
DP10019	(b) (6)	F		Non-ST elevated myocardial infarction	Acute myocardial infarction		5d	
DP10018		F		Biliary colic	Biliary colic		7d	
DP10019		F		GI bleed	Gastrointestinal haemorrhage		8d	

Study	Pt ID	Sex	Treatment date/time	Verbatim term	Preferred term	AE onset	Time to onset*	AE end
DP10019	(b) (6)	F	(b) (6)	Altered mental status exacerbation	Mental status changes	(b) (6)	4d	(b) (6)
DP10018		M		Post-op bile leak	Post procedural bile leak		8d	
DP10018		F		Post operative ileus	Postoperative ileus		3d	
DP10019		F		Postop ileus	Postoperative ileus		5d	
DP10018		F		Postoperative tachyarrhytmia	Tachyarrhythmia		3d	
DP10019		F		Urinary tract infection	Urinary tract infection		5d	
20 mg APD421								
DP10006	(b) (6)	F		Post operative hematoma	Post procedural haematoma		3d	
DP10006		M		Postoperative bleeding	Post procedural haemorrhage		0d 0h 47m	

From Sponsor Response to IR dated January 8, 2018

Dropouts and/or Discontinuations Due to Adverse Effects

There was one TEAE (peritonitis) which led to withdrawal of a patient who received amisulpride 5 mg in combination with ondansetron (Study DP10017). The patient had a laparoscopic hysterectomy. She then had an episode peritonitis, for which she was hospitalized, treated and then discharged with resolution. It is unlikely that amisulpride caused the event of peritonitis. This is a known complication of surgery.

Significant Adverse Events

See Section 8.4.5, Analysis of Submission-Specific Safety Issue.

Treatment Emergent Adverse Events and Adverse Reactions

A summary of the TEAEs (PTs) reported in >5.0% of patients administered amisulpride 5 mg or 10 mg is provided in Table 67. Procedural pain was the most frequently reported TEAE (by PT) overall. The incidence of procedural pain in the amisulpride 10-mg dose group was extremely low and not directly comparable with the other pooled dose groups, as these data were only collected in the treatment setting, when an unusual degree of procedural pain is very uncommon. However, comparison of the incidence of procedural pain between the amisulpride dose groups and placebo in the treatment studies individually demonstrated no important difference. As there were some minor differences in TEAE pattern between the prophylaxis and treatment indications, due to the proximity of study drug administration to the anesthetic and surgical procedures, TEAEs are summarized by indication for the 5- and 10-mg dose groups and placebo in Table 68. There were no clinically significant differences between amisulpride at either dose and placebo.

Table 67. Treatment-Emergent Adverse Events Occurring in >5.0% of Patients, by Treatment

Table 2.7.4-3 Treatment-emergent Adverse Events (Preferred Terms) Occurring in >5.0% of Patients in Any Treatment Group by Treatment (Safety Population)

System Organ Class[a] Preferred Term	Placebo				APD421					
	Placebo – SA[b] N=814		Placebo + SA[c] N=575		5 mg – SA[b] N=823		5 mg + SA[c] N=572		10 mg N=418	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Patients with at least one TEAE	497 (61.1)	1478	280 (48.7)	636	456 (55.4)	1417	236 (41.3)	579	178 (42.6)	375
Gastrointestinal disorders	**212 (26.0)**	**334**	**100 (17.4)**	**135**	**207 (25.2)**	**316**	**83 (14.5)**	**112**	**90 (21.5)**	**131**
Nausea	74 (9.1)	83	34 (5.9)	36	73 (8.9)	82	34 (5.9)	37	45 (10.8)	46
Flatulence	67 (8.2)	67	22 (3.8)	22	67 (8.1)	69	19 (3.3)	19	30 (7.2)	30
Constipation	63 (7.7)	63	18 (3.1)	18	61 (7.4)	62	18 (3.1)	18	24 (5.7)	24
Injury, poisoning and procedural complications	**200 (24.6)**	**263**	**94 (16.3)**	**113**	**189 (23.0)**	**239**	**87 (15.2)**	**113**	**16 (3.8)**	**18**
Procedural pain	167 (20.5)	182	58 (10.1)	58	164 (19.9)	175	53 (9.3)	53	2 (0.5)	2
Procedural hypotension	5 (0.6)	5	16 (2.8)	16	7 (0.9)	7	20 (3.5)	20	5 (1.2)	5
Nervous system disorders	**65 (8.0)**	**73**	**48 (8.3)**	**52**	**64 (7.8)**	**75**	**32 (5.6)**	**34**	**32 (7.7)**	**33**
Headache	34 (4.2)	36	14 (2.4)	15	33 (4.0)	34	6 (1.0)	6	15 (3.6)	15
Dizziness	21 (2.6)	21	15 (2.6)	15	20 (2.4)	20	11 (1.9)	11	9 (2.2)	9
General disorders and administration site conditions	**76 (9.3)**	**81**	**39 (6.8)**	**42**	**79 (9.6)**	**84**	**46 (8.0)**	**52**	**37 (8.9)**	**41**
Infusion site pain	17 (2.1)	17	2 (0.3)	2	16 (1.9)	16	2 (0.3)	2	25 (6.0)	25
Pyrexia	15 (1.8)	15	4 (0.7)	4	13 (1.6)	14	9 (1.6)	9	2 (0.5)	2
Pain	8 (1.0)	9	2 (0.3)	2	12 (1.5)	13	6 (1.0)	6	0	0
Psychiatric disorders	**41 (5.0)**	**44**	**14 (2.4)**	**17**	**34 (4.1)**	**36**	**11 (1.9)**	**12**	**9 (2.2)**	**10**
Insomnia	19 (2.3)	19	1 (0.2)	1	16 (1.9)	16	4 (0.7)	5	7 (1.7)	7
Sleep disorder	13 (1.6)	13	3 (0.5)	3	9 (1.1)	9	3 (0.5)	3	0	0
Blood and lymphatic system disorders	**63 (7.7)**	**71**	**17 (3.0)**	**20**	**54 (6.6)**	**57**	**12 (2.1)**	**15**	**7 (1.7)**	**7**
Anaemia	25 (3.1)	25	13 (2.3)	13	25 (3.0)	25	10 (1.7)	10	4 (1.0)	4
Vascular disorders	**65 (8.0)**	**67**	**34 (5.9)**	**40**	**50 (6.1)**	**50**	**29 (5.1)**	**32**	**17 (4.1)**	**19**
Hypertension	25 (3.1)	25	11 (1.9)	12	14 (1.7)	14	7 (1.2)	7	8 (1.9)	8

E=total number of events; n=number of patients with event; PT=preferred term; SA=standard anti-emetic; SOC=system organ class; TEAE=treatment-emergent adverse event.
a Data presented for SOC totals are for all PTs reported in that SOC.
b Placebo and 5 mg APD421 groups from studies DP10006, DP10014, DP10015, DP10018 and DP10019.
c Placebo and 5 mg APD421 groups from study DP10017.
Source: Table 2.2.1.

Source: SCS page 15 Table 2.7.4-4

Table 68. Treatment-Emergent Adverse Events Occurring in >2.0% of Patients, by Indication

Table 2.7.4-4 Treatment-emergent Adverse Events (Preferred Terms) Occurring in ≥2.0% of Patients in the APD421 5 mg or 10 mg Groups by Indication (Safety Population)

System Organ Class Preferred Term	PONV Prophylaxis[a]		PONV Treatment[b]		
	Placebo +/- SA	APD421 +/- SA 5 mg	Placebo	APD421 5 mg	APD421 10 mg
	N=973	N=967	N=416	N=428	N=418
	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one TEAE	**598 (61.5)**	**539 (55.7)**	**209 (50.2)**	**176 (41.1)**	**178 (42.6)**
Gastrointestinal disorders	**159 (16.3)**	**171 (17.7)**	**100 (24.0)**	**89 (20.8)**	**82 (19.6)**
Nausea[c]	59 (6.1)	62 (6.4)	49 (11.8)	45 (10.5)	45 (10.8)
Flatulence	50 (5.1)	49 (5.1)	39 (9.4)	37 (8.6)	30 (7.2)
Constipation	48 (4.9)	52 (5.4)	33 (7.9)	27 (6.3)	24 (5.7)
Vomiting[c]	26 (2.7)	27 (2.8)	24 (5.8)	16 (3.7)	15 (3.6)
Abdominal distension	14 (1.4)	23 (2.4)	1 (0.2)	2 (0.5)	0
Injury, poisoning and procedural complications	**242 (24.9)**	**242 (25.0)**	**13 (3.1)**	**7 (1.6)**	**8 (1.9)**
Procedural pain	219 (22.5)	213 (22.0)	6 (1.4)	4 (0.9)	2 (0.5)
Anemia postoperative	41 (4.2)	40 (4.1)	3 (0.7)	1 (0.2)	1 (0.2)
Procedural hypotension	17 (1.7)	25 (2.6)	4 (1.0)	2 (0.5)	5 (1.2)
Nervous system disorders	**48 (4.9)**	**45 (4.7)**	**34 (8.2)**	**21 (4.9)**	**24 (5.7)**
Headache	26 (2.7)	24 (2.5)	22 (5.3)	15 (3.5)	15 (3.6)
Dizziness	22 (2.3)	21 (2.2)	14 (3.4)	10 (2.3)	9 (2.2)
Metabolism and nutrition disorders	**73 (7.5)**	**78 (8.1)**	**6 (1.4)**	**4 (0.9)**	**8 (1.9)**
Hyperglycemia	49 (5.0)	41 (4.2)	1 (0.2)	3 (0.7)	2 (0.5)
Hypokalemia	22 (2.3)	33 (3.4)	5 (1.2)	2 (0.5)	6 (1.4)
Hypocalcemia	30 (3.1)	33 (3.4)	0	0	2 (0.5)
Hypoproteinemia	28 (2.9)	28 (2.9)	0	0	0
Blood and lymphatic system disorders	**55 (5.7)**	**58 (6.0)**	**15 (3.6)**	**7 (1.6)**	**6 (1.4)**
Anemia	31 (3.2)	32 (3.3)	7 (1.7)	3 (0.7)	4 (1.0)
Leukocytosis	31 (3.2)	29 (3.0)	8 (1.9)	4 (0.9)	2 (0.5)
General disorders and administration site conditions	**22 (2.3)**	**29 (3.0)**	**24 (5.8)**	**20 (4.7)**	**28 (6.7)**
Chills	21 (2.2)	28 (2.9)	7 (1.7)	4 (0.9)	3 (0.7)
Infusion site pain	2 (0.2)	2 (0.2)	17 (4.1)	16 (3.7)	25 (6.0)
Skin and subcutaneous tissue disorders	**31 (3.2)**	**32 (3.3)**	**15 (3.6)**	**13 (3.0)**	**13 (3.1)**
Pruritus	31 (3.2)	32 (3.3)	15 (3.6)	13 (3.0)	13 (3.1)
Vascular disorders	**40 (4.1)**	**33 (3.4)**	**4 (1.0)**	**3 (0.7)**	**2 (0.5)**
Hypotension	40 (4.1)	33 (3.4)	4 (1.0)	3 (0.7)	2 (0.5)
Investigations	**3 (0.3)**	**27 (2.8)**	**0**	**0**	**0**
Blood prolactin increased	3 (0.3)	27 (2.8)	0	0	0

n=number of patients with event; PONV=post-operative nausea and vomiting; SA=standard anti-emetic.
a Includes studies DP10006, DP10014, DP10015 and DP10017.
b Includes studies DP10018 and DP10019.
c Nausea and vomiting occurring more than 24 hours after the end of surgery (prophylaxis indication) or more than 24 hours after treatment (treatment indication).
Source: Table 2.19, in text Table 6 of the ISS and in text Table 7 of the ISS.

SCS page 14 Table 2.7.4-3

Laboratory Findings

Clinical laboratory evaluations showed a decrease in hemoglobin from within normal range at baseline to below normal range postoperatively in approximately 30% of patients in both the placebo and amisulpride 5 mg treatment groups, with postoperative hemoglobin concentrations below

normal range in a lower proportion (20%) of patients treated with amisulpride 10 mg. Approximately 30% of patients in the placebo, amisulpride 5 mg and 10 mg groups had changes in WBC count from within normal range at baseline to above normal range postoperatively. Few patients had clinically significant changes in platelet counts or WBC counts and there were no consistent trends between the treatment groups at any time point.

There were no clinically important changes in clinical chemistry values between baseline and post-operation. Shifts from within the reference range at baseline to outside the reference ranges postoperatively were recorded for only a small proportion of patients for most parameters, with the exception of calcium, glucose, albumin, and prolactin. Calcium and albumin values decreased from within normal range at baseline to below normal postoperatively, while glucose increased from within normal limits at baseline to above normal postoperatively in patients treated with placebo and amisulpride 5 mg. The most notable change in any parameter was a rise in serum prolactin after amisulpride treatment. Postoperatively, a greater increase in prolactin values was reported for patients receiving amisulpride 5 mg than those receiving placebo in studies DP10014 and DP10015 (mean [SD] change from baseline, 18.03 [12.179] ng/mL versus 4.49 [12.108] ng/mL).

Some changes in laboratory tests would be expected in patients when pre-operative values are compared to post-op values. Drops in hemoglobin, elevations in WBC, and changes in electrolytes (including glucose) can typically be seen in this postoperative clinical setting, in addition to decreases in albumin level (accompanying the NPO status around surgery).

Given the mechanism of action of amisulpride (a D_2 receptor antagonist), it is anticipated that prolactin levels may be increased in the amisulpride treatment group as compared to placebo. However, the changes were short-lived and, therefore, not clinically significant.

Vital Signs

For most vital sign parameters, few patients had clinically significant findings. Similar proportions of patients demonstrated postoperative decreases of systolic blood pressure of ≥20 mmHg in the amisulpride 5 mg without standard anti-emetic (28%), 5 mg with standard anti-emetic (25%), and corresponding placebo groups (placebo without standard anti-emetic, 26%; placebo with standard anti-emetic, 27 %). Similar proportions of patients had postoperative decreases of diastolic blood pressure of ≥15 mmHg in the amisulpride 5 mg without standard anti-emetic (32%), 5 mg with standard anti-emetic (30%), and corresponding placebo groups (placebo without standard anti-emetic, 28%; placebo with standard anti-emetic, 28%). Given the dynamic fluid shifts that can occur during the peri-operative period, plus the multiple medications that are administered, it is not unexpected that blood pressure could be decreased.

Electrocardiograms

There were no notable changes for any ECG parameter measured and there were no notable differences between the amisulpride and placebo groups. Focusing specifically on the QT interval

(ms) and comparing 5 mg amisulpride with placebo[9], there were similar baseline mean values of 396 and similar mean post-operative values of about 280. The mean post-operative change from baseline was also similar, for the 5mg amisulpride group it was -15 (min, max; -136, 188) and for placebo, it was -18 (min, max; 362, 126). [10]

Given the limitations of pooled data and mean values, although the actual ECGs were not available, this reviewer reviewed the detailed ECG reports (including QT intervals) for each individual patient in the dose ranging Study DP10006[11]. For all dose groups [placebo (N=54), 1mg (N=58), 5mg (N= 50), and 20 mg (N=53)], most of the screening ECGs were normal and remained normal throughout the study. For all dose groups, there were also patients who entered the study with clinically insignificant findings[12] on ECG, which either remained unchanged throughout the study or normalized. One patient in each dose group (placebo, 1mg, 5mg, and 20 mg) had some QT prolongation which occurred 1 hour post-operatively, however normalized 24 hours post-operatively in all cases except the 5mg, where a 24 hour post-op ECG result was not reported.

There were no cases of Torsades de pointes.

QT

QT-interval prolongation was studied in a double blind, single IV dose, placebo- and positive-controlled, crossover ("thorough QT") study in 40 healthy, Caucasian and Japanese subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 5.0 (7.1) ms after a 2-minute IV infusion of 5 mg amisulpride and 23.4 (25.5) ms after an 8-minute IV infusion of 40 mg amisulpride. A significant exposure response relationship was identified between amisulpride concentration and ΔΔQTcF. Using this exposure-response relationship, 10 mg amisulpride infused intravenously over 4 min has a maximal predicted (95% upper confidence interval) ΔΔQTcF of 11.2 (12.6) ms.

This was a small study with four treatment groups [amisulpride 5mg (N=39), amisulpride 40 mg (N=39), moxifloxacin 400 mg (N=39), placebo (N=38). There were no deaths, no SAEs, no AEs that led to withdrawal and no severe adverse events. More than 50% of the TEAEs in the amisulpride 40 mg group were infusion-related reactions as compared to 0-5% in the other three groups. In addition, infusion site pain occurred more frequently in the amisulpride 40 mg group 18% vs 0-3% in the other three groups. There were a few mild TEAEs that occurred infrequently but only in the amisulpride 40 mg group: chest discomfort (once), chest pain (once), presyncope (once) and palpations (twice). However, due to the small number of subjects in each treatment group, it is difficult to draw definitive conclusions from this data. But, it is notable to mention given the submission specific safety issues. However, most importantly, the 40 mg dose used for

[9] in studies where ECG data was available

[10] although slightly different mean post- operative ranges (6, 496) for placebo and (280, 536) for amisulpride

[11] no standard anti-emetic was given in combination to amisulpride for prophylaxis

[12] these included for example, sinus bradycardia, right axis deviation, left axis deviation/left anterior hemi-block

this thorough QT study is 4x-8x the dose of amisulpride proposed for prophylaxis/treatment of PONV.

Immunogenicity

Not applicable

8.4.5. Analysis of Submission-Specific Safety Issue

8.4.5.1. QT prolongation

There were seven patients with QT prolongation observed during treatment; five in the 5 mg amisulpride group (two in the placebo group). Of the five events in the amisulpride group, four were mild and occurred anywhere from 2- 29 hours after treatment. These events were noted, but patients received no treatment and no consequences were associated with them. This included one patient with a new first-degree block and prolonged QT who developed these ECG changes 5 hours after treatment but was eventually discharged home with these changes and told to follow-up with her primary care doctor. This patient was in Study 17 and also received prophylaxis with standard of care drug ondansetron. See Table 69 below for further details.

There was only one case of QT prolongation that was classified as "moderate "[13]and was also a serious adverse event. This will be discussed in more detail below in 8.4.5.2 Cardiac Adverse Events and 8.4.5.3 Serious or Severe Cardiac Adverse Events.

Table 69. QT Prolongation Events Reported in Amisulpride Trials

Study	Pt ID	Sex	Treatment	Treatment date/time	Verbatim term	Preferred term	Serious?	Severity	AE onset	Time to onset*	AE end
DP10006	(b) (6)	F	placebo	(b) (6)	QTc-prolongation	Electrocardiogram QT prolonged	N	Moderate	(b) (6)	0d 7h 1m	(b) (6)
DP10017		F	placebo		Prolonged QT	Electrocardiogram QT prolonged	N	Mild		0d 3h 43m	
DP10017		F	5mg		New first degree AV block and prologed QTc compared to baseline.	Electrocardiogram change	N	Mild		0d 5h 28m	
DP10014		F	5mg		CS ECG long-QT	Electrocardiogram QT prolonged	N	Mild		1d 6h 31m	
DP10014		F	5mg		Long QT	Electrocardiogram QT prolonged	N	Mild		0d 3h 36m	
DP10015		M	5mg		Increased QTc 508	Electrocardiogram QT prolonged	N	Mild		0d 2h 41m	
DP10017		F	5mg		Prolonged QT interval	Electrocardiogram QT prolonged	Y	Moderate		0d 19h 18m	

Adapted from Sponsor's Response to IR received January 8, 2018

[13] TEAEs were classified as mild, moderate, severe or life threatening without exact definitions provided, with the exception of renal impairment which was defined by estimated glomerular filtration rate (eGFR). The classification of "moderate" for this TEAE seems reasonable since it persisted; however, its clinical significance was limited as patient was improving and was discharged home.

8.4.5.2. Cardiac Adverse Events

A summary of the frequency of cardiac AEs occurring after study drug administration in amisulpride clinical trials is presented in Table 70, alphabetically by preferred term. Events have been included if they fall into any of the following categories:

- Myocardial infarction[14], cardiac arrest or angina pectoris
- Syncope
- Any cardiac rhythm disturbance or conduction abnormality
- Any ECG abnormality
- Hypokalemia or hypomagnesaemia
- Hypotension, hypertension or other significant circulatory dysfunction, other than specifically procedural
- Cardiovascular disorder or cardiovascular insufficiency.

When an AE occurs very infrequently, it is difficult to draw definitive conclusions from data comparing treatment groups. However, even after combining equivalent preferred terms (e.g., hypokalemia/blood potassium decreased, hypertension/blood pressure increased) and further investigating the sponsor's ambiguous preferred terms. (e.g., cardiovascular disorder, cardiovascular insufficiency) in general, the frequency of cardiac events, overall and for each individual term, appears to be similar for placebo and any dose of amisulpride. Given the very low occurrence of some of the AEs and subsequent very low percentages (0.0 %, 0.1%, 0.2%), it is impossible to make ultimate conclusions regarding these. But, given that very few events occurred in the reasonably large safety population of the amisulpride clinical trials, at this time, the doses proposed demonstrate an acceptable safety profile regarding cardiovascular safety.[15]

[14] See Section 8.4.5.3. Serious or Severe Cardiac Adverse Events

[15] See Section 8.4.5.3. Serious or Severe Cardiac Adverse Events

Table 70. Frequency of Treatment-Emergent Cardiac Adverse Events in Amisulpride Clinical Trials

	Placebo	APD421 1mg	APD421 5mg	APD421 10mg	APD421 20mg	Total
Number of subjects in group	N=1389	N=58	N=1395	N=418	N=53	N=1924
Acute myocardial infarction			1 (0.1%)	1 (0.2%)		2 (0.1%)
Angina pectoris			1 (0.1%)	1 (0.2%)		2 (0.1%)
Atrial fibrillation			2 (0.1%)			2 (0.1%)
Atrial flutter			1 (0.1%)			1 (0.1%)
Atrioventricular block first degree	1 (0.1%)		1 (0.1%)			2 (0.1%)
Atrioventricular block second degree				1 (0.2%)		1 (0.1%)
Blood magnesium decreased				1 (0.2%)		1 (0.1%)
Blood potassium decreased	2 (0.1%)		3 (0.2%)			5 (0.3%)
Blood pressure increased	2 (0.1%)					2 (0.1%)
Bradyarrhythmia			1 (0.1%)			1 (0.1%)
Bradycardia	17 (1.2%)		16 (1.1%)	4 (1.0%)		37 (1.9%)
Cardiac arrest	1 (0.1%)					1 (0.1%)
Cardiovascular disorder	5 (0.4%)		5 (0.4%)	1 (0.2%)		11 (0.6%)
Cardiovascular insufficiency	4 (0.3%)		3 (0.2%)			7 (0.4%)
Circulatory collapse			2 (0.1%)			2 (0.1%)
ECG P wave inverted			1 (0.1%)			1 (0.1%)
ECG signs of ventricular hypertrophy			1 (0.1%)			1 (0.1%)
Electrocardiogram abnormal	1 (0.1%)					1 (0.1%)
Electrocardiogram change	1 (0.1%)		2 (0.1%)			3 (0.2%)
Electrocardiogram PQ interval prolonged	1 (0.1%)					1 (0.1%)
Electrocardiogram PR shortened			1 (0.1%)			1 (0.1%)
Electrocardiogram QT prolonged	2 (0.1%)		4 (0.3%)			6 (0.3%)
Electrocardiogram ST segment depression	1 (0.1%)					1 (0.1%)

From Sponsor Response to IR received February 27, 2018

Table 70. Frequency of Treatment-Emergent Cardiac Adverse Events in Amisulpride Clinical Trials (Cont'd)

	Placebo	APD421 1mg	APD421 5mg	APD421 10mg	APD421 20mg	Total
Number of subjects in group	N=1389	N=58	N=1395	N=418	N=53	N=1924
Electrocardiogram T wave abnormal			1 (0.1%)			1 (0.1%)
Extrasystoles				1 (0.2%)		1 (0.1%)
Haemodynamic instability			1 (0.1%)		1 (1.9%)	2 (0.1%)
Heart rate increased			1 (0.1%)			1 (0.1%)
Heart rate irregular	1 (0.1%)					1 (0.1%)
Hypertension	38 (2.7%)	1 (1.7%)	22 (1.6%)	8 (1.9%)	3 (5.7%)	72 (3.7%)
Hypertensive crisis	3 (0.2%)		4 (0.3%)	1 (0.2%)	1 (1.9%)	9 (0.5%)
Hypokalaemia	27 (1.9%)	2 (3.4%)	39 (2.8%)	6 (1.4%)		74 (3.8%)
Hypomagnesaemia	15 (1.1%)		16 (1.1%)			31 (1.6%)
Hypotension	48 (3.5%)		38 (2.7%)	2 (0.5%)		88 (4.6%)
Malignant hypertension	1 (0.1%)					1 (0.1%)
Nodal rhythm				1 (0.2%)		1 (0.1%)
Palpitations	1 (0.1%)					1 (0.1%)
Sinus bradycardia			1 (0.1%)			1 (0.1%)
Sinus tachycardia	2 (0.1%)		1 (0.1%)			3 (0.2%)
Supraventricular extrasystoles	1 (0.1%)					1 (0.1%)
Supraventricular tachyarrhythmia		1 (1.7%)				1 (0.1%)
Supraventricular tachycardia	1 (0.1%)					1 (0.1%)
Syncope	4 (0.3%)		1 (0.1%)			5 (0.3%)
Tachyarrhythmia	1 (0.1%)		1 (0.1%)	1 (0.2%)		3 (0.2%)
Tachycardia	18 (1.3%)		17 (1.2%)	1 (0.2%)		36 (1.9%)
Tachycardia paroxysmal	1 (0.1%)					1 (0.1%)
Ventricular arrhythmia	1 (0.1%)					1 (0.1%)
Ventricular extrasystoles			1 (0.1%)			1 (0.1%)
Ventricular fibrillation			1 (0.1%)			1 (0.1%)
Totals	**201 (14.5%)**	**4 (6.9%)**	**190 (13.6%)**	**30 (7.2%)**	**5 (9.4%)**	**430 (22.3%)**

8.4.5.3. Serious or Severe Cardiac Adverse Events

All serious or severe cardiac AEs are displayed in Table 71 and the events involving amisulpride are described in more detail below. Some of these cases have been described in previous sections (e.g., QT prolongation, deaths). Every event occurred more than 24 hours after amisulpride treatment, except one acute MI, which occurred after 18 hours and tachycardia which occurred after 17 hours.

One patient ([redacted] (b) (6)) was an 80-year-old female who had open abdominal surgery for suspected ovarian cancer. She had an intra-abdominal hemorrhage and a subsequent reoperation, where she had hypokalemia, tachycardia, and angina. However, these events occurred three and a half days after amisulpride treatment, thus it is doubtful that amisulpride was the cause of them.

There were two patients (amisulpride 10 mg) with events that occurred 3 days (tachyarrhythmia) and 5 days (acute MI) after amisulpride treatment. Once again, given the time course of events, it is unlikely that amisulpride was the cause of these events.

Patient [redacted] (b) (6) was 65 years old female with a past medical history significant for diabetes

mellitus and hypertension. She had an acute myocardial infarction (MI) 18 hours after amisulpride treatment. It is unlikely that amisulpride was the cause of her acute MI.

The last patient (b) (6)) was a 45-year-old female who underwent laparoscopic right salpingo-oophorectomy and was noted to have a prolonged QT interval on ECG 19 hours after amisulpride treatment. The QT prolongation although ongoing, was reportedly resolving, and the patient was discharged home to follow-up with cardiology. Of note, this patient also received prophylaxis with ondansetron and two additional doses of ondansetron doses as treatment (see Table 71 for further details.

Table 71. All Serious or Severe Cardiac Adverse Events

Study	Subject	Study drug	Date/time given	No. in group	Verbatim term	Preferred term	Serious?	Severity	AE start	AE end	Time of onset†	5HT3	Dose/ Route	Start date/ time	Indication
DP10015	(b) (6)	5mg	(b) (6)	176	NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION	ACUTE MYOCARDIAL INFARCTION	Y	SEVERE		(b) (6)	0d 18h 4m	None			
DP10015		placebo		166	SVT	SUPRAVENTRICULAR TACHYCARDIA	Y	SEVERE			0d 20h 56m	ONDANSETRON	4 mg IV	(b) (6)	Treatment (nausea)
												ONDANSETRON	4 mg IV		Treatment (nausea)
												ONDANSETRON	4 mg IV		Treatment (nausea)
												ONDANSETRON	4 mg IV		Treatment (nausea)
DP10017		placebo		575	ASYSTOLIA BASED ON ATRIO-VENTRICULAR BLOCK III	CARDIAC ARREST	Y	SEVERE			0d 21h 45m	ONDANSETRON	4 mg IV		Prophylaxis (combination antiemetic)
DP10017		5mg		572	ANGINA PECTORIS	ANGINA PECTORIS	Y	SEVERE			3d 12h 44m	GRANISETRON	1 mg IV		Treatment
					TACHYCARDIA	TACHYCARDIA	Y	SEVERE			3d 12h 44m	GRANISETRON	1 mg IV		Treatment (vomiting)
DP10017		5mg		572	INTERMITTENT ATRIAL FIBRILLATION	ATRIAL FIBRILLATION	N	SEVERE			1d 5h 10m	ONDANSETRON	4 mg IV		Prophylaxis (combination antiemetic)
					INTERMITTENT ATRIAL FLUTTER	ATRIAL FLUTTER	N	SEVERE			1d 4h 42m	ONDANSETRON	4 mg IV		Treatment (vomiting)
												ONDANSETRON	4 mg IV		Treatment (nausea)
DP10017		5mg		572	TACHYCARDIA	TACHYCARDIA	N	SEVERE			0d 17h 30m	ONDANSETRON	4 mg IV		Prophylaxis (combination antiemetic)
					PULSELESS VENTRICULAR TACHYCARDIA	VENTRICULAR FIBRILLATION	Y	SEVERE			2d 13h 30m	ONDANSETRON	4 mg IV		Treatment (vomiting)
DP10017		5mg		572	PROLONGED QT INTERVAL	ELECTROCARDIOGRAM QT PROLONGED	Y	MODERATE			0d 19h 18m	ONDANSETRON	4 mg IV		Prophylaxis (combination antiemetic)
												ONDANSETRON	4 mg IV		Treatment (nausea)
												ONDANSETRON	4 mg IV		Treatment (nausea)

Study	Subject	Study drug	Date/time given	No. in group	Verbatim term	Preferred term	Serious?	Severity	AE start	AE end	Time of onset†	5HT3	Dose/ Route	Start date/ time	Indication
DP10018	(b) (6)	10mg	(b) (6)	188	POSTOPERATIVE TACHYARRHYTMIA	TACHYARRHYTHMIA	Y	SEVERE		(b) (6)	3d	None			
DP10019		10mg		230	NON-ST ELEVATED MYOCARDIAL INFARCTION	ACUTE MYOCARDIAL INFARCTION	Y	SEVERE			5d	ONDANSETRON	4 mg IV	(b) (6)	Prophylaxis
												ONDANSETRON	4 mg IV		Treatment
												ONDANSETRON	4 mg IV		Secondary prophylaxis

From Sponsor Response to IR received February 27, 2018

8.4.5.4. Extrapyramidal Symptoms (EPS)

The Standardised **MedDRA** Query (**SMQ**) "Extrapyramidal syndrome" comprises four SMQs: akathisia, dyskinesia, dystonia, and Parkinson-like events. Each SMQ includes many PTs that

could possibly be attributed to an extrapyramidal syndrome, as described in the list below.

Akathisia (SMQ): Akathisia; Extrapyramidal disorder; Hyperkinesia; Hyperkinesia neonatal; Motor dysfunction; Movement disorder; Psychomotor hyperactivity; Restlessness **Dyskinesia (SMQ)**: Athetosis; Ballismus; Buccoglossal syndrome; Chorea; Choreoathetosis; Dopamine dysregulation syndrome; Dyskinesia; Dyskinesia neonatal; Dyskinesia oesophageal; Grimacing; Oculogyric crisis; Pharyngeal dyskinesia; Protrusion tongue; Rabbit syndrome; Respiratory dyskinesia; Tardive dyskinesia; Abnormal involuntary movement scale; Chronic tic disorder; Complex tic; Drooling; Extrapyramidal disorder; Motor dysfunction; Movement disorder; Muscle twitching; Provisional tic disorder; Secondary tic; Tic

Dystonia (SMQ): Dopa-responsive dystonia; Dystonia; Dystonic tremor; Early onset primary dystonia; Emprosthotonus; Meige's syndrome; Oculogyric crisis; Opisthotonus; Oromandibular dystonia; Pleurothotonus; Spasmodic dysphonia; Torticollis; Trismus; Writer's cramp; Blepharospasm; Chronic tic disorder; Complex tic; Drooling; Extrapyramidal disorder; Facial spasm; Gait inability; Laryngospasm; Motor dysfunction; Movement disorder; Muscle contractions involuntary; Muscle spasms; Muscle spasticity; Muscle tightness; Muscle tone disorder; Muscle twitching; Musculoskeletal stiffness; Oesophageal spasm; Oropharyngeal spasm; Posture abnormal; Posturing; Provisional tic disorder; Risus sardonicus; Secondary tic; Tic; Tongue spasm; Torticollis psychogenic; Uvular spasm

Parkinson-like events (SMQ): Akinesia; Bradykinesia; Cogwheel rigidity; Freezing phenomenon; Hypertonia; Hypertonia neonatal; Muscle rigidity; On and off phenomenon; Parkinson's disease; Parkinson's disease psychosis; Parkinsonian crisis; Parkinsonian gait; Parkinsonian rest tremor; Parkinsonism; Parkinsonism hyperpyrexia syndrome; Resting tremor; Action tremor; Bradyphrenia; Drooling; Dysphonia; Extrapyramidal disorder; Fine motor skill dysfunction; Gait disturbance; Hypokinesia; Hypokinesia neonatal; Laryngeal tremor; Micrographia; Mobility decreased; Motor dysfunction; Movement disorder; Muscle tone disorder; Musculoskeletal stiffness; Postural reflex impairment; Postural tremor; Reduced facial expression; Tremor; Tremor neonatal; Walking disability

Of these PTs, eight have been reported in the amisulpride clinical trial program: restlessness, laryngospasm, muscle spasms, muscle spasticity, muscle tightness, hypertonia, dysphonia, and tremor. Although, a vast list of potential EPS symptoms, the frequency of possible EPS appears to be similar for placebo and any dose of amisulpride. See Table 72 below.

Table 72. Possible Extra-Pyramidal Symptoms Reported in Amisulpride Trials

Study	Pt ID	Sex	Treatment	Treatment date/time	Verbatim term	Preferred term	Serious?	Severity	AE onset	Time to onset*	AE end
DP10018	(b) (6)	F	placebo	(b) (6)	Hoarseness	Dysphonia	N	Mild	(b) (6)	2d	(b) (6)
DP10006		M	placebo		Cramps painful	Muscle spasms	N	Mild		0d 21h 26m	
DP10014		F	placebo		Cramps	Muscle spasms	N	Mild		0d 14h 33m	
DP10015		F	placebo		Muscle spasms	Muscle spasms	N	Mild		1d 11h 0m	
DP10015		F	placebo		Muscle spasms	Muscle spasms	N	Mild		1d 5h 22m	
DP10015		F	placebo		Muscle spasms	Muscle spasms	N	Mild		0d 20h 38m	
DP10017		F	placebo		Muscle cramps	Muscle spasms	N	Mild		0d 19h 41m	
DP10017		F	placebo		Muscle spasms	Muscle spasms	N	Moderate		2d 1h 0m	
DP10019		F	placebo		Muscle spasm	Muscle spasms	N	Moderate		2d	
DP10014		F	placebo		Restlessness	Restlessness	N	Mild		1d	
DP10017		F	placebo		Severe restlessness	Restlessness	N	Moderate		3d	
DP10018		F	placebo		Restlessness	Restlessness	N	Moderate		3d	
DP10019		F	placebo		Leg tremor	Tremor	N	Mild		1d	
DP10006		F	1mg		Hypertony	Hypertonia	N	Mild		2d 5h 34m	
DP10006		F	1mg		Laryngospasm	Laryngospasm	N	Mild		0d 1h 17m	
DP10006		F	1mg		Muscular tremor	Tremor	N	Mild		1d	
DP10015		M	5mg		Muscle spasms	Muscle spasms	N	Mild		0d 10h 20m	
DP10017		F	5mg		Muscle spasms	Muscle spasms	N	Moderate		1d 1h 58m	
DP10017		F	5mg		Right calf cramping	Muscle spasms	N	Mild		0d 14h 50m	
DP10014		F	5mg		Muscular tension	Muscle tightness	N	Moderate		3d 3h 53m	
DP10019		F	5mg		Muscle tension, right side of the body	Muscle tightness	N	Mild		1d	
DP10006		F	5mg		Restlessness	Restlessness	N	Mild		3d	
DP10014		F	5mg		Restlessness	Restlessness	N	Mild		5d	
DP10018		M	10mg		Trunk spasticity	Muscle spasticity	N	Moderate		4d	
DP10018		F	10mg		Restlessness	Restlessness	N	Mild		3d	
DP10019		M	10mg		Tremor	Tremor	N	Mild		1d	
DP10006		F	20mg		Dysphonia	Dysphonia	N	Mild		1d	

Neuroleptic Malignant Syndrome

There were no events of neuroleptic malignant syndrome identified in this amisulpride clinical development program.

Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable

8.4.6. Safety Analyses by Demographic Subgroups

Individual trials were not adequately powered to reach conclusions regarding the safety among demographic subgroups (e.g., sex, race, age, other); although pooled analyses, where appropriate, may have greater power, interpretations about the subgroup data should be made with caution.

Sex

An overall summary of TEAEs is provided by sex for the amisulpride 5 mg without standard anti-emetic, 5 mg with standard anti-emetic and 10-mg dose groups and respective placebo groups in Table 73. The much smaller sample size of males in the treatment groups (in particular, the amisulpride 5 mg with standard anti-emetic and placebo with standard anti-emetic) should be taken into account when making comparisons between sexes. Across all treatment groups (including placebo), TEAEs (all causality and treatment-related) were generally more frequently reported in female patients than male patients.

However, differences in the frequencies of TEAEs between the sexes were notable in just a few SOCs. TEAEs in the *Gastrointestinal disorders* were more frequently reported in female patients than male patients in the amisulpride 5 mg without standard anti-emetic (181/668 patients [27.1%] versus 26/155 patients [16.8%]) and amisulpride 5 mg with standard anti-emetic groups (82/552 patients [14.9%] versus 1/20 patient [5.0%]).

TEAEs in *Injury, poisoning, and procedural complications* were more frequently reported in female patients compared to male patients in the placebo with standard anti-emetic (93/557 patients [16.7%] versus 1/18 patient [5.6%]) and amisulpride 5 mg with standard anti-emetic (87/552 [15.8%] versus 0 patients) groups.

Serious TEAEs and TEAEs of life-threatening intensity were infrequent in both sex subgroups, across treatment groups. Related TEAEs and serious TEAEs in all SOCs were reported at a similar frequency in both sex subgroups across all treatment groups.

Table 73. Overview of Treatment-Emergent Adverse Events by Sex by Treatment (Safety Population)

	Placebo – SA[a]				Placebo + SA[b]				APD421 5 mg – SA[a]				APD421 5 mg + SA[b]				APD421 10 mg			
	Male N=155		Female N=659		Male N=18		Female N=557		Male N=155		Female N=668		Male N=20		Female N=552		Male N=65		Female N=353	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
TEAE	84 (54.2)	288	413 (62.7)	1190	4 (22.2)	7	276 (49.6)	629	72 (46.5)	273	384 (57.5)	1144	4 (20.0)	5	232 (42.0)	574	19 (29.2)	32	159 (45.0)	343
TEAE related to study medication[c]	18 (11.6)	32	71 (10.8)	87	2 (11.1)	3	22 (3.9)	26	15 (9.7)	28	65 (9.7)	85	0	0	22 (4.0)	29	5 (7.7)	5	38 (10.8)	42
TEAE of life threatening intensity	0	0	1 (0.2)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Serious TEAE	4 (2.6)	7	17 (2.6)	21	0	0	18 (3.2)	29	5 (3.2)	5	15 (2.2)	18	0	0	20 (3.6)	29	1 (1.5)	1	6 (1.7)	8
TEAE leading to study withdrawal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.2)	1	0	0	0	0
TEAE leading to death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.2)	8	0	0	0	0

E=total number of events; n=number of patients with event; SA=standard anti-emetic; TEAE=treatment-emergent adverse event.
a Placebo and 5 mg APD421 groups from studies DP10006, DP10014, DP10015, DP10018 and DP10019.
b Placebo and 5 mg APD421 groups from study DP10017.
c TEAE was related to study medication if study drug relationship was either probable, possible or missing.
Source: Table 2.1.1.3 and Table 2.1.1.4.

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Co-Administered Anti-Emetic

An overall summary of TEAEs is provided by the subgroups of co-administered anti-emetic and no co-administered anti-emetic for the amisulpride 5-mg without standard anti-emetic, 5-mg with standard anti-emetic and 10-mg dose groups and respective placebo groups in Table 74.

In the amisulpride 5 mg treatment group, the incidence of TEAEs was higher in the subgroup of patients that did not receive standard anti-emetic compared to the subgroup of patients that was co-administered anti-emetic (TEAEs, 55.4% versus 41.3%). This difference could represent that the co-administration of amisulpride with ondansetron or corticosteroid did not lead to more AEs, which is an important factor since in many high- risk patients, several anti-emetics are used concomitantly. However, as above, this subgroup analysis was not adequately powered to

provide formal conclusions regarding safety.

The incidence of TEAEs related to study medication was comparable between both subgroups in patients treated with placebo and amisulpride 5 mg. Serious TEAEs and TEAEs of life-threatening intensity were infrequent in both subgroups, across treatment groups. Related TEAEs and serious TEAEs in all SOCs were reported at a similar frequency in both subgroups across all treatment groups.

Table 74. Overview of Treatment-Emergent Adverse Events by Co-Administered Anti-Emetic by Treatment (Safety Population)

	Co-administered Anti-emetic Study DP10017				No Co-administered Anti-emetic Studies DP10006, DP10014, DP10015, DP10018 and DP10019					
	Placebo + SA N=575		APD421 5 mg + SA N=572		Placebo N=814		APD421 5 mg N=823		APD421 10 mg N=418	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
TEAE	280 (48.7)	636	236 (41.3)	579	497 (61.1)	1478	456 (55.4)	1417	178 (42.6)	375
TEAE related to study medication[a]	24 (4.2)	29	22 (3.8)	29	89 (10.9)	119	80 (9.7)	113	43 (10.3)	47
TEAE of life threatening intensity	0	0	0	0	1 (0.1)	1	0	0	0	0
Serious TEAE	18 (3.1)	29	20 (3.5)	29	21 (2.6)	28	20 (2.4)	23	7 (1.7)	9
TEAE leading to study withdrawal	0	0	1 (0.2)	1	0	0	0	0	0	0
TEAE leading to death	0	0	1 (0.2)	8	0	0	0	0	0	0

E=total number of events; n=number of patients with event; SA=standard anti-emetic; TEAE=treatment-emergent adverse event.
a TEAE was related to study medication if study drug relationship was either probable, possible or missing.
Source: Table 2.1.1.7 and Table 2.1.1.8.

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8.4.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable

Human Reproduction and Pregnancy

Amisulpride has not been studied in pregnant or lactating patients. Women who were pregnant or breast-feeding were excluded from the development program and women of childbearing potential were obliged to use adequate contraception. Only one case of pregnancy was documented in the amisulpride -treated groups during the clinical development program; no adverse fetal outcome was reported.

Pediatrics and Assessment of Effects on Growth

The applicant has not conducted an evaluation of the safety and efficacy of amisulpride in the pediatric population. Because the proposed product is a new molecular entity, approval of amisulpride for the prevention/treatment of PONV triggers the PREA (21 U.S.C. 355c). Per the Food and Drug Administration Safety and Innovation Act (FDASIA), the applicant submitted an initial Pediatric Study Plan (iPSP).

The Division discussed the Agreed iPSP with the Pediatric Review Committee (PeRC) on August 29, 2018. The Division conveyed their agreement with the proposed pediatric development
program in the Agreed iPSP. PeRC concurred with the Division but recommended that the applicant modify the timeline for submissions as follows:

- Pharmtox study completed: 1Q 2019
- Clinical protocol submission (both): January 2019
- Study completion: March 2022
- Final study report submission: October 2022 (due to the delay in the submission of this NDA).

Refer to Section 10 for further details on pediatrics.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no evidence of abuse potential for amisulpride reported in the literature, despite widespread, chronic use at high doses in psychiatric practice for more than 30 years.

Thus, Controlled Substances Staff recommends that (1) the drug label for the amisulpride product should not include Section 9 Abuse and Dependence; (2) amisulpride should not be recommended for scheduling under the Controlled Substances Act.

Amisulpride is administered under medical supervision from a vial that contains only a 5 mg quantity of amisulpride, thus, the risk of either deliberate or inadvertent overdose is negligible. The primary adverse consequence of amisulpride overdose is likely to be QT prolongation and a risk of torsades de pointes (TdP). According to QT-IRT review by Christine Garnett, Pharm.D. dated June 15, 2018:

“The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 5.0 (7.1) ms after a 2-minute intravenous infusion of 5 mg BARHEMSYS and 23.4 (25.5) ms after an 8-minute intravenous infusion of 40 mg BARHEMSYS.”

TdP has been reported in the literature in the context of very large oral doses of amisulpride, generally in excess of 3 g to 4 g. In the event of overdose, ECG monitoring and immediate access to cardiac resuscitation equipment is warranted.

8.4.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Post-marketing surveillance (PMS) data for oral amisulpride were obtained from the European Medicines Agency’s Eudravigilance database of adverse drug reaction reports from 2003 to 2017. Table 75 and Table 76 list the most common post marketing AEs.The most common AEs reported are those that would be expected with a dopamine antagonist. In addition, given the known risk of QT prolongation, it is not surprising that QT prolongation was seen, as well as the

subsequent clinical occurrences that could occur with doses exceeding the recommended daily oral dose.

In contrast, intravenous (IV) amisulpride is proposed as a single dose, for inpatient treatment. The proposed labeling adequately communicates the potential risks regarding QT prolongation. In addition, IV amisulpride will only be administered in the operating room and/or post-anesthesia care unit (PACU). Patients will be uniquely located in the hospital's most acute care setting wherein they will receive intensive monitoring. Thus, it is unlikely that many of the reactions which are typically seen with chronic oral use will occur.

Table 75. Adverse Events in EMA Postmarketing Safety Database 2003 to 2017

	Dose of oral amisulpride (mg)				
	≤ 200	201-1200	>1200	Unknown	Total
Neuroleptic malignant syndrome	65	118	1	82	266
Hyperprolactinaemia	67	127		67	261
Galactorrhoea	69	124		51	244
Electrocardiogram QT prolonged	36	78	42	83	239
Extrapyramidal disorder	56	105	7	70	238
Weight increased	52	72		73	197
Tremor	54	80	2	53	189
Blood prolactin increased	62	67		49	178
Dyskinesia	41	72		63	176
Blood creatine phosphokinase increased	44	81	1	48	174
Akathisia	56	83		34	173
Amenorrhoea	57	66		41	164
Dystonia	26	71	2	56	155
Parkinsonism	44	61	1	43	149
Tardive dyskinesia	34	56		57	147
Tachycardia	22	42	16	47	127
Drug ineffective	37	35		47	119
Anxiety	29	44	3	41	117
Intentional overdose	8	12	37	56	113
Psychotic disorder	28	43		38	109
Suicide attempt	15	12	27	55	109
Pyrexia	22	40	1	45	108
Somnolence	22	32	11	41	106
Drug interaction	23	41	4	36	104
Agitation	23	34	3	36	96

From Sponsor Response to IR dated January 8, 2018

Table 76. Adverse Events in EMA Postmarketing Safety Database 2003 to 2017 (cont'd)

Disorientation	7	10		22	39
Sleep disorder	8	19		12	39
Cardiac arrest	8	17	4	8	37
Death	8	14	1	14	37
Off label use	3	16		17	36
C-reactive protein increased	4	11	2	18	35
Diarrhoea	4	5		26	35
Pulmonary embolism	10	15		10	35
Syncope	15	11		9	35
Gynaecomastia	11	15		8	34
Mental impairment	6	12		16	34
Parkinson's disease	5	18		11	34
Torticollis	10	19		5	34
Muscle spasms	11	13		9	33
Sinus tachycardia	7	13	3	10	33
Chills	8	19		5	32
Decreased appetite	12	9		11	32
Deep vein thrombosis	10	7		15	32
Diabetes mellitus	11	11		10	32
Dysarthria	5	15		12	32
Neutrophil count increased	10	5		17	32
Thrombocytopenia	6	14		12	32
Weight decreased	10	11		11	32
Abnormal behaviour	12	13		6	31
Gamma-glutamyltransferase increased	9	6		16	31
Loss of consciousness	11	6	3	11	31
Pituitary tumour benign	9	18		4	31
Trismus	7	11		13	31
Lower respiratory tract infection	14	8		8	30
Mania	7	3		20	30
Ventricular fibrillation	8	5	11	6	30
Aggression	6	7	1	15	29
Arrhythmia	4	9		16	29
Completed suicide	2	17		10	29
Leukocytosis	6	13		10	29
Liver function test abnormal	16	6		7	29
Agranulocytosis	5	11		12	28
Breast discomfort	4	23		1	28
Oedema peripheral	8	16		4	28
Pain in extremity	14	5		9	28
Ventricular extrasystoles	9	11		8	28
Akinesia	10	12		5	27
Haemoglobin decreased	8	12	2	5	27
Hallucination	3	13		11	27
Obsessive-compulsive disorder	9	18			27
Paranoia	13	6		8	27
Torsade de pointes	4	1	15	7	27
Vision blurred	5	12	4	6	27
Withdrawal syndrome	17	3		7	27

From Sponsor Response to IR dated January 8, 2018

Expectations on Safety in the Postmarket Setting

The Eudravigilance database included 2,765 patients with adverse reactions for which amisulpride was the suspected drug. Of these, 165 have interpretable cumulative dose information; 24 of these have one or more cardiac events reported. The cumulative dose data are summarized in Table 77. According to these data, cumulative doses of oral amisulpride associated with cardiac events appear to be very large, generally above 1,000 mg and in many cases above 10,000 mg. For the indications of prevention/treatment of PONV, **a single dose is**

proposed. As long as inpatient practitioners follow the label correctly, it is not anticipated that amisulpride will be the cause of cardiac adverse events.

Table 77. Summary of Suspected Amisulpride Cardiac Adverse Reactions in Postmarketing Data

Preferred Term	Number of Patients	Mean Cumulative Dose to Start of Reaction (mg)	Range
Angina pectoris	1	1,000	
Atrial fibrillation	1	18,600	
Atrioventricular block (complete)	1	73,200	
Atrioventricular block first degree	1	5,550	
Blood pressure fluctuation	1	2,400	
Bradyarrhythmia	1	73,200	
Bradycardia	1	1,200	
Cardiac arrest	1	7,200	
Cardiac discomfort	1	300	
Cardiovascular disorder	2	16,050	100 to 32,000
Cardiovascular insufficiency	1	73,200	
Cardioversion	1	73,200	
Chest pain	1	7,200	
Circulatory collapse	2	508,600	800 to 1,016,400
Conduction disorder	2	3,025	500 to 5,550
Cytotoxic cardiomyopathy	1	73,200	
Electrocardiogram PQ interval prolonged	1	5,550	
Electrocardiogram QT interval abnormal	1	3,100	
Electrocardiogram QT prolonged	5	47,210	200 to 101,850
Hypotension	3	11,033	500 to 32,000
Long QT syndrome	3	5,133	800 to 13,400
Pulse absent	1	94,800	
Sinus tachycardia	1	200	
Sudden death	2	1,300	800 to 1,800
Syncope	4	10,944	3,100 to 18,150
Tachycardia	1	500	
Torsade de pointes	1	32,000	
Ventricular fibrillation	1	13,400	
Ventricular parasystole	1	25,200	
Ventricular tachycardia	2	63,400	32,000 to 94,800

SCS page 28 Table 2.7.4-6

SUMMARY AND CONCLUSIONS

8.5. Statistical Issues

There were no major statistical issues affecting the overall conclusions regarding the treatment efficacy. There was an issue with regards to multiplicity adjustment in study DP10018, which does not affect the overall conclusion. In study DP10018, the multiplicity plan in the protocol differed from the multiple testing approach used in the clinical study report.

Based on the pre-specifed multiple comparison using Bonferroni adjustment, neither one of the amisulpride arms reach the pre-specifed 2-sided statistically significant level of 0.025. On the other hand, the reported p-values of 0.03 are close to the pre-specifed level. In addition, more thoughtful multiple comparison procedures, including the ad hoc Hommel procedure used by the sponsor in the clincal study report, would have allowed a claim of statistically significant treatment difference between each of the two doses and the placebo.

8.6. Conclusions and Recommendations

In general, our results were in agreement with those of the applicant's. All analyses were performed on the ITT population which was defined as "all patients who had signed informed consent form, were randomized and were treated with either amisulpride or placebo."

The totality of data in the amisulpride clinical development program demonstrated statistically significant efficacy for both the prevention of PONV (5 mg) and the treatment of PONV (10 mg). The data show an acceptable safety profile with appropriate labeling recommendations in place to mitigate the potential for dose-dependent QT prolongation (including specific instructions regarding concomitant ondansetron administration). As such, from a clinical perspective, we find the risk/benefit profile of amisulpride for the proposed indications to be acceptable.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was convened for this application.

10. Pediatrics

See under the Postmarketing Requirements and Commitment section for the Pediatric Research Equity Act (PREA) requirements.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted the proposed proprietary name, BARHEMSYS, which was found to be acceptable by Division of Medication Error Prevention and Analysis (DMEPA). Although a labeling review is deferred due to the Complete Response action recommended for this review, the following are preliminary recommendations:

Table 78. Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling
8.1 (continued below)	Reproduction studies have been performed with oral amisulpride doses up to 250 mg/kg per day in pregnant rabbits and 300 mg/kg per day in pregnant rats (an exposure equivalent to approximately 145 and 242 times, respectively, greater than that delivered by the highest recommended human intravenous dose of 10 mg, based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus. [**2.6.6.6**] There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BARHEMSYS should only be used during pregnancy where the benefits clearly outweigh the risks.	Available data with amisulpride use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, there were no adverse developmental effects observed with oral administration exposures about 43 and 645 times, respectively, the exposure delivered by the highest recommended human dose *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.1 (continued)		Animal Data Reproduction studies of amisulpride were conducted in pregnant rats administered oral doses up to 160 mg/kg per day (43 times the exposure based on area under the cure (AUC) at the highest recommended dose of 10 mg) throughout the period of organogenesis. No adverse embryo-fetal developmental effects were observed at any dose level. Maternal animals exhibited a dose-related decrease in overall mean body weight gain. In rabbits administered amisulpride throughout the period of organogenesis, oral doses up to 210 mg/kg/day (645 times the exposure based on AUC at the highest recommended dose of 10 mg) had no adverse developmental effects on the fetus. Maternal animals exhibited reduced mean body weight gain at doses of 100 and 210 mg/kg/day and reduced food intake was observed at 210 mg/kg/day. The prenatal and postnatal developmental effects of amisulpride were assessed in rats administered oral doses of 60, 100, or 160 mg/kg/day during the periods of organogenesis and lactation. At 160 mg/kg/day (43 times the exposure based on AUC at the highest recommended dose of 10 mg), maternal animals exhibited a reduction in mean body weight gain and decrease in food intake during lactation. Amisulpride had no effect on maternal pregnancy parameters, litter survival or pup growth, development or maturation at any dose tested.
8.3	Amisulpride is excreted in breast milk. Caution should therefore be exercised when BARHEMSYS is administered to a nursing woman. [**2.7.4.5.4**]	Infertility In animal fertility studies, administration of repeated doses of amisulpride over a 10-day period to female rats resulted in infertility that was reversible *[see Nonclinical Toxicology (13.1)].*

12.1	Amisulpride is a potent and selective dopamine D_2/D_3 receptor antagonist. It has no appreciable affinity for any other receptor types apart from 5-HT_{2B} and 5-HT_7 receptors. [2.7.2]	Amisulpride is a dopamine-2 (D_2) receptor antagonist. Dopamine D_2 receptors are located in the chemoreceptor trigger zone (CTZ) and respond to the dopamine released from the nerve endings. Activation of CTZ relays stimuli to the vomiting center which is involved in emesis. Studies conducted in ferrets have shown that amisulpride inhibits emesis caused by apomorphine, with an estimated ED_{50} of <1 µg/kg, subcutaneously; and inhibits cisplatin-induced emesis at 2 mg/kg and morphine-induced emesis at 3 to 6 mg/kg, when given intravenously. Amisulpride also has an affinity for dopamine D_3 receptors and has no appreciable affinity for any other receptor types apart from low affinities for 5-HT_{2B} and 5-HT_7 receptors.
13.1	In vitro testing indicates that amisulpride does not have carcinogenic or mutagenic potential. Oral administration of amisulpride up to 300 mg/kg per day in rats and 250 mg/kg per day in rabbits (equivalent to approximately 145 and 242 times the highest recommended human intravenous dose, respectively, based on body surface area) did not significantly affect fertility or general reproductive performance of male and female animals. [2.6.6]	Long-term studies to assess the carcinogenic potential of amisulpride have not been conducted. Amisulpride was not genotoxic in the bacterial reverse mutation assay, the in vitro human peripheral blood lymphocytes assay, and the in vivo rat bone marrow micronucleus assay. The effect of amisulpride on fertility was studied in rats at oral doses up to 160 mg/kg/day (43 times the exposure based on AUC at the highest recommended dose of 10 mg). Most female animals (90 to 95%) at each dose level remained in diestrus and failed to mate. However, this effect on mating reversed following cessation of treatment. No treatment-related effects were observed on uterine/implantation parameters or sperm counts, sperm motility or sperm morphology.

The QT prolongation risk can be mitigated via labeling and appropriate monitoring during drug administration. To mitigate the risk of QT prolongation, we recommended the following labeling language:

- In each of the Sections 2 (Dosage and Administration), 5 (Warnings and Precautions), and 7 (Drug Interactions), a statement should be included that if the 10mg dose of amisulpride is used in combination with ondansetron for the treatment of PONV, amisulpride 10 mg should be administered at least 30 minutes before or 10 minutes after the end of the ondansetron infusion.
- In Section 5 (Warnings and Precautions), a statement should be included that use of amisulpride should be avoided in patients with congenital long QT syndrome and in patients taking droperidol.
- In Section 5 (Warnings and Precautions), a statement should be included that ECG

monitoring is recommended in patients with pre-existing arrhythmias/cardiac conduction disorders; electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia); congestive heart failure; and in patients taking other medicinal products or with other medical conditions known to prolong the QT interval.

- In Section 8.6 (Use in Specific Populations – Renal Impairment), a statement should be included that amisulpride use should be avoided in patients with severe renal impairment.

12. Risk Evaluation and Mitigation Strategies

A REMS is not necessary for amisulpride to ensure the benefits outweigh the risks.

Adequate management of PONV is important to ensure patient recovery and prevent potential complications of surgery. While multiple treatment options are available, amisulpride can offer an additional option for patients whose PONV is not adequately managed by available therapies.

Based on the results from trials DP10015, DP10017, DP10018, and DP10019, amisulpride demonstrated efficacy and safety based on complete response of PONV versus patients treated with placebo.

An increased risk of QT prolongation exists with the 10-mg dose of amisulpride for the treatment of PONV. The proposed labeling includes the risk of QT prolongation in the Warnings and Precautions (Section 5), as well as considerations for use with other drugs that prolong the QT interval in the Drug Interactions (Section 7.2). Currently, the proposed label advises that caution should be exercised when amisulpride is prescribed to patients with increased intrinsic risk of arrhythmias (e.g., (b) (4) other pre-existing arrhythmias and cardiac conduction disorders or electrolyte abnormalities such as hypokalaemia or hypomagnesemia); and when other drugs known to prolong the QT interval significantly, are co-administered. Ondansetron is used for the same indication and in the same setting, with a similar risk of QT prolongation, which is currently communicated via labeling. This risk can be managed in the perioperative and postoperative setting for which its use is intended and is a risk which is known and already managed, since it is a potential risk with currently approved therapies. Patients in this setting are under close monitoring by various healthcare providers, including the anesthesiologist, and nursing staff.

DRISK agrees that the AE profile of the drug does not warrant risk mitigation beyond labeling. Based on the currently available data, we concur that a REMS is not necessary to ensure the benefits of amisulpride outweigh the risks.

13. Postmarketing Requirements and Commitment

The discussion of postmarketing requirements and commitments is deferred because an approval action cannot be taken until the sponsor satisfactorily resolves deficiencies observed during the inspection of the manufacturing facility for this application. However, the following studies will be required:

- A pharmacokinetic study following a single dose of amisulpride in patients with severe renal impairment and end-stage renal disease (i.e., eGFR < 30 mL/min/1.73 m^2) and healthy subjects as a control group.
    - The effects of severe renal impairment on PK were not adequately characterized. PK data for amisulpride in severe renal impairment were only available in one patient (eGFR 8.2 mL/min/1.73 m2), whose AUC_{inf} was 2.1-fold higher than that observed in patients with normal renal function. Because of this limited information, the dosing for patients with severe renal impairment cannot be supported by PK data and use of amisulpride will not be recommended in patients with severe renal impairment.

- Studies required under PREA:
    - Confirmatory repeat dose intravenous toxicity study in juvenile rats.
    - Randomized, double-blind, placebo-controlled, dose-ranging study of intravenous amisulpride injection as prophylaxis for postoperative nausea and vomiting in children aged 0 to 17 years.
    - Randomized, double-blind, active-controlled, dose-ranging study of intravenous amisulpride injection as treatment of children aged 0 to 17 years with postoperative nausea and vomiting.

14. Division Director (Clinical)

I concur with the recommendation for a Complete Response formulated by the Office of Product Quality (OPQ) given the deficiencies identified at the (b) (4) manufacturing.

15. Office Director (or Designated Signatory Authority)

I concur with the recommendations of the Division of Gastroenterology and Inborn Errors Products (DGIEP) and the Office of Product Quality (OPQ) to issue a Complete Response Letter for NDA 209510 (Barhemsys – amisulpride injection for intravenous use). Barhemsys (amisulpride injection), a dopamine D_2 / D_3 receptor antagonist, is a New Molecular Entity (NME) proposed for the prevention and treatment of postoperative nausea and vomiting in adults.

As discussed in detail in this review, the benefits of Barhemsys (amisulpride injection) outweigh the risks for the indications sought. However, the pre-approval inspection of the drug substance manufacturing facility (b) (4) found significant risks to the manufacturing process or final product. Therefore, the facility was determined to be unacceptable to support the approval of NDA 209510. Since the Applicant does not have an alternative drug substance manufacturing facility for this NDA, an approval action of this application cannot be taken until the Applicant satisfactorily resolves the deficiencies observed during the inspection of the drug substance manufacturing facility.

16. Appendices

16.1. References

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16.2. Financial Disclosure

In compliance with 21 CFR Part 54, the applicant provided Certification/Disclosure Forms from clinical investigators who participated in covered clinical studies for amisulpride. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).
The covered clinical studies as defined in 21 CFR 54.2(e) were Trial DP10006, Trial DP10014, Trial DP10015, Trial DP10017, Trial DP10018, and Trial DP10019 which provided the primary data to establish effectiveness and safety of this product.[16]

Was a list of clinical investigators provided:	**Yes ☒**	**No ☐ (Request list from Applicant)**
Total number of investigators identified: __103___		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

OCP Appendices (Technical Documents Supporting OCP Recommendations)

[16] Trial DP10006 and Trial DP10014 were primarily used as supportive for safety

16.2.1. Individual Clinical Pharmacology Study Review

16.2.1.1. Study DP10020: An open label, single dose, single period study to assess the mass balance recovery, metabolite profile and metabolite identification of [14C]-amisulpride administered via the intravenous route to healthy male subjects (A mass balance study)

DP10020 was an open-label investigation of the metabolism and elimination of ^{14}C-radiolabelled amisulpride in six healthy, adult, male subjects. A single IV 10-mg dose of [^{14}C]-amisulpride, containing 1.784 MBq of radioactivity, was infused over 4 minutes. Blood samples were collected at pre-dose, and 4, 8, 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96 hours after dose. Cumulative urine samples were collected for the following intervals: pre-dose, 0 to 12 h, 12 to 24 h, and then daily until 168 h post-dose. Cumulative feces samples were collected at pre-dose and then daily until 168 h post-dose.

As a result, more than 96% of the radioactivity was recovered in urine and feces within 144 hours after dosing, indicating no significant retention of amisulpride in the body. Elimination was predominantly in urine (73.6% of dose) and to a lesser extent in feces (22.8% of dose) (Table 79). Elimination was biphasic, primarily urinary phase over the first 12 to 24 hours, followed by a slower phase mainly in feces, almost completely by 96 hours.

Table 79. Cumulative Total Radioactivity Excretion Over Time After Single Intravenous 10-mg Dose of [^{14}C]-Amisulpride

Mean cumulative TR (%)	Collection interval (h)							
	0-12	**12-24**	**24-48**	**48-72**	**72-96**	**96-120**	**120-144**	**144-168**
Urine	62.8	69.2	72.5	73.2	73.4	73.5	73.6	73.6
Faeces	2.8		13.2	20	21.9	22.6	22.8	22.8
Total	65.6	72	85.6	93.2	95.3	96.2	96.4	96.4

TR = total radioactivity

Source: Study DP10020 study report, Tables 10

Renal clearance of amisulpride was not specifically calculated in our PK studies. However, in response to the information request dated 4/26/2018, renal clearance was provided based on total radioactivity (SDN 24, 4/30/2018). Even though the radioactivity measured includes the extent of all metabolites as well as parent form, the estimated renal clearance seems to be close approximation given the low extent of metabolism of amisulpride.

$$\text{Renal clearance of total radioactivity} = \frac{\text{Ae (urine)}}{\text{AUC}} = \frac{7.25 \text{ mg eq}}{353 \text{ h.ng eq.mL}^{-1}} = 20.5 \text{ L.h}^{-1}$$

The 20.5 L/hr (=341.6 mL/min) is greater than a typical GFR value, 125 mL/min, which suggests that amisulpride undergoes active renal secretion. The clearance by active renal secretion is expected to be approximately 254 mL/min based on the equation, i.e., active secretion = renal clearance – (fu,p × GFR). Given that the total systemic clearance in healthy subjects is 24.1 L/h (=401.6 mL/min), active renal secretion accounts for around 50% of the total clearance assuming there is no re-absorption.

Metabolite profiling was conducted in plasma, urine, and feces in this study using liquid chromatography-coupled tandem mass spectrometry (LC-MS/MS) with in-line radiometric detection. A total 78.1% of dose (57.5% and 20.6% in urine and feces, respectively) was excreted in unchanged form in the first 48 hours. The remainder was accounted for four metabolites, formed by: oxygenation (C1); N-dealkylation (C2); oxygenation plus di-dehydrogenation or methylation plus dehydrogenation (C3); and oxygenation plus dehydrogenation (C4). The four metabolites together represented 15.0% and 6.1% of the dose excreted in the first 48 hours via urine and feces, respectively (Table 80, Table 81). However, only parent drug was detected in plasma.

Table 80. Metabolites of Amisulpride Detected in Urine

Compound	Percent of dose excreted			
	0-12 h	**12-24 h**	**24-48 h**	**Total (0-48 h)**
C1	4.1	0.8	ND	4.9
C2	2.6	1.0	ND	3.6
C3	1.5	ND	ND	1.5
C4	5.0	ND	ND	5.0
[^{14}C]-APD421	49.6	4.6	3.3	57.5
Total	**62.8**	**6.4**	**3.3**	**72.5**

ND = not detected
Source: Study DP10020 study report, Table 8

Table 81. Metabolites of Amisulpride Detected in Feces

Compound	Percent of dose excreted				
	0-24 h	**24-48 h**	**48-72 h**	**72-96 h**	**Total (0-96 h)**
C1	ND	0.8	0.8	0.5	2.1
C2	ND	1.1	0.6	0.3	2.0
C4	ND	1.3	ND	0.7	2.0
[^{14}C]-APD421	4.2	9.2	5.5	1.7	20.6
Total	**4.2**	**12.4**	**6.9**	**3.2**	**26.7**

ND = not detected

Source: Study DP10020 study report, Table 9

The ratio of whole blood to plasma total radioactivity concentrations was very close to 1 at all the time points indicating free passage of the drug in and out of red cells and consistent with the low.

16.2.1.2. Study DP10013: A Randomized, Double-blind, Four-period Crossover Study to Investigate the Effect of Intravenous amisulpride on Cardiac Conduction as Compared to Placebo and Moxifloxacin in Healthy Adult Subjects (thorough QT study)

DP10013 was a randomized, double blind, placebo- and positive-controlled, crossover design, to assess the effect of intravenous amisulpride on the QTc interval at single dose of amisulpride 5 mg and 40 mg in 40 healthy subjects. For detailed review of Study DP10013, a thorough QT study, please see the QT-IRT review dated January 12, 2018, by Lars Johannsen, PhD et al.

16.2.1.3. Effect of Renal Impairment on Pharmacokinetics of Amisulpride: a subset study of Study DP10014, DP10018, and DP10019

The effect of renal impairment on PK was investigated using a PK subset population in phase 3 studies DP10014 and DP10018/19. Originally, patients were classified by the severity of renal impairment differently between DP10014 and DP10018/19. In other words, in DP10014, creatinine clearance calculated (CrCL) using the Cockcroft-Gault (C-G) formula was used whereas in DP10018/19, estimated glomerular filtration rate (eGFR) calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation was used.

In DP10014, 13 of the 26 patients with a full PK profile had a degree of renal impairment determined by estimated creatinine clearance, calculated using the C-G formula. In DP10018 and DP10019, 11 out of 21 patients in the 5-mg dose group and 10 out of 27 in the 10-mg group had impaired renal function by eGFR, calculated using the abbreviated MDRD (Table 82).

Overall, no clear trend in terms of mean C_{max} was observed between patients with normal, mildly impaired or moderately impaired renal function. However, patients with mild to moderate renal impairment showed slightly higher AUC_{inf} up to around 1.3-fold whereas one patient with severe renal impairment (eGFR 8.2 mL/min/1.73 m^2) showed 2.1-fold higher AUC_{inf} compared to patients with normal renal function.

Table 82. Geometric Mean PK Parameters for Amisulpride by Degree of Renal Impairment

	DP10014 (C-G formula)			DP10018/DP10019 (MDRD)					
	5 mg			5 mg			10 mg		
Renal Impairment	**N**	**C_{max}**	**AUC_{inf}**	**N**	**C_{max}**	**AUC_{inf}**	**N**	**C_{max}**	**AUC_{inf}**
Normal	13	141	230	11	117	178	20	195	360
Mild	10	168	275	8	99	192	6	227	382
Moderate	3	147	280	2	168	227	-	-	-
Severe	-	-	-	-	-	-	1	275	781

Normal function: CLcr ≥90 mL/min or eGFR ≥90 mL/min/1.73 m^2
Mild impairment: CLcr =60 to 89 mL/min or eGFR =60 to 89 mL/min/1.73 m^2
Moderate impairment: CLcr =30 to 59 mL/min or eGFR =30 to 59 mL/min/1.73 m^2
Severe impairment: CLcr =15 to 29 mL/min or eGFR =15 to 29 mL/min/1.73 m^2
Source: 2.7.2. Summary of Clinical Pharmacology, Table 2.7.2-22

Originally, the abbreviated MDRD equation that used by the Applicant was slightly different from the equation quoted in FDA guidance:

The equation that the Applicant originally used:

eGFR (mL/min/1.73 m^2) = (b) (4) x (serum creatinine in mg/dL)$^{-1.154}$ x (age in years)$^{-0.203}$ [x 1.212 if race is "black"] [x 0.742 if female]

The equation quoted in FDA guidance:

eGFR (mL/min/1.73 m^2) =**175** x (serum creatinine in mg/dL)$^{-1.154}$ x (age in years)$^{-0.203}$ [x 1.212 if race is "black"] [x 0.742 if female].

Later, in response to the information request dated 5/24/2018, the Applicant re-assessed the degree of renal impairment using the MDRD equation that quoted in the FDA guidance (EDR 28, 5/25/2018) (Table 83).

CrCL versus eGFR

When either the C-G and the MDRD equations was applied to all of the subset patients with renal impairment, 20 out of the 74 patients were re-classified into a different renal impairment group by the C-G and the MDRD methods even though the overall trend in the PK results was not changed (Table 83). This difference in classification between using two equations is probably because C-G formula tends to over-estimate renal function in individuals with a higher body weight. Given the tendency of over-estimation in the C-G equation, we recommend using the values based on eGFR for the labeling purpose.

Table 83. PK Parameters for Amisulpride in Renal Impairment by Used Methods for Renal Function Assessment

Renal Impairment		Mean (SD)											
		DP10014			DP10018/DP10019						DP10014/ DP10018/DP10019		
		5 mg			5 mg			10 mg					
		N	C_{max} ng/mL	AUC_{inf} ng.h/mL	N	C_{max}	AUC_{inf}	N	C_{max}	AUC_{inf}	N	C_{max} /Dose*	AUC_{inf} /Dose†
C-G	Normal	13	145 (31)	238 (68)	17	109 (52)	174 (44)	23	309 (499)	368 (99)	53	27 (33)	39 (12)
	Mild	10	184 (80)	280 (55)	3	211 (66)	327 (172)	2	228 (111)	586 (353)	15	36 (15)	58 (19)
	Moderate	3	154 (61)	286 (77)	1	208 (-)	361 (-)	1	230 (-)	401 (-)	5	31 (11)	57 (16)
	Severe	0	-	-	0	-	-	1	275 (-)	781 (-)	1	28 (-)	78 (-)
MDRD	Normal	11	145 (30)	259 (68)	9	134 (78)	189 (73)	14	357 (639)	365 (86)	34	31 (41)	41 (14)
	Mild	12	177 (76)	254 (65)	10	114 (57)	211 (111)	12	232 (95)	411 (169)	34	27 (13)	45 (17)
	Moderate	3	154 (61)	286 (77)	2	172 (52)	252 (154)	0	-	-	5	32 (10)	54 (19)
	Severe	0	-	-	0	-	-	1	275 (-)	781 (-)	1	28 (-)	78 (-)

*ng/mL per mL of dose
†ng.h/mL per mL of dose

Source: Response to information request, SDN 26 dated 5/25/2018

Of note, per the label approved by the UK agency, i.e., MHRA, oral amisulpride as an antipsychotic (400 to 800 mg/day) is recommended that the dose be reduced to half in patients with moderate renal impairment (CrCL 30 to 60 mL/min) and to a third in patients with severe renal impairment (CrCL <30 mL/min). Per the MHRA review, the dose adjustment was

determined based on the finding in nine patients with renal impairment compared to 6 healthy subjects following a single 50 mg intramuscular injection; a 2-fold increase in the AUC of amisulpride was shown in moderate renal impairment (CrCL 30 to 60 mL/min) while patients with severe renal impairment (CrCL 12 to 29 mL/min) showed almost 4-fold increase in the AUC compared to subjects with normal renal function. However, from the review of MHRA, any individual data or the exact values was not available. Also, another product label of oral amisulpride with 50 to 400 mg strengths which is approved by UK agency describes that the AUC of amisulpride in moderate renal impairment (CrCL 30 to 60 mL/min) increase 2-fold and almost 10-fold in severe renal impairment (CrCL 10 to 30 mL/min).

16.2.1.4. In Vitro Drug Interaction Studies

Substrate of Transporters

Amisulpride was assessed for its potential to be a substrate for the panel of transporters by measuring its efflux or uptake (Study CYP1369 R3). P-gp and BCRP were studied using MDR1-MDCK cells and Caco-2 cells, respectively. All other transporters were investigated using human embryonic kidney HEK293 cells transiently transfected with individual transporters.

Amisulpride was a substrate of P-gp, BCRP, MATE1, and MATE2-K, with weak uptake also observed with OCT1 but no significant uptake was seen with OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 (Table 84).

Given that amisulpride undergoes active renal excretion, MATE1 and/or MATE2-K seems to contribute to active renal secretion.

Table 84. Substrate Identification Data for Amisulpride

Transporter	Parameter	Amisulpride values					Positive control (value)
		1 µM	10 µM	50 µM	100 µM	500 µM	
P-gp[a]	Efflux ratio	12.0	12.6	15.3	–	24.0	Prazosin (29.0)
BCRP[b]	Efflux ratio	8.7	13.9	14.7	–	25.2	Estrone 3-sulfate (66.8)
OATP1B1[c]	Uptake ratio	1.0	1.2	1.2	0.9	–	Estradiol 17β-D-glucuronide (26)
OATP1B3[c]	Uptake ratio	1.1	0.7	0.7	0.8	–	Estradiol 17β-D-glucuronide (10)
OAT1[c]	Uptake ratio	0.7	0.8	0.9	0.8	–	*p*-aminohippuric acid (33)
OAT3[c]	Uptake ratio	1.8	1.7	1.7	1.6	–	Estrone 3-sulfate (30)
OCT1[d]	Uptake ratio	3.8	3.0	1.9	1.5	–	Tetraethylammonium (8.6)

OCT1[c]	Uptake ratio	2.7	1.9	1.4	1.2	–	Tetraethylammonium (35)
OCT2[c]	Uptake ratio	1.1	1.0	0.9	0.9	–	Metformin (15)
MATE1[c]	Uptake ratio	6.5	8.4	6.4	3.6	–	Tetraethylammonium (31)
MATE2-K[d]	Uptake ratio	21	14	7.3	4.9	–	Tetraethylammonium (22)
MATE2-K[c]	Uptake ratio	2.4	2.3	1.8	1.3	–	Tetraethylammonium (8.0)

a: MDR1-MDCK permeability; b: Caco-2 permeability; c: HEK293 uptake (after 20 mins incubation);
d: HEK293 uptake (after 2 mins incubation)
– not done

Source: 2.7.2. Summary of Clinical Pharmacology, Table 2.7.2-11

Inhibition of Transporters

Inhibition of transporters by amisulpride was investigated at concentrations from 0.3 to 100µM (Study CYP1369 R3). Inhibition of P-gp and BCRP were studied using MDR1-MDCK cells and Caco-2 cells, respectively. The other transporters were investigated using human embryonic kidney HEK293 cells transiently transfected with individual transporters.

Amisulpride was determined to be an inhibitor of transport mediated by OCT1, MATE1, and MATE2-K; a weak inhibitor of OCT2, OAT3; and not to inhibit P-gp, BCRP, OATP1B1, OATP1B3 and OAT1. When the ratio of the highest in vivo concentration of amisulpride to the IC_{50} is considered, only MATE1 exceeds the threshold of 0.1 considered relevant for potential clinical drug-drug interactions (Table 85).

Table 85. Inhibitions of Human Efflux and Solute Carrier Transporters by Amisulpride

Transporter	Probe Substrate	Positive control inhibitor(s)	IC_{50} for amisulpride (µM)	Ratio [I]/IC_{50}†
P-gp	Loperamide	Ketoconazole, Cyclosporin A	>100	<0.01
BCRP	Estrone 3-sulfate	Novobiocin, Fumitremorgin C	>100	<0.01
OATP1B1	[^{3}H]-Estradiol 17β-D-glucuronide	Rifamycin SV	No inhibition	NA
OATP1B3	[^{3}H]-Estradiol 17β-D-glucuronide	Cyclosporin A	No inhibition	NA
OAT1	[^{3}H]-p-Aminohippuric acid	Probenecid	No inhibition	NA
OAT3	[^{3}H]-Estrone 3-sulfate	Probenecid	>100*	<0.01
OCT1	[^{14}C]-Tetraethylammonium	Verapamil	16.1	0.06
OCT2	[^{14}C]-Metformin	Verapamil	>100**	<0.01
MATE1	[^{14}C]-Metformin	Cimetidine	2.62	0.37
MATE2-K	[^{14}C]-Metformin	Cimetidine	10.1	0.10

†[I] = highest concentration of amisulpride, calculated as 0.97 µM based on mean C_{max} of 357 ng/mL for 10 mg dose of IV APD421 in Study DP10020 (see Table 2.7.2-15)
*23.6% inhibition at 100 µM; **48.5% inhibition at 100 µM; NA = not applicable
Source: 2.7.2. Summary of Clinical Pharmacology, Table 2.7.2-10

Metabolism by CYP Enzymes

In vitro, metabolism of amisulpride was assessed by monitoring disappearance of parent compound (Study CYP1369 R4) during incubation with human cytochrome P450 isoforms and amisulpride up to 45 minutes. Little or no metabolism of amisulpride by the isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 was observed, with more than 85% of unchanged amisulpride remaining at the end of incubation (Table 86).

Table 86. Cytochrome P450 Reaction Phenotyping Data for Amisulpride

Isoform	Cytochrome P450 Reaction Phenotyping							
	t½ (min)	SE t½ (min)	n	Compound Remaining (% of 0 min)				
				0 min	5 min	15 min	30 min	45 min
1A2	-869	1050	5	100	94.7	94.8	96.0	102
	-1940	5200	5	100	102	94.4	100	102
2B6	-1150	1840	5	100	108	101	104	106
	547	673	5	100	112	99.0	103	98.3
2C8	-529	300	5	100	105	107	109	107
	1160	1330	5	100	100.0	103	102	96.6
2C9	-757	509	5	100	98.7	103	105	102
	-637	417	5	100	102	107	107	105
2C19	1790	5180	5	100	108	105	107	100
	-1210	2230	5	100	92.2	100	97.6	99.8
2D6	532	296	5	100	93.6	93.8	94.6	91.3
	214	79.1	5	100	92.2	93.8	83.6	86.2
3A4	-7170	93800	5	100	89.7	97.7	95.7	96.2
	-21000	344000	5	100	101	102	104	99.4

Source: 5.3.2.2. Study CYP1369 R4 Report, Table 3

Inhibition or Induction of CYP Enzymes

Amisulpride also shows minimal in vitro inhibition or induction of CYP450 enzymes at clinically relevant concentrations (Study CYP1369 R4). Inhibition of CYP450 enzymes were studied using liver microsomes with 30-minute pre-incubation with amisulpride in the presence and absence of NADPH to evaluate reversible inhibition and time-dependent inhibition, respectively.

minute pre-incubation with amisulpride in the presence and absence of NADPH. Induction potential was studied using cryopreserved hepatocytes following incubation with amisulpride for 72 hours. Amisulpride was investigated at concentrations from 0.3 to 100µM. Amisulpride appeared to be a reversible, but not time-dependent, inhibitor of CYP2D6; but was neither a reversible nor time-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 (

Table 87).

Table 87. Reversible and Time-Dependent Inhibition of CYP Activity by Amisulpride

Isoform	Probe substrate	IC_{50} (µM)			
		Pre-incubation			
		None	30 min without NADPH	30 min with NADPH	Fold shift*
1A2	Phenacetin (30 µM)	>100	>100	>100	ND
2B6	Bupropion (110 µM)	>100	>100	>100	ND
2C8	Paclitaxel (7.5 µM)	>100	>100	>100	ND
2C9	Diclofenac (20 µM)	>100	>100	>100	ND
2C19	Mephenytoin (25 µM)	>100	>100	>100	ND
2D6	Dextromethorphan (5 µM)	46.3	69.6	83.3	0.835
3A4	Midazolam (2.5 µM)	>100	>100	>100	ND
3A4	Testosterone (50 µM)	>100	>100	>100	ND

*Fold shift = IC_{50} in absence of NADPH ÷ IC_{50} in presence of NADPH
ND: Unable to determine fold shift

Source: 2.7.2. Summary of Clinical Pharmacology, Table 2.7.2-8

Amisulpride did not induce significant mRNA expression at concentrations below 3µM for the isoforms tested. Induction by amisulpride of CYP1A2, CYP2B6 and CYP3A4 mRNA expression in cryopreserved human hepatocytes is summarized in Table 88.

Table 88. Induction of mRNA of CYP Enzymes in Human Hepatocytes by Amisulpride

Isoform	Positive control (maximal mean fold induction)	Donor	Mean fold induction					
			Concentration of amisulpride (µM)					
			0.3	1	3	10	30	100
1A2	Omeprazole (49.6)	1	1.16	1.10	1.02	1.06	0.99	1.05
		2	1.21	1.26	1.33	1.09	1.07	0.85
		3	1.27	0.94	1.41**	1.56***	1.26	0.85
2B6	Phenobarbital (11.4)	1	1.07	0.99	0.98	1.03	1.12	1.50**
		2	1.12	1.25	1.29	1.20	1.53**	1.59**
		3	1.11	0.88	1.24	1.35	1.31	1.18
3A4	Rifampicin (87.0)	1	1.29*	1.06	1.31*	1.79***	3.85***	8.67***
		2	1.15	1.35	1.73*	3.09***	6.51***	12.1***
		3	1.23	1.04	1.72***	2.99***	4.49***	7.27***

All fold shifts non-significant except *p < 0.05, **p < 0.01, ***p < 0.001 (one-way ANOVA with two-tailed Dunnett's post-test)

Source: 2.7.2. Summary of Clinical Pharmacology, Table 2.7.2-9

16.2.1.5. Amisulpride for PONV Versus Oral Amisulpride as an

Antipsychotic

Amisulpride in oral or intramuscular formulation has been used as an anti-psychotic in other countries at a dose range between 50 and 1200 mg/day, typically 400 to 800 mg/day for acute psychosis and 50 to 300 mg/day for schizophrenia with primarily negative symptoms. Although any relative bioavailability study between IV and oral formation was not conducted in this submission, based on between-study comparison, the C_{max} and AUC of amisulpride delivered by the proposed doses of amisulpride in PONV, i.e., 5 and 10 mg IV, are generally lower than those delivered by a typical 200 to 400 mg oral dose in psychiatric practice (Table 89). Per published literature (Rosenzweig et al. 2002), oral bioavailability is around 50%. Of note, although mean C_{max} after 10 mg amisulpride was lower than that of 200 mg in the cross-study comparison, due to the significant variability (%CV: 156%) of C_{max} noted with IV amisulpride 10 mg, we cannot conclude that C_{max} would be lower with the proposed 10 mg IV than oral amisulpride at 200 mg.

Table 89. Comparison of Mean (SD) Pharmacokinetic Parameters of Amisulpride Between IV Infusion at 5 and 10 mg Versus Oral Administration at 200 mg and 400 mg

PK parameters	Single IV infusion for 2 min (DP10018/DP10019)		Single oral tablet (MHRA Report*)	
	5 mg	10 mg	200 mg	400 mg
C_{max} (ng/mL)	127 (64)	285 (446)	424 (200)	1269 (512)
AUC_{inf} (ng*h/mL)	204 (94)	401 (149)	3549 (959)	8808 (1962)

*Pharmaceutical Assessment Report PL 19364 (UKPAR on amisulpride 50, 100, 200 and 400 mg oral tablets) issued by MHRA to support the approval of a generic amisulpride product

Bergemann et al (2004) reported that the mean trough plasma levels of amisulpride at steady-state was 424.4 ng/mL (range: 20 to 1904 ng/mL) following the maintenance dose ranged from 150-1600 mg/day (Bergemann et al. 2004). In a similar study, Muller et al (2007) indicated that the mean trough plasma levels of amisulpride at steady state was 315 ng/mL (range: 10 to 1682 ng/mL) at 100 to 1550 mg/day dose (Muller et al. 2007). From the two published studies, the mean trough levels were around 300 to 400 ng/mL in chronic use for antipsychotic indication, so peak plasma levels are expected to be much higher than the peak levels were observed, i.e., about 200-400 ng/mL, following single IV dose of amisulpride 5 to 10 mg for PONV indication. The Applicant proposed that published safety data on oral amisulpride as an antipsychotic can be extrapolated to intravenous amisulpride, especially when it comes to dose- or exposure-dependent safety concerns.

16.2.2. Population Pharmacokinetics Review

16.2.2.1. Applicant's Population PK Analyses and Simulation

16.2.2.1.1. Final Population PK Model

The Applicant's population PK analysis was performed with PK data from four studies outlined in Table 90.

Table 90. Summary of the Analysis Data Set

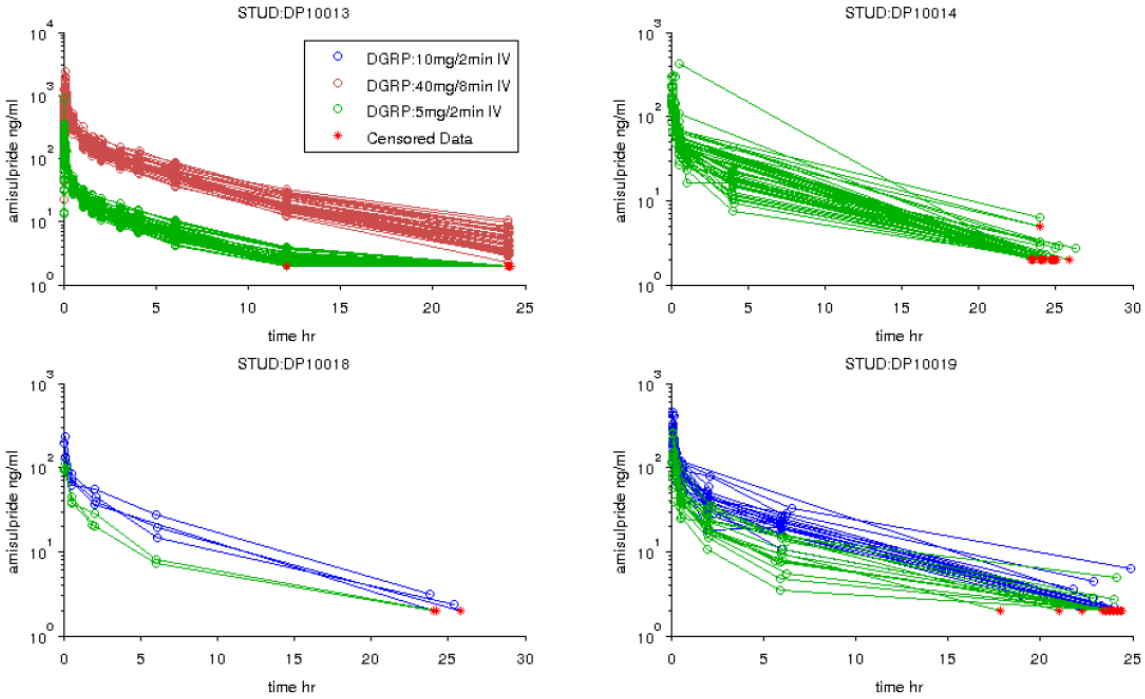
	DP10013	DP10014	DP10018	DP10019	Full
Type	tQT cross-over	Ph III	Ph III	Ph III	
Dosing	5mg/2min, 40mg/8min	5mg/1-2min	5mg/2min, 10mg/2min	5mg/2min, 10mg/2min	
Administration	IV infusion	IV infusion	IV infusion	IV infusion	
PK Samples	2, 8 mins, 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24 hrs	5, 15 mins, 0.5, 1, 4, 24 hrs (rich) or 0.5, 24 hrs (sparse)	5 mins, 0.5, 2, 6, 24 hrs	5 mins, 0.5, 2, 6, 24 hrs	
Total Conc Records	857	199	33	184	1273
Conc Records BQL	47 (5%)	38 (19%)	4 (12%)	21 (11%)	110 (9%)
Dose Records	78	48	8	48	182
Population	Healthy Subjects	Surgical Patients	Surgical Patients	Surgical Patients	
n	39	26 (rich) and 22 (sparse)	8	48	143
Male/Female	23/16	13/35	0/8	1/47	37/106
White/ Asian/ Black/ Other	22/17/0/0	44/0/0/4	8/0/0/0	42/1/5/0	116/18/5/4
Age[a] (yrs)	28 (21-45)	53 (22-80)	51 (19-79)	45 (22-78)	43 (19-80)
Body Weight[a] (kg)	66 (47-83)	71 (49-118)	78 (52-117)	76 (43-161)	70 (43-161)
Serum creatinine at screening[a] (μmol/L)	67 (42-86)	70 (32-124)	66 (59-72)	63 (44-519)	67 (32-519)
Creatinine clearance[ab] (ml/min)	121 (80-150)	95 (40-150)	118 (49-150)	111 (20-150)	112 (20-150)
Standardised renal function[ac]	1.3 (1.1-1.8)	1.0 (0.5-1.9)	1.0 (0.7-1.5)	1.0 (0.1-1.7)	1.1 (0.1-1.9)

[a] median (range)
[b] Calculated using the Cockcroft and Gault formula, truncated at 150 ml/min
[c] $RF = \frac{CrCL}{100ml/min} * \frac{70}{BW}$

(Source: Applicant's Population PK Report - 13Feb2018, Table 2)

For this model, that Applicant is updating a previous 3 compartment model with data from studies 0018 and 0019. The Applicant utilized Monolix software to perform the nonlinear mixed effect PK analysis. The observed concentrations from each study are depicted in Figure 14.

Figure 14. Observed Amisulpride Plasma Concentrations Over Time by Subject and Treatment.



(Source: Applicant's Population PK Report – 13Feb2018, Figure 1)

The Applicant's conclusions regarding the structural modeling and covariate modeling are as follows:

Structural Model Development:

The data from added studies DP10018 and DP10019 looked consistent with the data from the two studies already analyzed. The starting point was therefore the previously developed model as described in Applicant's Population PK Report submitted on Aug 3, 2018. A three-compartmental model with BW and renal function (RF) as covariates, without a non-renal clearance component.

As in the previous analysis estimating BSV for V3 did not decrease the objective function (OF) and the parameter was poorly estimated.

A two-compartmental model increased the OF by 374.

Removal of RF as covariate increased the OF by 55. RF was kept.

Estimating both a non-renal and renal clearance, with RF as a covariate on the renal clearance, decreased the OF by 15 and AIC by 12. This model seemed modestly better and both clearance components could be estimated, although they were highly correlated. This model was further developed and the same covariates were identified as for the renal clearance only model (as described below for the latter). The final two clearances model had an OF 34 lower than the final renal clearance model. However, the clearances were still highly correlated (0.98) and less well estimated (RSE of about 30% compared to 4% in the other model). The estimate for the renal and non-renal clearance was about the same in this model and somewhat dependent on the initial

values. No differences in overall model t was observed between the two models. The model with renal clearance only was selected as base model, since it was simpler, more robust and more conservative when considering the potential impact of renal failure, even if there is some support for a non-renal clearance component.

Covariate Model Analysis:

The univariate covariate analysis (added to the model including BW and RF) is summarized in Table 91. The effect of study population, age, sex and race were evaluated on clearance (CL), initial volume of distribution (V1) and inter compartmental clearance 1 (Q), since these parameters are important in determining the C_{max} and had reasonable data to support their estimation in most subjects. In addition, the effect of study population on the between subject variability (BSV) in these parameters was also evaluated.

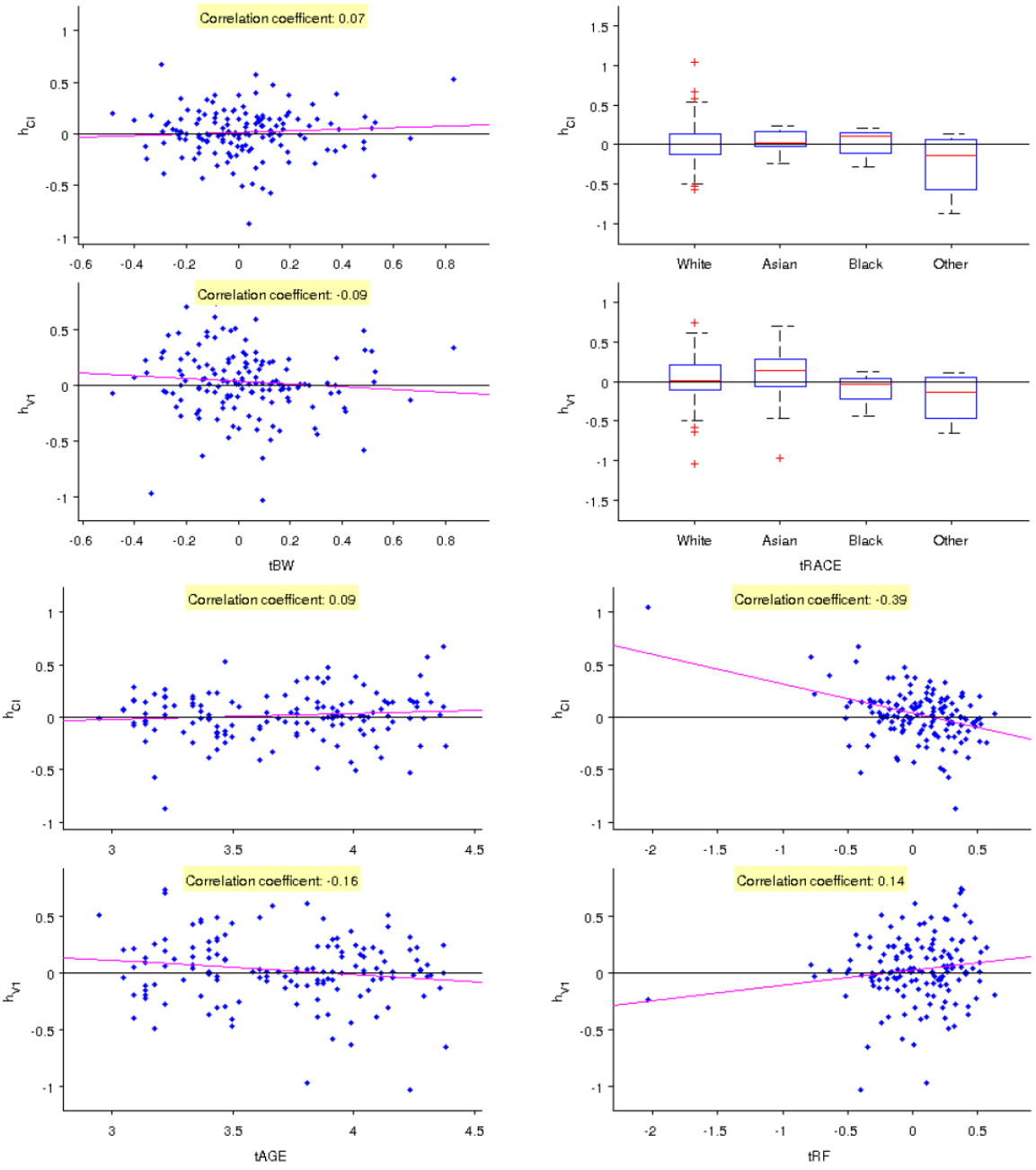
Table 91. Objective Function Changes When Adding a Covariate to the Base Model

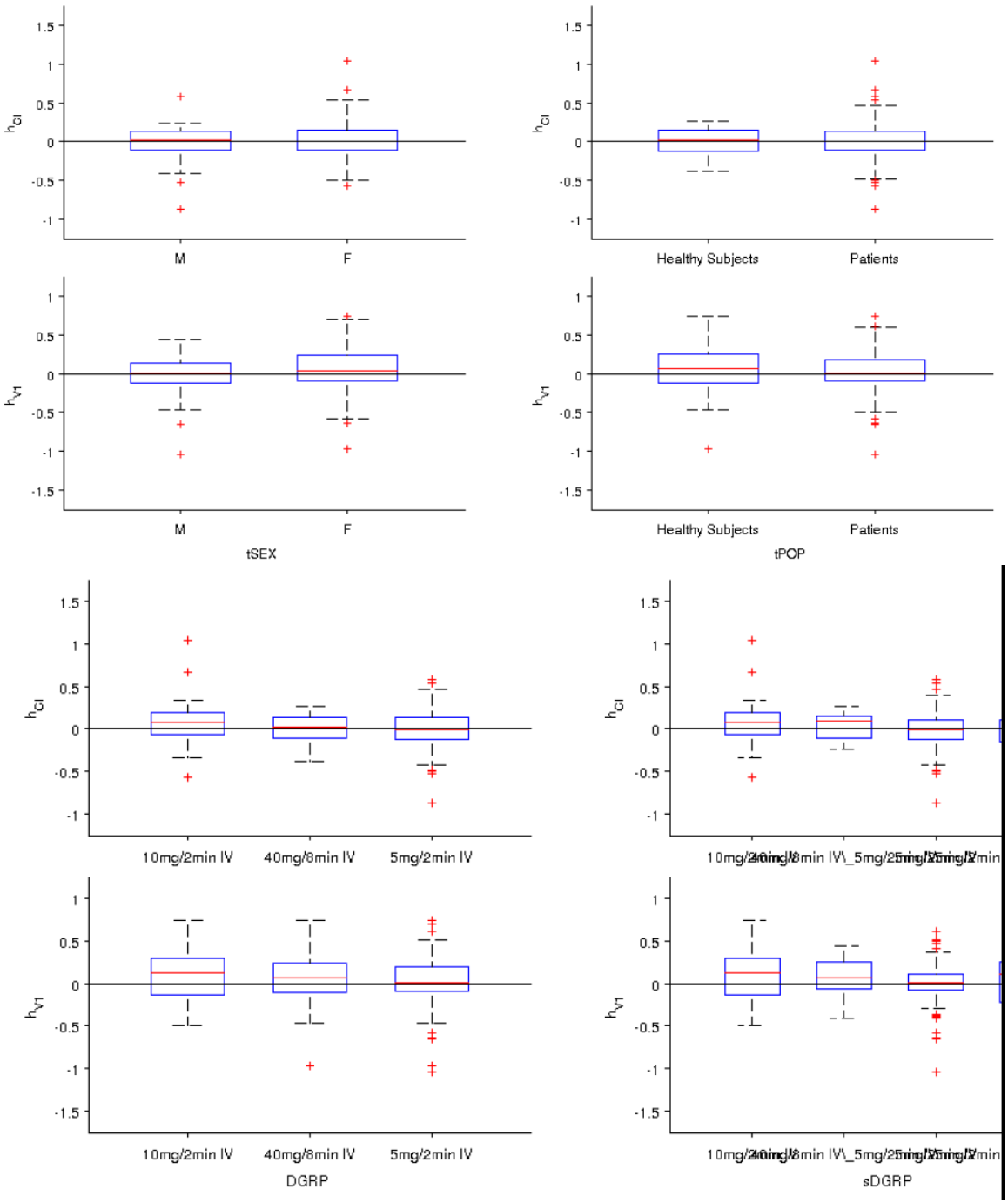
Covariate	CL	V1	Q	BSV CL	BSV V1	BSV Q
POP	**-9**	0	0	**-13**	-2	**-38**
RACE	**-10**	-3	+1	-	-	-
SEX	+1	0	-2	-	-	-
AGE	-1	+15	+7	-	-	-

(Source: Applicant's Population PK Report – 13Feb2018, Table 3)

A full model was generated including the covariate effects of population on CL and on the BSV of both CL and Q, as well as race on CL. Backward deletion of race on CL increased the OF by only 5. Race was removed from the model. Subsequently removal POP on CL increased the OF by 9. Although borderline, this covariate was kept in the model, since the effect was considered relevant and plausible, even if modest.

Figure 15. Relationship of Potential Covariates with ηCL and ηV1 for the Full Model





(Source: Applicant's Population PK Report – 13Feb2018, Figure 2 – Figure 5)

Visual inspection of the covariates vs individual ηs show that the effects of body weight and renal function are generally well accounted for and that there is little suggestion of any other remaining covariate effects (Figure 15).

For the standardized renal function, there seems to be some misspecification, mostly because of one subject with severe renal impairment. When the model with both non-renal and renal

clearance was evaluated, this misspecification disappeared. This misspecification was not considered a concern but it will result in a potential underprediction of the CL for subjects with severe renal function.

Final PK Model:

The FINAL population pharmacokinetic model for amisulpride was a three-compartmental model with body weight as a fixed covariate on the clearances and volumes of distribution. In addition, the clearance was related to the standardized renal function. The model included proportional between subject variability on most of the disposition parameters. The residual error was described by a proportional model. The clearance as well as the between subject variability in clearance and inter compartmental clearance 1 were different for the surgical patients in studies DP10014, DP10018 and DP10019, compared to healthy subjects (study DP10013) (Table 92).

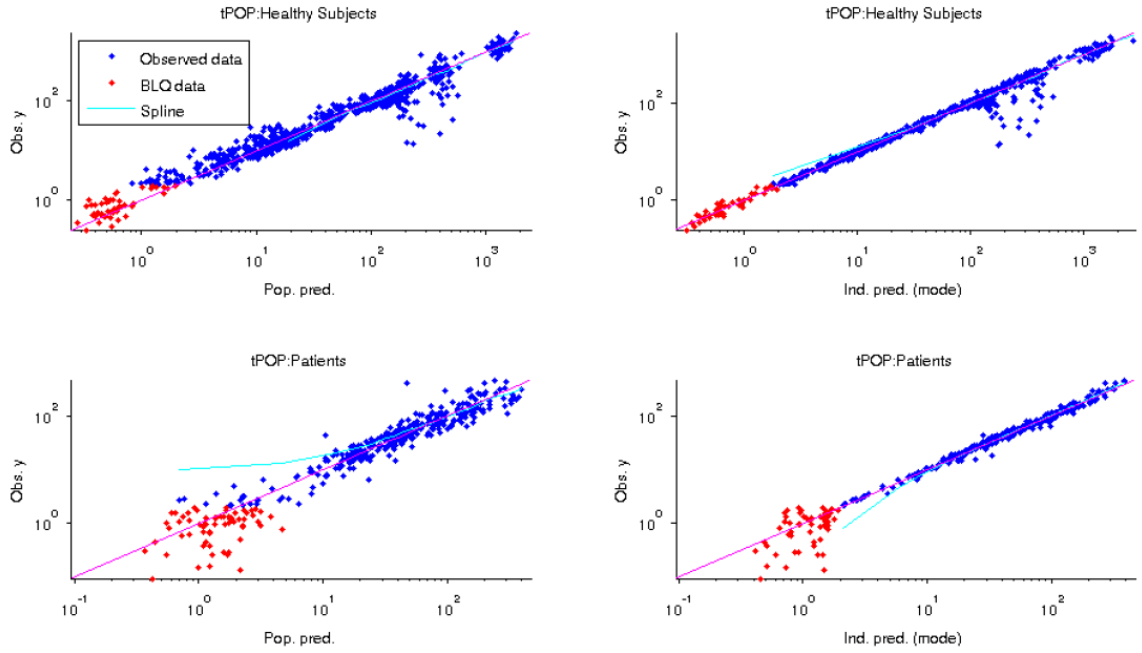
Table 92. Parameter Estimates for the Final Population PK Model.

Parameter		Estimate[a]	BSV[ab] [%]
	Healthy Subjects		
CL [L/hr]	Clearance[cd]	$24.1(3) * RF * \left(\frac{BW}{70}\right)^{0.75}$	17 (12)
V1 [L]	Central Volume of Distribution[d]	$23.9(4) * \left(\frac{BW}{70}\right)^{1}$	37 (9)
Q [L/hr]	Inter Compartmental Clearance 1[d]	$73.1(3) * \left(\frac{BW}{70}\right)^{0.75}$	10 (38)
V2 [L]	Peripheral Volume of Distribution 1[d]	$69.3(3) * \left(\frac{BW}{70}\right)^{1}$	16 (14)
Q2 [L/hr]	Inter Compartmental Clearance 2[d]	$5.6(13) * \left(\frac{BW}{70}\right)^{0.75}$	87 (14)
V3 [L]	Peripheral Volume of Distribution 2[d]	$84.9(5) * \left(\frac{BW}{70}\right)^{1}$	-
	Surgical patients receiving general anaesthesia		
CL [L/hr]	Clearance[cd]	$\mathbf{20.6}(4) * RF * \left(\frac{BW}{70}\right)^{0.75}$	**32** (9)
V1 [L]	Central Volume of Distribution[d]	$23.9(4) * \left(\frac{BW}{70}\right)^{1}$	37 (9)
Q [L/hr]	Inter Compartmental Clearance 1[d]	$73.1(3) * \left(\frac{BW}{70}\right)^{0.75}$	**75** (11)
V2 [L]	Peripheral Volume of Distribution 1[d]	$69.3(3) * \left(\frac{BW}{70}\right)^{1}$	16 (14)
Q2 [L/hr]	Inter Compartmental Clearance 2[d]	$5.6(13) * \left(\frac{BW}{70}\right)^{0.75}$	87 (14)
V3 [L]	Peripheral Volume of Distribution 2[d]	$84.9(5) * \left(\frac{BW}{70}\right)^{1}$	-
b	proportional residual error	0.183 (3)	

[a]Estimate with (Relative Standard Error %)
[b]Between Subject Variability
[c]RF= Standardised Renal Function=$\frac{CrCL}{100ml/min} * \frac{70}{BW}$
[d]BW = Body Weight [kg]

(Source: Applicant's Population PK Report, 13Feb2018, Table 4)

Figure 16. Final Model Observed Versus Predicted by Study Population



(Source: Applicant's Population PK Report – 13Feb2018,)

The Applicant's conclusions regarding their final Population PK model are as follows:

- Since the maximal predicted QT prolongation is based on the either the maximal mean amisulpride concentration or the mean amisulpride C_{max}, the model should describe C_{max} (end of infusion) well.
- The population PK of amisulpride was consistent and very similar to the previously developed model. But with the new (patient) data, a modestly lower clearance in surgical patients under general anesthesia compared to healthy subjects could be identified (20.6 L/hr vs 24.1 L/hr for a 70 kg subject with RF=1). This is not so surprising (it may be related to reduced blood flow) but unlikely to be of any clinical relevance, since, apart from being modest, for such rapid infusion C_{max} will not be much dependent on the clearance. In addition, part of the difference in between subject variability in exposures between patients and healthy subjects could be identified. The patients had a considerably larger between subject variability in both clearance and inter compartmental clearance 1 (Q).
- There was some suggestion that there may be a non-renal component of the clearance, which is not inconsistent with what is known about amisulpride (section 2.2). About 25% of unchanged amisulpride was found in the feces. However, the fraction of non-renal clearance could not be reliably estimated and it was considered prudent to select the more robust model assuming all clearance to be renal (and thus affected by renal impairment).
- The final population PK model described the mean and individual profiles very well and was considered adequate for evaluation of C_{max} (dose ranges 5 to 40 mg).

- The developed population pharmacokinetic model was considered appropriate to be used in future evaluations of the risk of QTc prolongation for various dosing regimens for amisulpride between 5 and 40 mg in a generally healthy adult subject population.
- Some differences in PK between healthy subjects and surgical patients under general anesthesia could be characterized.

The Applicant's population PK model is acceptable for evaluating renal function, BW, and patient population as covariates on CL and for describing the PK of amisulpride for labeling purposes.

16.2.2.1.2. Applicant's Simulation of C_{max} Values for different Infusion Durations with the 10-mg dose

The Applicant conducted additional simulation work utilizing their final population PK model to evaluate the C_{max} after short infusion durations (1, 2, and 4 minutes) of the high dose (10 mg) amisulpride.

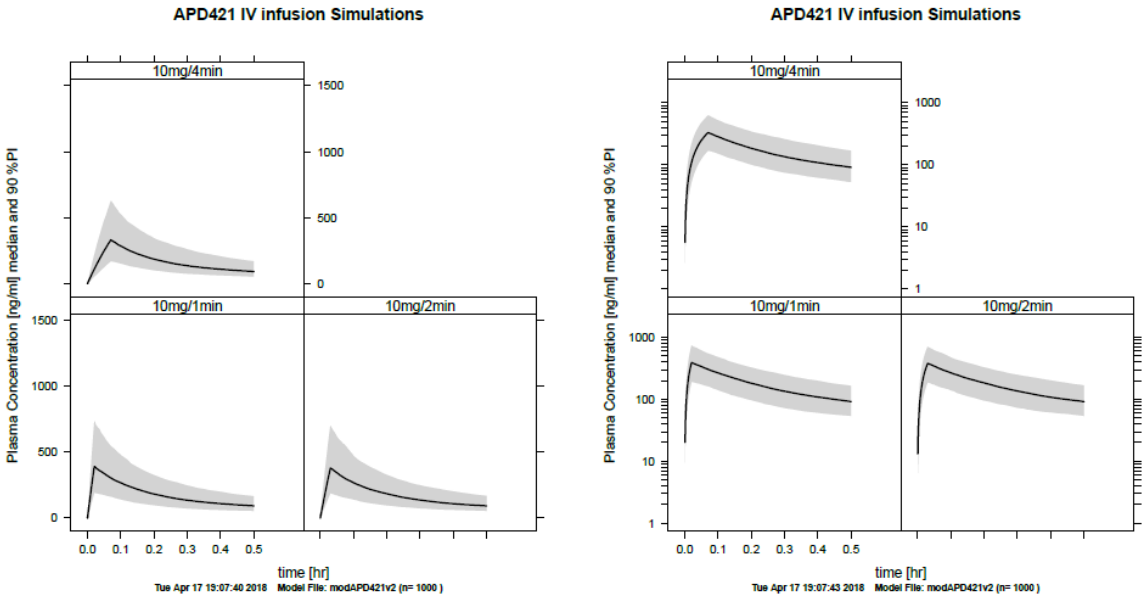
The simulations and all subsequent calculations were performed using R (version 3.2.3 (2015-11-30), The R Foundation for Statistical Computing, Platform: x86 64-pc-linux-gnu (64-bit)) and R-Studio (version 1.1.442 2009-2018 RStudio, Inc.).

- Simulations:
  The simulation was performed for surgical patients receiving general anesthesia.
- N=1000 subjects per dosing regimen
- Each subject (their covariate vector) was randomly sampled from the surgical patient part of the original popPK dataset (104 patients). The population in the simulations therefore represents a similar patient population as the one used in the popPK analysis.
- The pharmacokinetic profile for each subject was simulated using the population PK model.
  - The time point resolution for the simulation ranged from 0.001 hr in the first 0.1 hr to 2-hrs at the end of the 24 hr time interval.
  - The PK simulations included between subject variability in the parameters but not param-eter uncertainty or residual variability.
- C_{max} and Concentration at t=24 hr (C24) were observed directly from the simulated individual PK profiles.
- AUC(0-24) was calculated for each simulated individual PK profile using the trapezoidal rule based on a reduced selection of time points:
  - Every minute for the first 15 minutes
  - Every 5 minutes from 0.25 to 1 hr
  - Every 0.1 hr from 1 to 2 hr
  - After 2 hr all simulated time points
- The estimated exposures, C_{max}, AUC(0-24) and C24, were summarized by dosing regimen.

Results

The Applicant's time course of amisulpride concentrations are shown in Figure 17. The mean (90% CI) of the C_{max} values are shown in Table 93.

Figure 17. Predicted Amisulpride Exposures Over the First 0.5 Hour After Infusions Starts for Three Rapid IV Infusions of Amisulpride



(a) *linear* (b) *log-linear*

(Source: Applicant's apd421-pop-pk-simulation-report.pdf, Figure 3)

Table 93. Summary of the Predicted Amisulpride Exposures for Three Rapid IV Infusions of Amisulpride in Surgical Patients: Median (90% Prediction Interval)

Dosing Regimen	Cmax [ng/ml]	AUC(0-24) [ng*hr/ml]	C24 [ng/ml]
10 mg/1 min	390 (192-732)	434 (229-796)	2.5 (0.3-11)
10 mg/2 min	378 (188-699)	437 (241-794)	2.6 (0.3-10)
10 mg/4 min	331 (170-626)	437 (239-780)	2.7 (0.4-11)

(Source: Applicant's apd421-pop-pk-simulation-report.pdf, Table 2)

While there was a fair amount of shrinkage identified on the etas for CL (27%) and Volume of

distribution (29%), the simulation work for representing C_{max} values is acceptable. The nature of the IV infusion model combined with 3 compartments allows for more curvature in the time course to accurately capture the C_{max}. Additionally, there was minimal bias in the data for the high concentrations as indicated by the GOF plots in Figure 16.

16.2.2.2. Reviewer's Population PK Analysis

16.2.2.2.1. Introduction

The Applicant's model did not converge in our version of Monolix or NONMEM as they had indicated. A review of the model was performed to ensure covariate effects could be resolved properly and the effect of changing the infusion duration on C_{max} were evaluated.

16.2.2.2.2. Objectives

Analysis objectives are:

1. Perform sensitivity analyses to evaluate if covariate effects are appropriately identified
2. Simulate the effect of increasing infusion duration to limit C_{max} to avoid unnecessary QT prolongation

16.2.2.2.3. Methods

Data sets used are summarized in Table 94.

Table 94. Analysis Data Sets

Study Number	Name	Link to EDR
Population PK Update	Apd421-update-3.csv	\\cdsesub1\evsprod\NDA209510\0016\m5\datasets\apd421-pop-pk\misc

Monolix and NONMEM version 7.3 were utilized to run and evaluate the model structure. The statistical software R was utilized to create diagnostic plots and Berkeley Madonna was utilized to simulate the effect of different infusion duration on peak amisulpride concentrations.

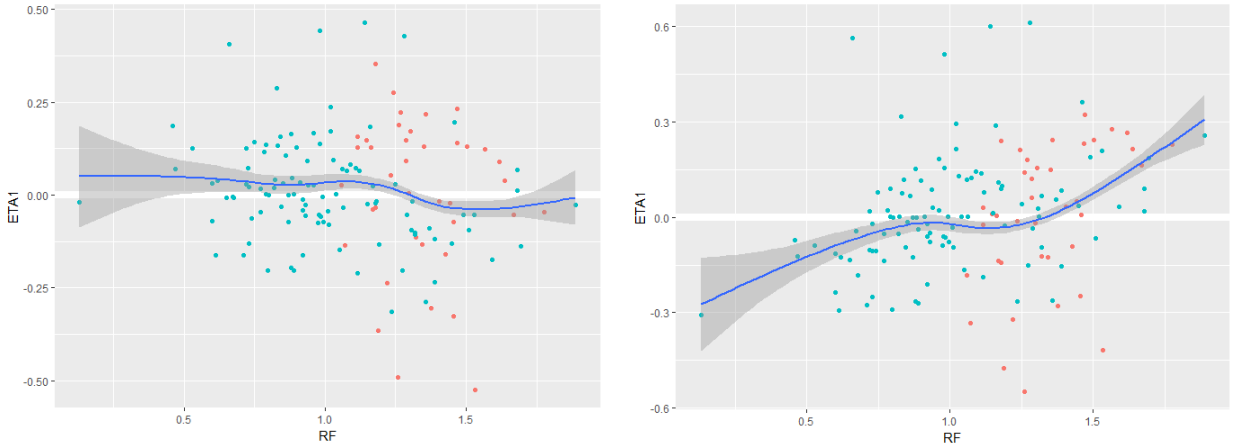
16.2.2.2.4. Results

Population PK Covariate Analysis:

The exclusion of either renal function, body weight and patient status were each evaluated to determine the relevance of the parameter on to the PK of amisulpride. A sensitivity analysis was performed for each covariate by removing the parameter from the model and refitting the data. Then the eta(CL) for each individual were plotted against the covariate of interest for both before and after the covariate was removed. If the covariate is relevant a trend in the ETA(CL) values should be evident when plotted against the tested covariate. Figure 18 through Figure 20 indicate just this. The panel on the right evidences a trend with the covariate compared to the panel on the left (Applicant's final model). The lack of bias in the left panel indicates the mathematical

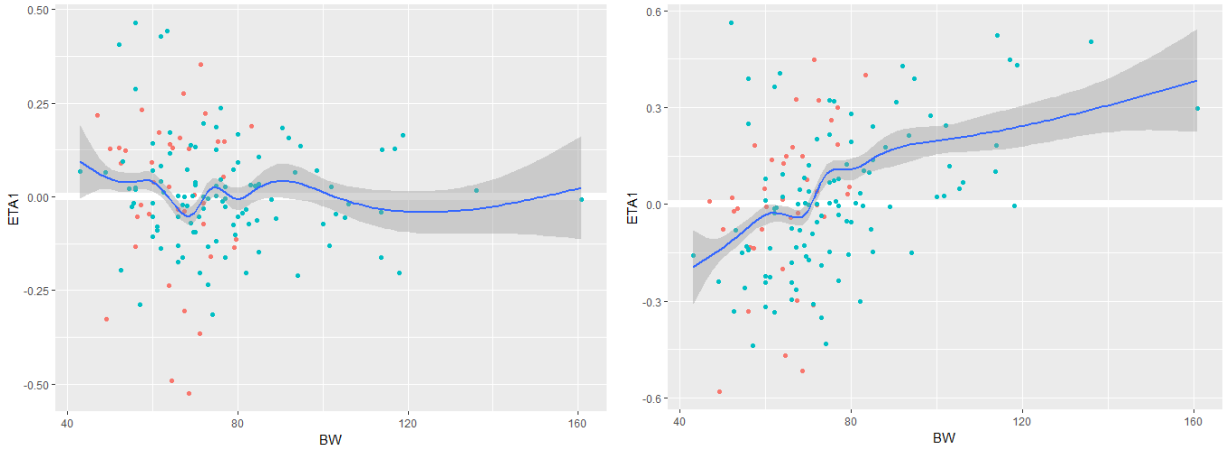
relationship for incorporating the covariate into the model is reasonable. Additionally, the model differences in OF, between subject variability on CL, and eta shrinkage were evaluated (Table 95).

Figure 18. ETA(CL) Versus Renal Function



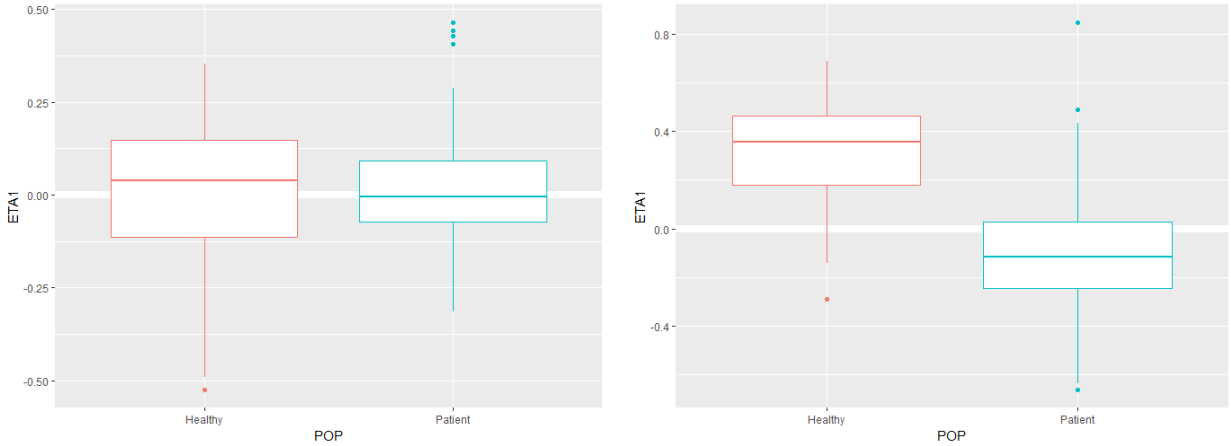
Before (left panel) and after (right panel) removing renal function as a covariate in the model. Red and blue points indicate healthy subjects and patients, respectively.
RF = renal function

Figure 19. ETA(CL) Versus Body Weight



Before (left panel) and after (right panel) removing body weight as a covariate in the model. Red and blue points indicate healthy subjects and patients, respectively.
BW = body weight

Figure 20. ETA(CL) Versus Patient Status



Before (left panel) and after (right panel) removing patient status as a covariate in the model. Red and blue boxes indicate healthy subjects and patients, respectively.

Table 95. Diagnostics of Covariate Relevance and Model Robustness Before and After Removing Body Weight, Renal Function, and Patient Status

Shrinkage in etaCL		
Parameter Removed	Before (Full Model)	After (Test Model)
Body Weight		20%
RF	29%	24%
Patient		18%
BSV on CL (%CV)		
Parameter Removed	Before (Full Model)	After (Test Model)
Body Weight		28.2
RF	21.8	25.5
Patient		36.3
OBJF		
Parameter Removed	Before (Full Model)	After (Test Model)
Body Weight		-1517.7
RF	-1553.00	-1529.0
Patient		-1486.6

RF = renal function

Allowing the exponents of the BW on CL and V to be estimated yielded a much more significant OF decrease (32 points) and a value of -1584. Shrinkage on clearance was 27% and 29% for V1. Between subject variability was 22.5% CV for clearance. The allometric coefficients were estimated to be 0.61 instead of 0.75 for clearance and 0.433 instead of 1.0 for volume parameters. Given that the Applicant's model appeared to capture the central tendency of the

data, along with the high value of shrinkage and minimal reduction in BSV, the reviewer did not alter the model to estimate the allometric coefficients and the Applicant's values were accepted.

C_{max} Simulation with Patient Demographics and Post Hoc Bayesian Parameters

The Applicant simulated C_{max} values by creating a population by resampling the demographics of the relevant covariates from the existing population and then simulating based on this new dataset. Their results are shown in Table 93. Given that the shrinkage around the CL and V parameters is not small the reviewer sought a simulation that may more closely capture the behavior of the studied patients. Thus, the reviewer simulated C_{max} values for demographics of the studied population based on the Applicant's final model structure estimated in NONEM. The estimates of C_{max} came up lower despite using the same model structure (Table 96). It should be noted that despite the same model structure, the NONEM estimates for the model were a bit different than the Applicants (Table 97). Despite this difference, the Applicant's values were utilized for the QTcF assessment for the 10-mg dose as this is a more conservative when considering potential adverse effects of the drug (i.e., QT prolongation).

Table 96. Simulated C_{max} Values at the End of Infusion for Healthy Subjects and Patients Receiving 10 mg Amisulpride with Three Different Infusion Durations

	Cmax (90%CI), ng/mL	
	Healthy	Patients
10 mg, 1 minute IV	302 (175 - 469)	313 (182 - 599)
10 mg, 2 minute IV	294 (171 - 453)	304 (179 - 569)
10 mg, 4 minute IV	281 (134 - 426)	286 (163 - 426)

Table 97. Theta Parameter Estimates for the NONMEM Fitting of the Applicant's Final Model Structure

Theta	Description	Estimate	FIX
1	CL	16	-
2	V1	30.9	-
3	Q2	73	-
4	V2	85.9	-
5	Q3	15.9	-
6	V3	991	-
7	BWonCL	0.75	FIX
8	BWonV	1	FIX
9	error	0.277	-
10	Patient	0.582	-

The FOCE w. Interaction estimation algorithm was utilized.

Table 98. Omega and Sigma Parameter Estimates for the NONMEM Fitting of the Applicant's Final Model Structure

Omega	Description	Estimate	Etabar	p val	Shrinkage
1,1	iivCL	0.0476	0.007 (0.013)	0.5776	28.8%
2,2	iivV1	0.105	0 (0.019)	0.9858	28.4%
3,3	iivQ2	0	-0 (0)	0.7234	98.7%
4,4	iivV2	0.0103	-0.001 (0.003)	0.8605	60.3%
5,5	iivQ3	0.016	-0.003 (0.004)	0.4548	58.1%
6,6	Error	0.0661	-0.043 (0.016)	0.0065	25.8%
Sigma	Description	Estimate	Shrinkage		
1,1	.	1	3.7%		

* Correlations in omega are shown as the off-diagonal elements. SAME blocks are not shown.

Table 99. Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
AmisulprideSimulationDataset.R	Code to create NONMEM simulation dataset and analyze results with	..\Reviews\PM Review Archive\2018\amisulpride_NDA209510_JCE\PPK Analyses

16.2.3. Summary of Bioanalytical Method Validation and Performance

In five studies (i.e., DP10020, DP10013, DP10014, DP10018 and DP10019) where pharmacokinetic blood samples were collected, amisulpride was measured in plasma using validated bioanalytical assay methods based on LC-MS/MS.

Amisulpride is a racemic drug containing 50% each of R- and S-amisulpride. Originally, two enantiomers were not separately measured for PK in this application. Later, the Applicant supplemented amisulpride enantiomer analysis report (SDN 11 dated 1/8/2018) measuring each enantiomer in plasma samples collected in DP10013 and DP10020. It suggested that R- and S-amisulpride behave in virtually the same way in humans.

The plasma samples obtained in the studies were analyzed in (b) (4) (b) (4). In support of bioanalytical assay, the Applicant submitted following bioanalytical method validation reports and final analytical reports were submitted as follows:

- Validation report: "Validation of an LC-MS/MS method for the measurement of amisulpride in human plasma" (Project No: (b) (4) 115501QB02)
- Analytical report:
  - DP10020: "Determination of amisulpride in human plasma from clinical study DP10020 (Project No: (b) (4) 286061QB01)
  - DP10013: "Determination of amisulpride in human plasma samples by LC-MS/MS from clinical Thorough QT (TQT) study DP10013" (Project No: (b) (4) 256196QB01)
  - DP10014: "Determination of amisulpride in human plasma samples by LC-MS/MS from clinical study DP10014" (Project No: (b) (4) 115501QB03)

- DP10018 & DP10019: "Determination of Amisulpride in human plasma samples by LC-MS/MS from clinical studies DP10018 & DP10019" (Project No: (b) (4) 294618QB01)

A method was validated for measuring amisulpride in human plasma in K_2EDTA tube. Plasma samples (each 50 µL) were extracted by a liquid-liquid extraction procedure followed by liquid chromatography/tandem mass spectrometry (LC-MS/MS). The accuracy and precision for each analyte was acceptable. The bioanalysis was conducted within 253 days after sample collection, which is shorter than the time frame that the long-term stability is established, i.e., 259 days. Please see Table 100.

Table 100. Bioanalytical Method Validation Summary

Attribute	Results
Analyte and internal standard	Amisulpride (m/z 370.3 → 214.1) IS: amisulpride-D5 (m/z 375.3 → 242.1)
Linear range	2–2000 ng/mL
LLOQ	2 ng/mL
ULOQ	2000 ng/mL
Selectivity, Calibration curve Accuracy (%RE) Precision (% CV),	The response of blank sample was <20% of the LLOQ calibration standard peak area for the analyte and 5% for the internal standard. % RE =1.0% at LLOQ; -2.1% to 2.0% at the other concentrations % CV =5.7% at LLOQ; 2.1 to 5.5% at the other concentrations
QC Concentration	2, 6, 60, 1500 ng/mL
Intra-day precision (% CV)	(0.8, 6.6)
Intra-day accuracy (% RE)	(-4.0, 11.5)
Inter-day precision (% CV)	(1.1, 7.9)
Inter-day accuracy (% RE)	(1.0, 5.5)
Freeze and thaw stability	4 cycles at -20°C
Long-term stability	259 days at -20°C
Short-term stability	Whole blood: 2 h at 30°C and 37°C Plasma: 28 h at room temperature Extracts: 4 days at 4°C

RE = relative error; CV = coefficient of variation; LLOQ = lower limit of quantitation; QC = quality control; ULOQ = upper limit of quantitation

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MIMI T PHAN
10/05/2018

DRAGOS G ROMAN
10/05/2018

VICTOR CRENTSIL
10/05/2018