Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 213801 and NDA 202611/S-017
Link to EDR	\\CDSESUB1\evsprod\NDA213801\0001 \\CDSESUB1\evsprod\NDA202611\0017
Submission Date	9/28/2020
Submission Type	Priority
Brand Name	MYRBETRIQ and MYRBETRIQ GRANULES
Generic Name	Mirabegron extended-release tablets and mirabegron extended-release granules for oral suspension
Dosage Form and Strength	Tablets: 25 mg and 50 mg Granules for oral suspension: 8.3 g of granules containing 830 mg mirabegron per bottle
Route of Administration	Oral
Proposed Indication	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older
Applicant	Astellas Pharma Global Development, Inc.
Associated IND	IND 069416
OCP Review Team	Peng Zou, PhD; Yun Wang, PhD; Jingyu Yu, PhD; Yanhui Lu, PhD
OCP Final Signatory	Yanhui Lu Team Leader Office of Clinical Pharmacology

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1. EXECUTIVE SUMMARY

Myrbetriq® (mirabegron, 25 mg and 50 mg extended-release tablets) is currently approved in the US for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency in adults (NDA 202611) in 2012. In the NDA approval letter dated June 28, 2012, to satisfy the Pediatric Research Equity Act (PREA) requirements, FDA requested the Applicant Astellas Pharma Global Development, Inc. (Astellas) to develop mirabegron ER microgranule-based suspension in children from 5 to < 18 years of age with neurogenic detrusor overactivity (NDO) as a postmarketing requirement (PMR). FDA requested two PMR studies:

- PMR 1898-1: Open label, multicenter single ascending dose study to evaluate pharmacokinetics, safety and tolerability of mirabegron modified release microgranule based suspension in children from 5 to < 18 years of age with NDO or OAB (178-CL-202 and 178-CL-203).
- PMR 1898-2 Open label, baseline-controlled, multi-center, sequential dose titration study followed by a fixed dose observation period to evaluate pharmacokinetics, safety and efficacy of mirabegron modified release microgranule-based suspension in children from 5 to < 18 years of age with NDO (178-CL-206/206A).

On March 18, 2016, FDA issued a written request thereby lowering the minimum age in the pediatric population from 5 years to 3 years for the pivotal phase 3 study 178-CL-206A.

The final reports for Studies 178-CL-202 and 178-CL-203 were submitted to IND 069416 on February 24, 2016 and March 31, 2017, respectively. The applicant received the fulfillment of PMR 1898-1 letter on December 27, 2018. NDA 213801 and concurrent efficacy supplement-17 (S-17) to NDA 202611 were filed on September 28, 2020 to fulfill the PMR 1898-2 and to satisfy the written request dated March 18, 2016. The proposed indication in current submission is for the treatment of pediatric patients aged 3 to < 18 years with NDO. In addition to the approved Myrbetriq® extended-release (ER) tablets, Astellas has developed mirabegron ER granules (mirabegron for oral suspension) for pediatric patients.

1.1 Recommendations

The Office of Clinical Pharmacology Division of Cardiometabolic and Endocrine Pharmacology and Division of Pharmacometrics have reviewed the information contained in NDA 213801 and NDA 202611/S-017 recommend approval of this NDA. The information also satisfies the PREA requirements 1898-1 and 1898-2 outlined in the approval letter for NDA 202611 dated Jun 28, 2012 and the written requests issued on Mar 18, 2016.

Key clinical pharmacology review issues with specific recommendations/comments are summarized in the table below:

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	Based on cross-study comparison, population pharmacokinetic (popPK) analysis showed that steady-state AUC_{0-t} values of mirabegron for pediatric subjects receiving the proposed maximum dose (PED50, defined at the bottom of this table) fell within the range (42 – 854 ng*h/mL) of observed adult exposures receiving approved mirabegron tablets 50 mg once daily. Median steady-state AUC_{0-t} values in children aged 3 to < 12 years (277 ng*h/mL) and adolescents aged 12 to < 18 years (260 ng*h/mL) receiving PED50 were slightly higher than that in adults (188 ng*h/mL) receiving 50 mg once daily. Similarly, steady-state AUC_{0-t} values of mirabegron for pediatric subjects receiving the proposed starting dose (PED25,

	defined at the bottom of this table) fell within the range (17 – 578 ng*h/mL) of observed adult exposures receiving approved mirabegron tablets 25 mg once daily.
General dosing instructions	MYRBETRIQ Tablet or Granules should be taken with food in pediatric patients. The body weight-based doses are listed below: • Patients with body weight ≥ 35 kg: tablets 25 - 50 mg once daily (QD); granules 48 – 80 mg QD • Patients with body weight ≥ 22 kg and < 35 kg: granules 32 – 64 mg QD • Patients with body weight < 22 kg: granules 24 – 48 mg QD
Dosing in patient subgroups (intrinsic and extrinsic factors)	The daily dose of MYRBETRIQ Tablet or Granules should not exceed the recommended starting dose in the following populations: • Pediatric patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2). • Pediatric patients with moderate hepatic impairment (Child-Pugh Class B). MYRBETRIQ Tablet or Granules is not recommended for use in pediatric patients with end-stage renal disease (ESRD) or in pediatric patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustment is needed for pediatric patients with mild-to-moderate renal impairment and pediatric patients with mild hepatic impairment.
Labeling	Refer to Section 2.4 for the review team's recommendations.
Bridge between the to-be-marketed and clinical trial formulations	To-be-marketed (TBM) formulations of mirabegron ER granules for oral suspension and the approved mirabegron tablets were used in the pivotal clinical trial (Study 178-CL-206A).
Other (specify)	None.

PED50: pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 50 mg tablet once daily.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

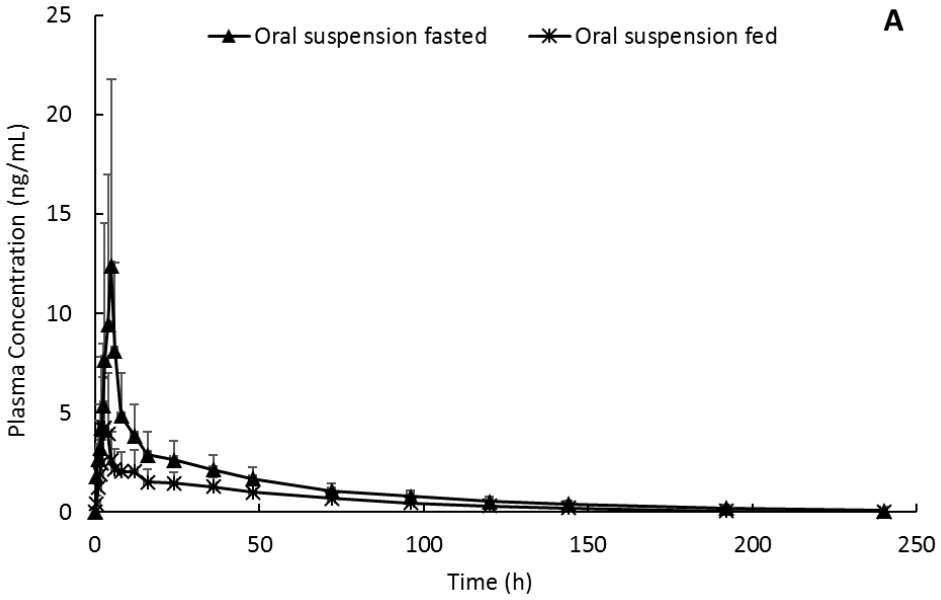
2.1 Pharmacology and Clinical Pharmacokinetics

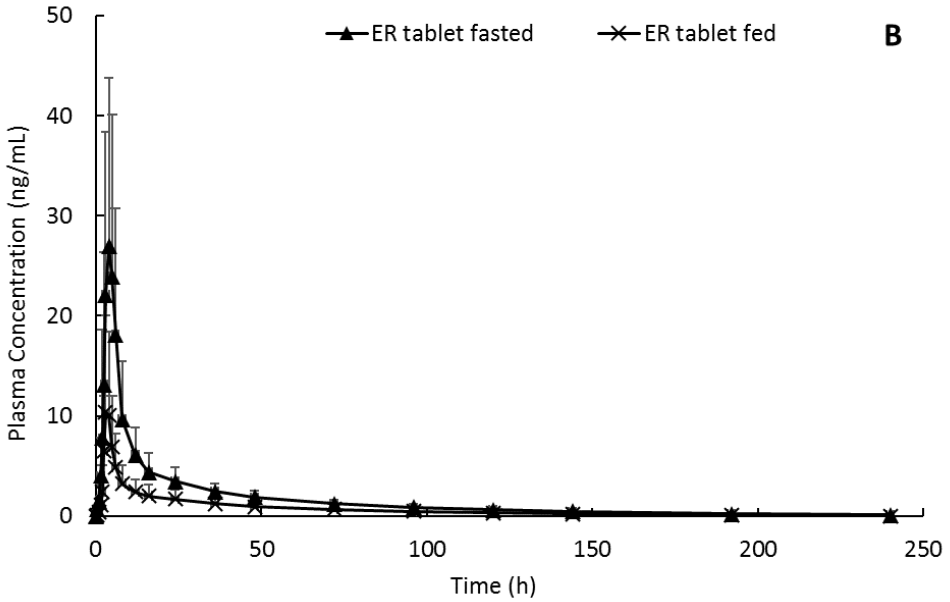
Mirabegron, also known as YM178, is an agonist of the human beta-3 adrenergic receptor (AR). Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR which increases bladder capacity. For pediatric patients ≥ 35 kg, the recommended starting dose is 25 mg once daily (QD) or 6 mL (8 mg/mL) QD with food, for mirabegron ER tablets and granules, respectively. The ER granules were reconstituted with water to prepare a suspension with a concentration of 8 mg/mL oral suspension. Based on individual patient efficacy and tolerability, the dose may be increased to 50 mg or 10 mL (i.e. 80 mg) once daily after 4-8 weeks for mirabegron ER tablets and oral suspension, respectively. For patients with body weight ≥ 22 kg and < 35 kg, the recommended starting dose and maximum doses are 4 mL and 8 mL of oral suspension QD, respectively, orally administered with food. For patients with body weight ≥ 11 kg and < 22 kg, the recommended starting dose and maximum doses are 3 mL and 6 mL of oral suspension QD, respectively, orally administered with food.

Absorption: Across different studies, the median T_{max} of mirabegron following oral administration of a single dose of mirabegron ER tablets and oral suspension in pediatric patients under fed state was 4-5 hours. Within the dosing range of 25 – 75 mg QD, pediatric patients receiving higher doses of mirabegron ER tablets showed greater extent of absorption compared to patients receiving lower doses of mirabegron ER tablets. In healthy adult subjects, the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} of mirabegron oral suspension 50 mg administered under fed state were 56%, 63% and 82% lower than that of mirabegron ER tablet 50 mg administered under fed state. PopPK analysis showed that mirabegron oral suspension formulations had 57.1% lower bioavailability (BA) compared to the tablet formulation in pediatric patients at the same dose.

In healthy adult subjects, a high-fat meal decreased the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} of mirabegron oral suspension by 45%, 49% and 63%, respectively. Similarly, in healthy adult subjects, a high-fat meal decreased the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} of mirabegron ER tablets by 57%, 60% and 60%, respectively. In phase 3 study, mirabegron ER tablets or oral suspension were taken orally within 1 hour before or after breakfast. In drug label, both mirabegron ER tablets and oral suspension are proposed to be administered with food in pediatric NDO patients.

Figure 1. Mean (+SD) Plasma Concentration-Time Profiles of Mirabegron Following Oral Administration of a Single Dose of (A) Mirabegron Oral Suspension 88 mg and (B) ER tablet 50 mg in Healthy Adult Subjects Under Fasted and Fed States





Source: Reviewer's plots based on Applicant's data from Studies 178-CL-201 and 178-CL-208

Distribution: Mirabegron volume of distribution was relatively large in pediatric patients (the range of Vz/F under fed state across studies: 4895 – 13726 L) and increased with increasing body weight.

Elimination: The terminal elimination half-life ($T_{1/2}$) of mirabegron is approximately 26 to 31 hours in pediatric patients. PopPK model predicted that mirabegron clearance in pediatric patients increased with body weight.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

MYRBETRIQ tablet and granules are not bioequivalent. For the two dosage forms, different body weight-based starting doses and maximum doses are proposed for pediatric patients.

Pediatric patients weighing less than 35 kg: use MYBETRIQ granules only

Body Weight Range	Starting Dose (PED25)	Maximum Dose (PED50)
11 kg to less than 22 kg	3 mL (24 mg) QD	6 mL (48 mg) QD
22 kg to less than 35 kg	4 mL (32 mg) QD	8 mL (64 mg) QD

Note: PED25: pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 25 mg tablet once daily; PED50: pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 50 mg tablet once daily.

Pediatric patients weighing 35 kg or more: use MYBETRIQ tablets or MYBETRIQ granules
For use of MYRBETRIQ tablets, the recommended starting dosage (PED25) is 25 mg QD orally. If needed, increase to a maximum dose (PED50) of MYRBETRIQ 50 mg QD orally. For use of MYRBETRIQ granules, the recommended starting dosage (PED25) is 6 mL (48 mg) QD orally. If needed, increase to a maximum dosage (PED50) of MYRBETRIQ granules 10 mL (80 mg) QD orally.

Both MYBETRIQ tablets and MYBETRIQ granules should be orally administered under fed state.

2.2.2 Therapeutic individualization

Renal Impairment: In pediatric phase 3 trial (Study 178-CL-206A), pediatric patients with mild-to-moderate renal impairment (eGFR < 90 mL/min and > 30 mL/min) were included and no dose adjustment was applied to these patients. Pediatric patients with severe renal impairment (eGFR < 30 mL/min) were excluded from Study 178-CL-206A. The clinical pharmacology review team does not recommend dose adjustment for pediatric patients with mild-to-moderate renal impairment. The team recommends that the dose for pediatric patients with severe renal impairment not exceed the recommended MYBETRIQ tablet or granule starting dose. MYBETRIQ tablets or MYBETRIQ granules have not been studied in patients with end-stage renal disease (ESRD) (CLcr less than 15 mL/min or eGFR less than 15 mL/min/1.73 m^2) or patients requiring hemodialysis. The use of MYBETRIQ tablets or MYBETRIQ granules in patients with ESRD or patients requiring hemodialysis is not recommended.

Hepatic Impairment: In Study 178-CL-206A, pediatric patients with mild hepatic impairment were enrolled while pediatric patients with moderate-to-severe hepatic impairment were excluded. The clinical pharmacology review team does not recommend dose adjustment for pediatric patients with mild hepatic impairment. The team recommends that the dose for pediatric patients with moderate hepatic impairment not exceed the recommended MYBETRIQ tablet or granule starting dose. MYBETRIQ tablets or MYBETRIQ granules have not been studied in patients with severe hepatic impairment (Child-Pugh Class C). The use of MYBETRIQ tablets or MYBETRIQ granules in patients with severe hepatic impairment is not recommended.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following Labeling recommendation and comments:

Section 2.5: proposed doses for pediatric patients with server renal impairment or moderate hepatic impairment.
Section 7.1: deleted (b) (4).
Section 12.3: updated pharmacokinetic information for pediatric patients and MYBETRIQ granules.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

In addition to Myrbetriq® (mirabegron, 25 mg and 50 mg extended-release tablets) approved by the FDA under NDA 202611, Astellas has developed mirabegron granules (mirabegron for oral suspension) for pediatric indication. These granules form an oral suspension (8 mg/mL mirabegron) when reconstituted with water. In support of NDA 213801 and NDA 202611/S-17, Astellas conducted 5 clinical studies including four phase 1 studies (two relative bioavailability/food effect studies and two single ascending dose studies) and one phase 3 study. The clinical trials that support the safety and efficacy of MYBETRIQ and MYBETRIQ granules in pediatric NDO patients were conducted under IND 069416.

At the meeting with Astellas held on November 6, 2019, FDA agreed that the development program appeared sufficient to support the submission of an efficacy and safety supplement and new NDA for the

proposed indication for mirabegron tablets and granules for treatment of NDO in pediatric patients. Based on these comments, Astellas canceled pre-NDA meeting.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology				
Mechanism of Action	Mirabegron, an agonist of the human beta-3 adrenergic receptor (AR), relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR which increases bladder capacity.			
Active Moieties	Mirabegron			
QT Prolongation	No clinically significant ECG abnormalities or QTcF prolongation were observed in Study 178-CL-206A			
General Information				
Bioanalysis	Two liquid chromatography–mass spectrometry (LC-MS) methods were used to measure plasma mirabegron concentrations.			
Healthy vs. Patients	No comparison of PK between pediatric NDO patients and healthy pediatrics was conducted.			
Drug exposure at steady state (Mean ± SD)	AUC_{0-t} for PED25: 166.3 ng*h/mL (children, N = 1, SD not calculated); 137.8 ± 53.1 ng*h/mL (adolescents, N = 3) AUC_{0-t} for PED50: 310.1 ± 163.1 ng*h/mL (children, N = 43); 291.6 ± 171.8 (adolescents, N = 24)			
Range of effective dose or exposure	Dose-response analysis for mean volume voided in adult patients with overactive bladder showed that 52%, 85%, and 98% of the maximum efficacy was achieved at the doses of 25 mg, 50 mg, and 100 mg QD, respectively. The mean steady-state AUC_{0-t} in adult patients receiving Myrbetriq tablets 25 mg QD was 69 ng*h/mL.			
Maximally tolerated dose or exposure	300 mg QD for 14 days and a single dose of 400 mg in adult patients			
Pharmacodynamics	The mean systolic blood pressure increased by 5.9 mm Hg and the mean diastolic blood pressure increased by 2.3 mm Hg above baseline in patients less than 8 years of age on MYRBETRIQ/MYRBETRIQ Granules at a dose equivalent of MYRBETRIQ 50 mg daily dose in adults.			
Dose Proportionality	PopPK analysis showed that both MYRBETRIQ and MYRBETRIQ Granules exhibited more than proportional PK in pediatric patients in the dose range of PED25 – PED50.			
Accumulation	Tablets: children (fed) 1.6 - 1.8; adolescents (fed) 1.6 - 2.4 (Study 178-CL-202)			
Variability (CV)	Tablets: children (fed) AUC 50.8 – 64.6%, C_{max} 67.6 – 72.6%; adolescents (fed) AUC 28.1 – 52.0%, C_{max} 57.4 – 81.6% Granules: AUC (fed) 62.3%, C_{max} (fed) 63.7%			
Absorption				
Bioavailability	Tablets: 29% at 25 mg dose and 35% at 50 mg dose			
Fasted T_{max} (Median and Range)	Tablets: 3.95 h (3.47 – 4.27 h)			
Food Effect Following a High-Fat Meal (Fed/fasted) [90% CI]	**Drug component**	**$AUC_{0-\infty}$**	**C_{max}**	**T_{max} (Median, hour)**
	Tablets	43% [37% - 49%]	40% [31% - 52%]	Fed: 3.0, Fasted: 4.0
	Granules	55% [50% - 61%]	37% [29% - 47%]	Fed: 3.0, Fasted: 4.0

Distribution	
Volume of Distribution	Steady-state V_d/F: 4895 – 13726 L
Plasma Protein Binding	71%
Substrate transporter systems	In vitro data showed that mirabegron is a substrate of P-gp, OCT1, OCT2 and OCT3
Elimination	
Terminal Elimination half-life (Mean ± SD)	Tablets: 29.0 ± 6.1 h; Granules: 26.0 ± 5.8 h
CL/F (Mean ± SD)	Tablets: children 113 ± 63 L/h; adolescents 230 ± 137 L/h Granules: 254 ± 165 L/h
Metabolism	
Fraction metabolized (% dose)	64% of dose recovered in feces and urine is metabolized.
Primary metabolic pathway(s)	CYP3A4, CYP2D6, butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), and possibly alcohol dehydrogenase
Excretion	
Primary excretion pathways (% dose) ±SD	-- mirabegron in feces: 34% (approximately 0% unchanged) -- mirabegron in urine: 55% (approximately 25% unchanged)
In vitro interaction liability (as a perpetrator)	
Inhibition/Induction of metabolism	Mirabegron is a moderate and time-dependent inhibitor of CYP2D6, and a weak inhibitor of CYP3A.
Inhibition/Induction of transporter systems	Mirabegron is a weak inhibitor of P-gp.

PED25: pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 25 mg tablet once daily.
PED50: pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 50 mg tablet once daily.

3.3 Clinical Pharmacology Review Questions

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

Based on cross-study comparison, clinical pharmacology information showed that pediatric subjects' exposure to mirabegron fell within the range of adult exposures, and the mean steady-state exposure in pediatric patients was higher than that in adult patients. PopPK analysis showed that the steady-state AUC_{0-t} values of mirabegron for pediatric subjects in pivotal efficacy study (Study 178-CL-206A) receiving PED50 (pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 50 mg tablet once daily) fell within the range (42 – 854 ng*h/mL) of observed adult exposures receiving 50 mg once daily (NDA 202611, original submission). The median steady-state AUC_{0-t} values in children (277 ng*h/mL) and adolescents (260 ng*h/mL) patients receiving PED50 were slightly higher than that (188 ng*h/mL) in adults receiving 50 mg once daily. The steady-state AUC_{0-t} values of mirabegron for pediatric subjects in Study 178-CL-206A receiving PED25 (pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 25 mg tablet once daily) fell within the range (17 – 578 ng*h/mL) of observed adult exposures receiving 25 mg once daily (NDA 202611, original submission). The median steady-state AUC_{0-t} values in children (166 ng*h/mL) and adolescents (137 ng*h/mL) patients receiving PED25 were higher than that (69 ng*h/mL) in adults receiving 50 mg once daily. Refer to Section 3.3.2 for more information.

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

Yes, the proposed dose regimen is appropriate for treatment of NDO in pediatric patients aged 3 years and older. The proposed pediatric regimen is supported by clinical efficacy and safety data in pediatric patients, matching to adult drug exposure, and exposure-response for safety. For more information related to clinical efficacy and safety data in pediatric patients, refer to clinical and statistical reviews in DARRTS.

Mirabegron exposure matching:
The approved starting and maximum doses for adult patients with overactive bladder (OAB) is 25 mg QD and 50 mg QD, respectively. MYBETRIQ and MYBETRIQ granules are not bioequivalent. PopPK simulation predicted that mirabegron granule formulation had 57.1% lower bioavailability compared to tablet formulation in pediatric patients. In Study 178-CL-206A, the starting pediatric dose PED25 and the maximum pediatric dose PED50 for MYBETRIQ and MYBETRIQ granules were optimized to match steady-state mirabegron exposures in adults taking MYBETRIQ 25 mg tablet QD and 50 mg tablet QD, respectively. Based on popPK simulation, the body weight categories for oral suspension dosing selection were determined to be 11-< 22 kg, 22-<35 kg and >=35 kg. For oral suspension, the PED25 doses of 24, 32, and 48 mg (3, 4, and 6 mL) and FED50 doses of 48, 64, and 88 mg (6, 8, and 11 mL) were selected for the three body weight groups, respectively (Table 3.3.2.1). The body weight cutoff for tablet dosing selection was determined as 35 kg. Subjects >= 35 kg could take tablets at doses of 25 mg and 50 mg for PED25 and PED50, respectively.

Table 3.3.2-1. Body weight-based PED25 and PED50 doses for MYBETRIQ and MYBETRIQ granules in pediatric NDO patients in Study 178-CL-206A

Dose	Body Weight Range (kg)	Suspension Volume (mL)†	Tablet Dose (mg)
PED25	11 to < 22	3	Not allowed
	22 to < 35	4	Not allowed
	≥ 35	6‡	25
PED50	11 to < 22	6	Not allowed
	22 to < 35	8	Not allowed
	≥ 35	11‡	50

PED25: pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 25 mg tablet once daily; PED50: pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 50 mg tablet once daily.

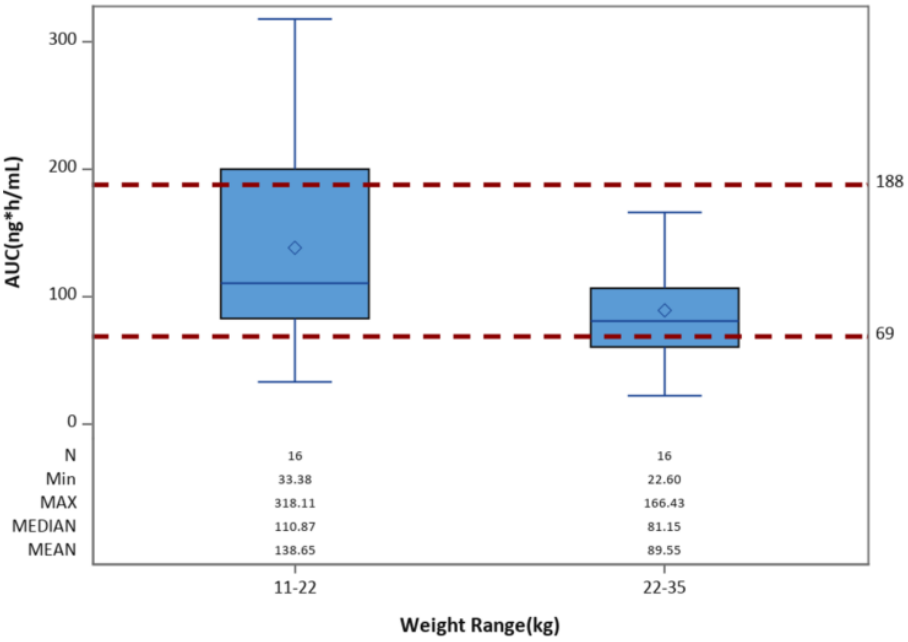
† Mirabegron oral suspension of formulation C (granules were reconstituted with water to prepare a suspension with a concentration of 8 mg/mL).

‡ For patients with a body weight ≥ 35 kg who did not want to or were unable to take tablets, the oral suspension could be administered.

Source: Summary of Clinical Pharmacology Studies, Table 4

According to clinical pharmacology review team's analysis, in Study 178-CL-206A, the proposed starting doses (3 mL for body weight range 11 kg to less than 22 kg; 4 mL for body weight range 22 kg to less than 35 kg) generated median steady-state AUC_{0-t} similar to or slightly higher than that in adult patients taking MYBETRIQ 25 mg tablet QD (Figure 3.3.2-1). Refer to Section 4.3 Population PK Analysis for more information.

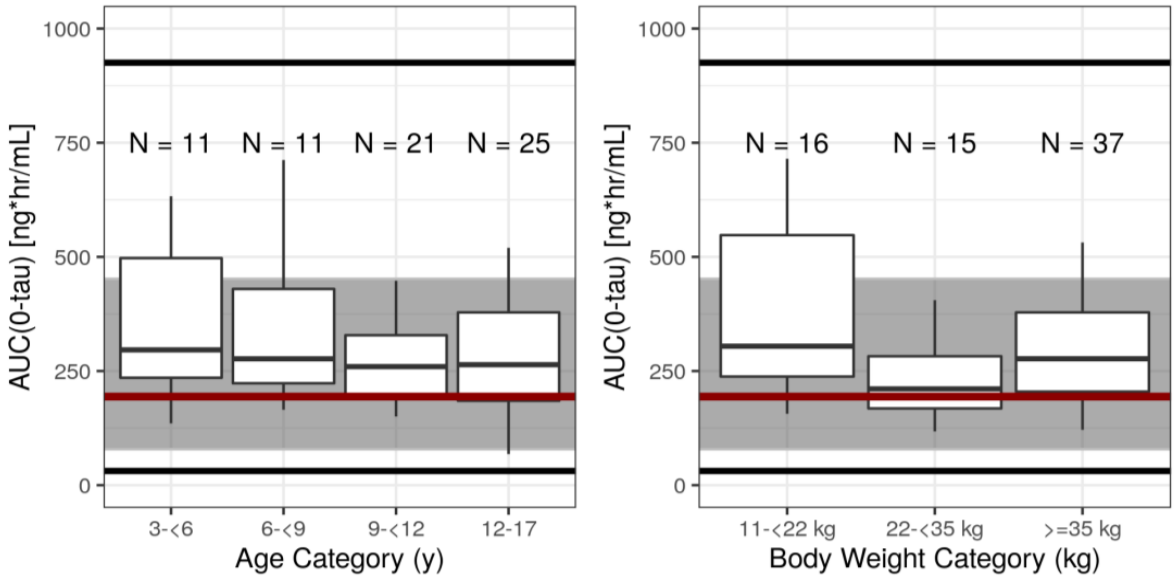
Figure 3.3.2-1. A comparison of AUC for starting dose of mirabegron oral suspension in NDO patient with body weight less than 35 kg*



***** The red dash line corresponding to the targeted AUC exposure in adults, which is 69 and 188 ng*h/mL for starting and maximum dose, respectively.
Source: Reviewer's popPK analysis

The individual steady-state AUC_{0-t} values for pediatric patients in Study 178-CL-206A taking PED50 dose (68 out of 71 patients that had measurable PK concentrations) were calculated using popPK analysis and compared graphically to that of adults taking MYBETRIQ 50 mg tablets by age and body weight category (Figure 3.3.2-2). All pediatric subjects' exposure fell within the range of adult exposures, and the majority fall within the 5^{th}-95^{th} percentile of adult data. The median steady-state AUC_{0-t} values across age- and body weight-based subgroups were similar to or slightly higher than that in adults (188 ng*h/mL). Refer to Section 4.3 Population PK Analysis for more information.

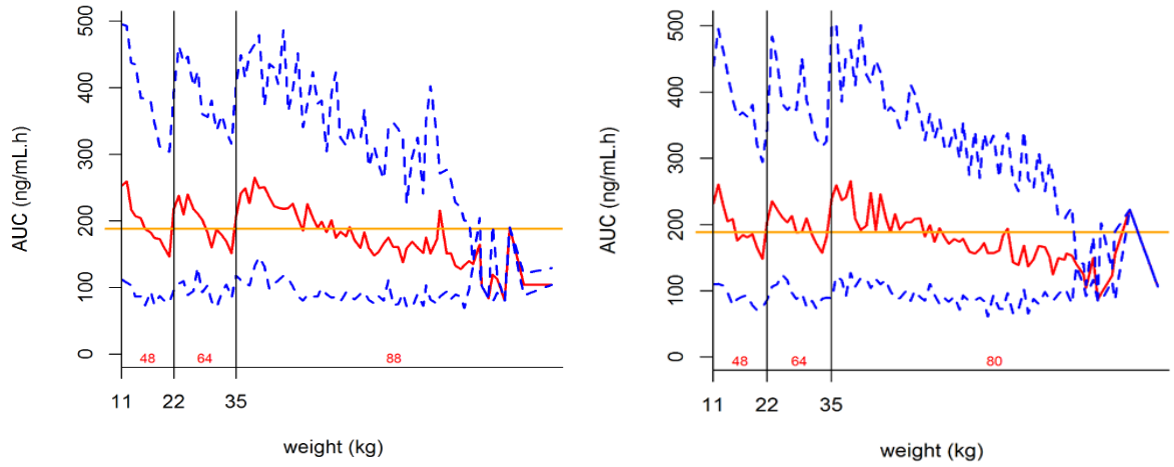
Figure 3.3.2-2. Steady-state AUC at PED50 for pediatric patients in Study 178-CL-206A compared to adult mirabegron exposure at 50 mg by age (left) and body weight (right) category



*The boxplots represent percentiles for the pediatric subgroups: the box shows the 25th, 50th, and 75th percentiles, and the ends of the whiskers are the 5th and 95th percentile in each category. The distribution of adult exposures is shown as annotations on the plots: solid black lines represent the minimum and maximum, the solid red line is the median, and the gray shaded band is the 5th-95th percentile of adult exposures. The adult exposure distribution was based on individual predicted exposures from the final population PK model in adults [Study No. 178-PK-015 in approved mirabegron ER tablet].
Source: IR response 2020-Dec-14, Figure 1

For the oral suspension, while 88 mg or 11 mL was administered in pediatric patients with body weight ≥ 35 kg in Study 178-CL-206A, the Applicant proposed to reduce the dose of oral suspension to 80 mg or 10 mL in the drug label in order to dose the oral suspension with a single dosing device administration. The Applicant provided popPK simulation results to support the proposed dose reduction. As shown in Figure 3.3.2-3, for each body weight in the population, the median and 5th and 95th percentiles for predicted AUCs were calculated and plotted versus body weight. Based on the simulation data, the proposed dose reduction from 88 mg QD to 80 mg QD had a limited impact on the median steady-state AUCs in pediatric patients with body weight ≥ 35 kg. The oral suspension dose of 80 mg QD generated mirabegron exposures in pediatric patients comparable to that in adult patients. The proposed dose reduction appears reasonable. Refer to Section 4.3 Population PK Analysis for more information.

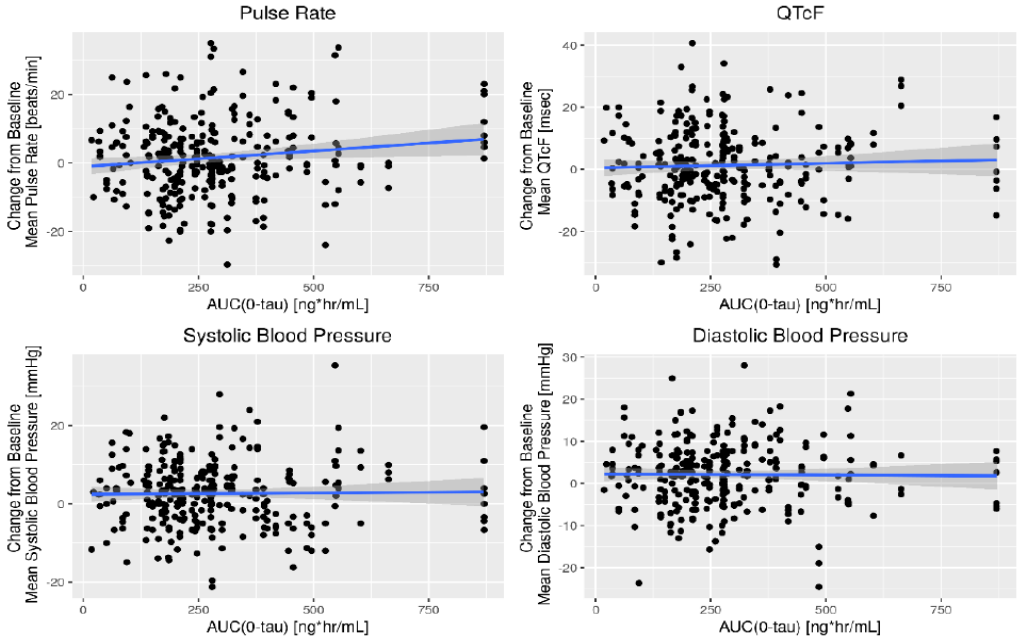
Figure 3.3.2-3. Simulated impact of dose reduction from 88 mg QD to 80 mg QD on the steady-state AUC in pediatric patients with body weight ≥ 35 kg taking oral suspension in Study 178-CL-206A (left plot 88 mg QD and right plot 80 mg QD)*



*The orange line is the target AUC level (188 ng*h/mL) which is determined from adult study data in approved tablet formulation. The red curve is the median simulated AUC, and the two blue curves represent the 5th and 95th percentiles of predicted AUCs.
Source: IR response 2021-Jan-11, Figure 1

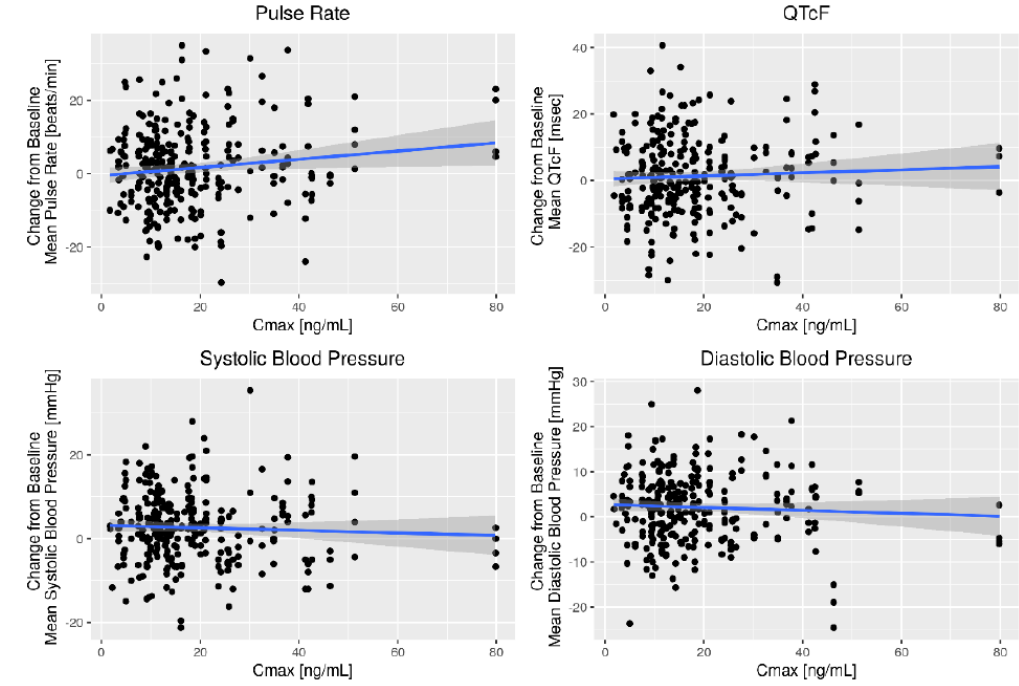
Exposure-response for safety:
The Applicant conducted mirabegron exposure-response analysis for vital sign endpoints including pulse rate, blood pressure, and QTcF interval. No trend was observed with systolic blood pressure, diastolic blood pressure, and QTcF interval at the observed range of $AUC_{0\text{-}t}$ (0 – 870 ng*h/mL) or C_{max} (0 – 80 ng/mL) (Figure 3.3.2-4 and Figure 3.3.2-5). A positive trend is noted for pulse rate or heart rate in the pediatric studies. PopPK analysis showed that the mean ± SD steady-state $AUC_{0\text{-}t}$ of mirabegron in children and adolescents taking PED50 in Study 178-CL-206A was 310 ± 163 and 292 ± 172 ng*h/mL, respectively. The mean ± SD steady-state C_{max} of mirabegron in children and adolescents taking PED50 was 20.6 ± 13.6 and 18.4 ± 12.5 ng/mL, respectively. At the observed mirabegron exposure levels in pediatric patients, no obvious increase in heart rate was observed.

Figure 3.3.2-4. Change from baseline mean pulse rate, QTcF interval, and systolic and diastolic blood pressure versus individual predicted mirabegron steady-state AUC_{0-t} for patients in Study 178-CL-206A



*Solid blue line (grey shaded region) represents prediction (95% confidence interval) from a linear regression. Steady-state AUC_{0-t} calculated based on the dose administered on the day of observation.
Source: IR response 2021-Jan-14, Figure 4

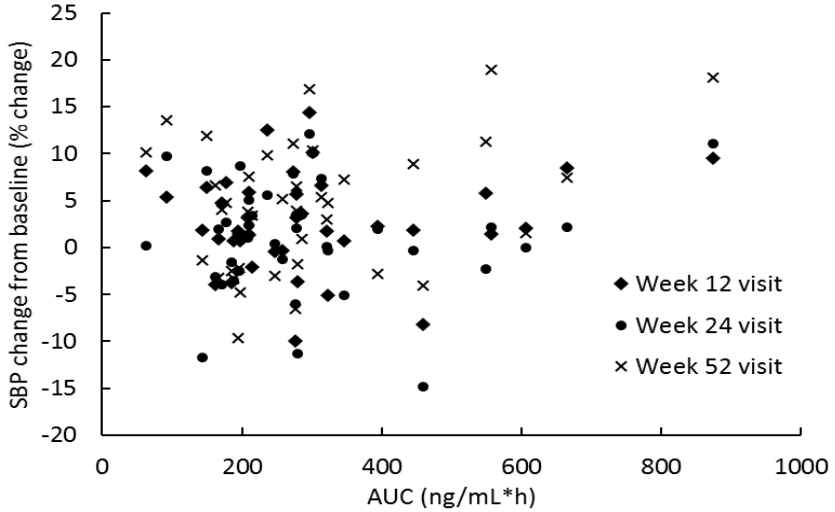
Figure 3.3.2-5. Change from baseline mean pulse rate, QTcF interval, and systolic and diastolic blood pressure versus individual predicted mirabegron steady-state C_{max} for patients in Study 178-CL-206A



*Solid blue line (grey shaded region) represents prediction (95% confidence interval) from a linear regression. Steady-state C_{max} calculated based on the dose administered on the day of observation.
Source: IR response 2021-Jan-14, Figure 5

In Study 178-CL-206A, mean systolic blood pressure (SBP) in children aged ≥ 3 years and < 12 years increased from baseline by 9.7%, 7.0% and 11.1% at weeks 12, 24, and 52, respectively. The blood pressure increases were larger in patients aged 4 – 7 years. Exposure-response analysis for change in SBP was conducted in children patients (Figure 3.3.2-6). Although 10-20% increase in SBP from baseline was observed in 3 among 5 children with AUC > 500 ng*h/mL, more than 10% increase in SBP was also observed in children with AUC < 400 ng*h/mL. The review team concluded that there was no clear exposure-response relationship between blood pressure elevations and mirabegron exposure in children.

Figure 3.3.2-6. Exposure-response analysis for % change in systolic blood pressure from baseline in children patients by visit



Source: Reviewer's exposure-response analysis based on blood pressure data in Study 178-CL-206A

3.3.3 Is there a management strategy required for subpopulations based on intrinsic factors?

Yes, body weight-based dose regimen was selected to ensure that the mirabegron exposures in pediatric patients across age- and body weight categories could match adult exposure. In addition, dose adjustments are needed for pediatric patients with severe renal or moderate hepatic impairment.

Renal Impairment:
In adult volunteers with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2), C_{max} and AUC were increased by 23% and 66%, respectively. In adult volunteers with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC values were 92% and 118% higher compared to healthy subjects with normal renal function. In pediatric phase 3 trial (Study 178-CL-206A), pediatric patients with mild-to-moderate renal impairment (eGFR < 90 and > 30 mL/min/1.73 m^2) were included and no dose adjustment was applied to these patients. Pediatric patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) were excluded from Study 178-CL-206A. The clinical pharmacology review team does not recommend dose adjustment for pediatric patients with mild-to-moderate renal impairment. The team recommends that the dose for pediatric patients with severe renal impairment not exceed the recommended MYBETRIQ tablet or granule starting dose. MYBETRIQ tablets or MYBETRIQ granules have not been studied in patients with end-stage renal disease (ESRD) (eGFR less than 15 mL/min/1.73 m^2) or patients requiring hemodialysis. The use of MYBETRIQ tablets or MYBETRIQ granules in patients with ESRD or patients requiring hemodialysis is not recommended.

Hepatic Impairment:

In adult volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC were increased by 9% and 19%, relative to adult volunteers with normal hepatic function. In adult volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC values were 175% and 65% higher. In Study 178-CL-206A, pediatric patients with mild hepatic impairment were enrolled while pediatric patients with moderate-to-severe hepatic impairment were excluded. The clinical pharmacology review team does not recommend dose adjustment for pediatric patients with mild hepatic impairment. The team recommends that the dose for pediatric patients with moderate hepatic impairment not exceed the recommended MYBETRIQ tablet or granule starting dose. MYBETRIQ tablets or MYBETRIQ granules have not been studied in patients with severe hepatic impairment (Child-Pugh Class C). The use of MYBETRIQ tablets or MYBETRIQ granules in patients with severe hepatic impairment is not recommended.

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

Yes, the AUC and C_{max} of mirabegron decrease when MYBETRIQ or MYBETRIQ Granule is taken with a meal. In Study 178-CL-206A, mirabegron ER tablets or oral suspension were taken orally within 1 hour before or after breakfast. In the proposed drug label, pediatric patients are instructed to take MYBETRIQ or MYBETRIQ granules with food.

Food Effects on MYBETRIQ:

The effects of food on the PK of MYBETRIQ tablets was evaluated in healthy adults in Study 178-CL-201. In the fed conditions, subjects received a standardized light breakfast (dosing 30 minutes after completion of the light breakfast) and a light lunch 2 hours after dosing. Following administration of MYBETRIQ tablets under fed state, the $AUC_{0\text{-}inf}$ and C_{max} of mirabegron were 57% and 60% lower, respectively, when compared to exposures under fasting conditions (Table 3.3.4-1). Similarly, popPK model predicted that the pediatric patients receiving mirabegron tablets in the fed state would have 45% of steady-state $AUC_{0\text{-}t}$ relative to an equal dose administered in the fasted state.

Table 3.3.4-1. The Effects of Food on the PK Parameters of MYBETRIQ Tablets (Study 178-CL-201, N = 23)

Parameters	Least Squares Geometric Means (N = 23)		% Test/Ref Ratio (90% CI)
	Fed [Test]	Fasted [Reference]	
$AUC_{0\text{-}inf}$ (ng•h/mL)	151.08	355.0	42.56 (36.67 – 49.39)
$AUC_{0\text{-}t}$ (ng•h/mL)	130.44	328.4	39.72 (33.99 – 46.42)
C_{max} (ng/mL)	12.46	30.83	40.42 (31.37 – 52.09)
T_{max} (h)*	3.02 (1.98 – 6.00)	4.02 (1.98 – 5.03)	N.A.

*Median (minimum – maximum).
$AUC_{0\text{-}inf}$ = area under the curve from 0 to infinity; $AUC_{0\text{-}t}$ = area under the curve from time 0 to time t; C_{max} = maximum concentration; N.A. = not available; PK = pharmacokinetic; T_{max} = time to maximum concentration
Source: Reviewer's analysis

Food Effects on MYBETRIQ Granules:

The effects of food on the PK of MYBETRIQ granules was evaluated in healthy adults in Study 178-CL-208. In the fed conditions, subjects received a standardized light breakfast (dosing 30 minutes after completion of the light breakfast) and a light lunch 2 hours after dosing. Following administration of MYBETRIQ granules under fed state, the $AUC_{0\text{-}inf}$ and C_{max} of mirabegron were 45% and 63% lower, respectively, when compared to exposures under fasting conditions (Table 3.3.4-1).

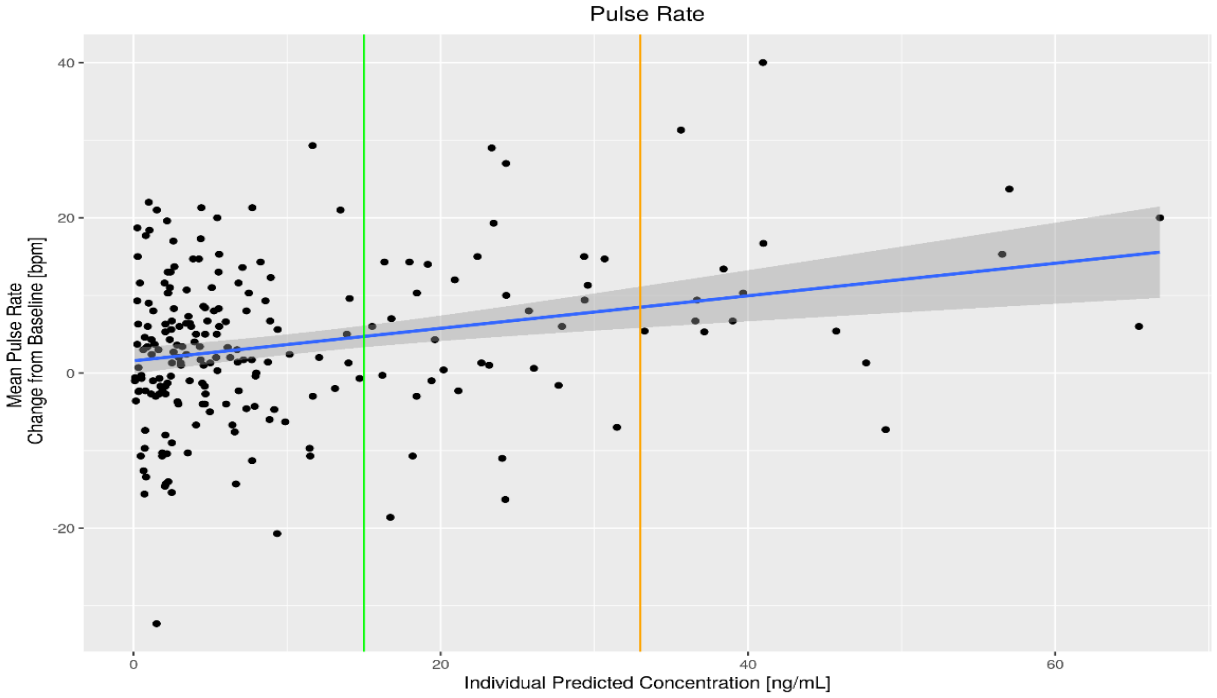
Table 3.3.4-1. The Effects of Food on the PK Parameters of MYBETRIQ Granules (Study 178-CL-208, N = 23)

Parameters	Least Squares Geometric Means (N = 24)		% Test/Ref Ratio (90% CI)
	Fed [Test]	Fasted [Reference]	
$AUC_{0\text{-}inf}$ (ng•h/mL)	138.5	252.6	54.83 (49.65 – 60.55)
$AUC_{0\text{-}t}$ (ng•h/mL)	119.8	234.0	51.19 (46.04 – 56.91)
C_{max} (ng/mL)	4.46	12.09	36.91 (29.24 – 46.59)
T_{max} (h)*	3.00 (2.50 – 12.0)	4.00 (2.50 – 5.98)	N.A.

*Median (minimum – maximum).
$AUC_{0\text{-}inf}$ = area under the curve from 0 to infinity; $AUC_{0\text{-}t}$ = area under the curve from time 0 to time t; C_{max} = maximum concentration; N.A. = not available; PK = pharmacokinetic; T_{max} = time to maximum concentration
Source: Reviewer's analysis

Based on the food effect data collected in Studies 178-CL-201 and 178-CL-208 and popPK analysis, mirabegron exposure appears to increase by approximately two-fold when mirabegron oral suspension or mirabegron tablets are administered under fasting conditions compared to when they are administered in the fed state. The clinical pharmacology team raised a concern with potential risks if a patient takes mirabegron oral suspension or mirabegron tablets on an empty stomach. In the response letter dated January 15, 2021, the Applicant provided exposure-response analysis for change in mean pulse rate from baseline (Figure 3.3.4-1). The median steady-state C_{max} for all patients in Study 178-CL-206A receiving the PED50 dose was predicted to be 16 ng/mL based on administration of mirabegron with food. The Applicant assumed that the median steady-state C_{max} increases by approximately 2.2-fold to 35 ng/mL if patients continually received mirabegron under fasted meal conditions. Based on the linear regression shown in Figure 3.3.4-1, the Applicant predicted that administering mirabegron in the fasted state rather than the fed state would increase the pulse rate by approximately additional 4 beats per minute.

Figure 3.3.4-1. Mean change from Baseline Pulse Rate Versus Individual Predicted Mirabegron Concentration with Annotations for Median Fed and Fasted Steady-State C_{max} in Study 178-CL-206



Solid blue line (grey shaded region) represents prediction (95% confidence interval) from a linear regression. Green vertical line represents median predicted Cmax value for patients in Study 178-CL-206A (16 ng/mL) and the orange vertical line represents extrapolated median Cmax value for patients receiving mirabegron under persistent fasted meal conditions (35 ng/mL).
Source: IR response 2021-Jan-14, Figure 6

The clinical pharmacology review team noted that popPK model predicted a higher median steady-state C_{max} in children receiving the PED50 dose under fed state (17.7 ng/mL) than that in adolescents receiving the PED50 dose under fed state (14.1 ng/mL) in Study 178-CL-206A. Because food decreased the C_{max} of MYBETRIQ granules by 63%, the median steady-state C_{max} in children would be increased approximately 2.7-fold to 48 ng/mL if patients continually receive mirabegron granules under fasted conditions. Based on the linear regression shown in Figure 3.3.4-1, the review team expects that under the worst-case scenario, continually receiving mirabegron granules under fasted conditions would increase the pulse rate in children by approximately additional 7 beats per minute, compared to administrating mirabegron granules under fed conditions. To mitigate the potential risk of increase in heart rate, pediatric patients should take MYBETRIQ or MYBETRIQ granules with food.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Yes, the to-be-marketed (TBM) formulations of mirabegron ER tablets and granules for oral suspension were used in the pivotal clinical trial (Study 178-CL-206A). The mirabegron ER tablets used in all clinical studies in current NDA 213801 were the FDA approved Myrbetriq® (mirabegron, 25 mg and 50 mg ER tablets). No bioequivalence study is needed to bridge the TBM formulations to phase 3 trial formulations.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Two liquid chromatography–mass spectrometry (LC-MS) methods (178-ME-085 and 178-ME-136) were developed to support analysis of plasma mirabegron concentrations. Method 178-ME-085 has an analytical range of 0.2 to 100 ng/mL and was used in Studies 178-CL-201 and 178-CL-208. Method 178-ME-136 has an analytical range of 0.1 to 50 ng/mL and was used in Studies 178-CL-202, 178-CL-203 and 178-CL-206A. The established long-term stability (513 days at −20°C and −70°C for Method 178-ME-085 and 722 days at −20°C and −70°C for Method 178-ME-136) covered the maximum storage periods for corresponding studies. Method validation parameters, including matrix stability parameters, for each method are summarized in Table 4.1-1. The method validation reports are adequate for measuring human plasma concentrations of mirabegron.

An LC-MS method (178-ME-138) was developed for determining plasma concentrations of eight mirabegron metabolites in human sodium heparin plasma containing sodium fluoride in Study 178-CL-202. A partial validation report for Method 178-ME-138 was submitted by the Applicant on January 15, 2021. The validation report was not reviewed because the plasma concentrations of mirabegron metabolites collected from Study 178-CL-202 were not used to support regulatory decision making or drug labeling.

Table 4.1-1. Bioanalytical method validation parameters for quantitation of mirabegron in plasma

Study Number	178-ME-085		178-ME-136	
Matrix	Plasma		Plasma	
Analyte	Mirabegron		Mirabegron	
Analytical instrument and detection method	LC-MS/MS		LC-MS/MS	
Sample preparation technique	LLE		SLE	
Lower limit of quantitation (ng/mL)	0.2		0.1	
Amount of matrix used (mL)	0.25		0.1	
Concentration range (ng/mL)	0.2 to 100		0.1 to 50	
Within-run accuracy (%RE)	−12.1 to −2.49		−12.2 to −1.6	
Between-run accuracy (%RE)	−8.91 to −4.63		−8.0 to −4.2	
Within-run precision (%CV)	0.915 to 9.62		0.9 to 6.1	
Between-run precision (%CV)	2.05 to 7.04		3.1 to 5.6	
Dilution Integrity Accuracy (%RE) Precision (%CV)	4-fold −2.75 3.43	10-fold 0.220 1.79	2-fold −3.3 3.5	10-fold −7.8 1.7
Short-term stability	24 h at room temperature		25 h on ice 14 h at room temperature	
Long-term stability	513 days at −20°C and −70°C		722 days at −20°C and −70°C	
Freeze-thaw stability	6 cycles thawed at room temperature and frozen at −20°C		5 cycles thawed on ice and frozen at −20°C or −70°C	
Whole blood stability	Not tested		4 h at 2 to 8°C 2 h at room temperature	
Test facility	(b) (4)		(b) (4)	
Clinical study in which the method was used	178-CL-201 178-CL-208		178-CL-202 178-CL-203 178-CL-206A	

CV: coefficient of variation; LC-MS/MS: liquid chromatography-tandem mass spectrometry; LLE: liquid/liquid extraction; (b) (4) RE: relative error; SLE: supported liquid extraction.

Source: Summary of Biopharmaceutical Studies, Appendix Table 2

4.2 Clinical BA/BE and Ascending Dose Studies

Two relative bioavailability (BA)/food effect studies (Studies 178-CL-201 and 178-CL-208) and two single dose ascending studies (Studies 178-CL-202 and 178-CL-203) were submitted in this NDA (Table 4.2-1).

Initially, Formulation A was developed and supplied for the relative bioavailability study (178-CL-201). Formulation A is composed of extended-release granules which is reconstituted with the vehicle to prepare an oral suspension of 2 mg/mL. Next , Formulation B was developed. Formulation was also extended-release granules, which was reconstituted with water to prepare an oral suspension with a concentration of 2 mg/mL and used in Study 178-CL-203 and Study 178-CL-208. Because a relatively

large administration volume was required when using formulation B with the drug concentration of 2 mg/mL, Formulation C was developed. The extended-release granules of formulation C are reconstituted with water to prepare an oral suspension with a concentration of 8 mg/mL. Formulation C is the to-be-marketed formulation and used in Study 178-CL-206A and Study 178-CL-208.

Table 4.2-1. List of clinical studies submitted in this NDA

Study Number/ Development Agreement/ Status	**Design**	**Patients**	**Treatments Number of Patients Exposed**
178-CL-201/ EMA PIP/ Completed	Phase 1, 4-period crossover study to assess the bioavailability of a mirabegron oral suspension relative to the mirabegron ER tablet and to assess the effect of food on the pharmacokinetics of mirabegron oral suspension	Young healthy men and women 18 to < 26 years of age	Single dose 50 mg mirabegron oral suspension of formulation A (2 mg/mL): n = 25 50 mg ER tablet: n = 23
178-CL-202/ WR, PMR 1898-1 EMA PIP/ Completed	A phase 1, multicenter, open-label, single ascending dose study to evaluate the pharmacokinetics, safety, and tolerability of mirabegron ER tablets	Pediatric patients with NDO or OAB 5 to < 18 years of age	Single dose, ER tablets 25 mg: n = 13 (NDO: 4) 50 mg: n = 14 (NDO: 4) 75 mg: n = 7 (NDO: 3)
178-CL-203/ WR, PMR 1898-1 EMA PIP/ Completed	A phase 1, multicenter, open-label, single dose study to evaluate the pharmacokinetics, safety, and tolerability of mirabegron oral suspension	Pediatric patients with NDO or OAB 3 to < 12 years of age	Single dose oral suspension of formulation B 2 mg/mL 80 mg: n = 2 (NDO: 2) 100 mg: n = 4 (NDO: 2) 110 mg: n = 2 (NDO: 1) 130 mg: n = 1 (NDO: 1)
178-CL-208/ WR, PMR 1898-1 Completed	A phase 1, single dose, 3-period study to assess the bioavailability of an suspension of 8 mg/mL mirabegron to the oral suspension of 2 mg/mL mirabegron and to assess the effect of on the pharmacokinetics of the oral suspension of 8 mg/mL mirabegron	Healthy men and Women 18 to 45 years of age	Single dose 88 mg mirabegron oral suspension of formulation C (8 mg/mL): n = 24 88 mg mirabegron oral suspension of formulation B (2 mg/mL): n = 23
178-CL-206A/ WR, PMR 1898-2 EMA PIP Completed	A 52-week phase 3, open-label, baseline-controlled, multicenter, dose- titration study followed by a fixed-dose observation period to evaluate efficacy, safety and pharmacokinetics of mirabegron	Pediatric patients with NDO 3 to < 18 years of age	52 weeks, starting at PED25 mg and titrated to PED50 mg 8 mg/mL oral suspension of formulation C: n = 39 25 mg and 50 mg ER tablets: n = 47

Source: Summary of Clinical Pharmacology Studies, Table 1

4.2.1 Study 178-CL-201

Title: A Phase 1, Single Dose, 4-Period Crossover Study to Assess the Bioavailability of an Mirabegron Oral Suspension Relative to the Mirabegron Prolonged Release Tablet and to Assess the Effect of Food on the Pharmacokinetics of Mirabegron Oral Suspension in Healthy Young Male and Female Subjects

Objectives:

- To assess the bioavailability of 50 mg mirabegron oral suspension relative to that of the 50 mg mirabegron modified release tablet when dosed under fasted conditions.
- To assess the effect of food on the pharmacokinetics of 50 mg mirabegron oral suspension.

Study Design:
This was a Phase 1, open-label, randomized, single dose, 4-period crossover clinical study. A washout of at least 14 days was included between two periods. A total of 24 healthy adult subjects were randomly assigned to one of four sequences of Treatment A, B, C, and D outlined below.

● Sequence 1: ACBD
● Sequence 2: BADC
● Sequence 3: CDAB
● Sequence 4: DBCA

● Treatment A: 50 mg mirabegron oral suspension (Formulation A, 2 mg/mL) administered under fasted conditions.
● Treatment B: 50 mg mirabegron oral suspension (Formulation A, 2 mg/mL) administered under fed conditions.
● Treatment C: 50 mg mirabegron modified release tablets administered under fasted conditions.
● Treatment D: 50 mg mirabegron modified release tablets administered under fed conditions.

For assessment of the food effect, at 30 minutes before dosing, subjects received a standardized light breakfast rather than a high-fat breakfast as the impact of a light breakfast on the exposure of mirabegron tablets was shown to be larger than that of a high-fat breakfast in original NDA 202611 submission. Subjects in fed-state arms also received a light lunch 2 hours after dosing.

PK Results:
A total of 25 subjects were enrolled in the study. Subject [redacted] (b) (6) discontinued treatment on day -1 of treatment period 2 due to noncompliance with the inclusion/exclusion criteria drug screening positive for ethanol. Subject [redacted] (b) (6) withdrew from the study on day 11 of treatment period 2. The two subjects were not included in PK analysis. Data of 23 subjects was included in relative BA and food effect analysis. For the two one-sided test based on the analysis of log-transformed C_{max}, AUC_{0-t}, and AUC_{∞}, the point estimates and the corresponding 90% CIs of relative BA calculated by the reviewer are presented in Table 4.2.1-1. The results show that the AUC_{0-inf} and C_{max} of mirabegron following a single dose of oral suspension 50 mg (Formulation A) were approximately 55% and 73% lower, respectively, compared to that of a single dose of ER tablet 50 mg.

Table 4.2.1-1. Statistical assessment of the relative bioavailability of the mirabegron oral suspension Formulation A versus tablets when dosed under fasted conditions

Parameters	**Least Squares Geometric Means (N = 23)**		**% Test/Ref Ratio (90% CI)**
	Formulation A, Fasted [Test]	**ER Tablets, Fasted [Reference]**	
AUC_{0-inf} (ng•h/mL)	158.7	355.0	44.70 (38.58 – 51.80)
AUC_{0-t} (ng•h/mL)	140.1	328.4	42.68 (36.59 – 49.78)
C_{max} (ng/mL)	8.40	30.83	27.25 (21.23 – 34.98)
T_{max} (h)*	4.08 (2.00 – 5.33)	4.02 (1.98 – 5.03)	N.A.

Source: Reviewer's analysis

Statistical analysis of the food effect of mirabegron oral suspension formulation is shown in Table 4.2.1-2. A light breakfast decreased the $AUC_{0\text{-inf}}$ and C_{max} of oral suspension Formulation A by 59% and 73%, respectively. Statistical analysis of the food effect of mirabegron oral tablet formulation was presented earlier in Table 3.3.4-1.

Table 4.2.1-2. Statistical evaluation of the food effect of mirabegron oral suspension Formulation A

Parameters	**Least Squares Geometric Means (N = 23)**		**% Test/Ref Ratio (90% CI)**
	Formulation A, Fed [Test]	**Formulation A, Fasted [Reference]**	
$AUC_{0\text{-inf}}$ (ng•h/mL)	65.46	158.7	41.25 (35.23 – 48.29)
$AUC_{0\text{-t}}$ (ng•h/mL)	49.42	140.1	35.26 (30.30 – 41.04)
C_{max} (ng/mL)	2.255	8.40	26.84 (20.98 – 34.33)
T_{max} (h)*	3.00 (1.03 – 12.0)	4.08 (2.00 – 5.33)	N.A.

Source: Reviewer's analysis

Reviewer's Comments:

- *The reviewer's relative BA and food effect analyses are similar to the Applicant's results.*
- *Formulation A was used in Study 178-CL-201 only and Formulation A is not the TBM formulation. Therefore, the relative BA and food effect results obtained from this study were considered exploratory.*

4.2.2 Study 178-CL-208

Title: A Phase 1, Single-dose, 3-period Crossover Study to Assess the Bioavailability of an Oral Suspension of 8 mg/mL Mirabegron Relative to the Oral Suspension of 2 mg/mL Mirabegron and to Assess the Effect of Food on the Pharmacokinetics of the Oral Suspension of 8 mg/mL Mirabegron in Healthy Male and Female Adult Subjects

Objectives:

- To assess the bioavailability of 88 mg mirabegron oral suspension (Formulation C, 8 mg/mL) relative to that of 88 mg mirabegron oral suspension (Formulation B, 2 mg/mL) when dosed under fasted conditions.
- To assess the effect of food on the pharmacokinetics of 88 mg mirabegron oral suspension (Formulation C, 8 mg/mL).

Study Design:
This was an open-label, randomized, single-dose, 3-period crossover study in healthy subjects to assess the bioavailability of a 8 mg/mL mirabegron oral suspension (Formulation C) relative to the 2 mg/mL mirabegron oral suspensions (Formulation B), to assess the effect of food on the pharmacokinetics of the 8 mg/mL mirabegron oral suspension (Formulation C). A total of 24 healthy adult subjects were randomly assigned to one of six treatment sequences.

- Treatment A: 88 mg mirabegron oral suspension (8 mg/mL) administered under fasted conditions.
- Treatment B: 88 mg mirabegron oral suspension (2 mg/mL) administered under fasted conditions.
- Treatment C: 88 mg mirabegron oral suspension (8 mg/mL) administered under fed conditions.

For assessment of the food effect, subjects received a standardized light breakfast (dosing 30 minutes after completion of the light breakfast) and a light lunch 2 hours after dosing.

PK Results:
Data of all 24 enrolled subjects was included in relative BA and food effect analysis. One subject discontinued before period 3 because the subject was tested positive for amphetamine. For the two one-sided test based on the analysis of log-transformed C_{max}, AUC_{0-t}, and AUC_{∞}, the point estimates and the corresponding 90% CIs of relative BA calculated by the reviewer are presented in Table 4.2.2-1. When administered under fasted conditions, the 90% CIs of AUC ratio between Formulation C and Formulation B are within 80-125%. The relative BA of Formulation C in terms of C_{max} was 106.12% of Formulation B with estimated 90% CIs of the ratio equal to 83.77 - 134.42%. The upper 90% CI was slightly higher than 125%.

Table 4.2.2-1. Statistical assessment of the relative bioavailability of mirabegron granules Formulation C versus mirabegron granules Formulation B when dosed under fasted conditions

Parameters	**Least Squares Geometric Means**		**% Test/Ref Ratio (90% CI)**
	Formulation C, Fasted N = 24 [Test]	**Formulation B, Fasted, N =23 [Reference]**	
AUC_{0-inf} (ng•h/mL)	252.6	251.5	100.44 (90.80 – 111.10)
AUC_{0-t} (ng•h/mL)	234.0	232.2	100.79 (90.50 – 112.25)
C_{max} (ng/mL)	12.09	11.39	106.12 (83.77 – 134.42)
T_{max} (h)*	4.00 (2.50 – 5.98)	5.00 (2.00 – 5.98)	N.A.

Source: Reviewer's analysis

Statistical analysis of the food effect of Formulation C is shown in Table 4.2.2-2. A light breakfast decreased the AUC_{0-inf} and C_{max} of oral suspension Formulation A by 45% and 63%, respectively.

Table 4.2.2-2. Statistical evaluation of the food effect of mirabegron granules Formulation C

Parameters	**Least Squares Geometric Means (N = 24)**		**% Test/Ref Ratio (90% CI)**
	Formulation C, Fed [Test]	**Formulation C, Fasted [Reference]**	
AUC_{0-inf} (ng•h/mL)	138.5	252.6	54.83 (49.65 – 60.55)
AUC_{0-t} (ng•h/mL)	119.8	234.0	51.19 (46.04 – 56.91)
C_{max} (ng/mL)	4.46	12.09	36.91 (29.24 – 46.59)
T_{max} (h)*	3.00 (2.50 – 12.0)	4.00 (2.50 – 5.98)	N.A.

Source: Reviewer's analysis

Reviewer's Comments:

- *According to the Applicant's analysis, the relative BA of Formulation C in terms of Cmax was 106.74% of Formulation B with estimated 90% CIs of the ratio equal to 84.24 - 135.24%. The reviewer's relative BA and food effect analyses for Formulation C are consistent with the Applicant's results.*
- *Mirabegron granules Formulation C was used in pivotal study (178-CL-206A) and is the TBM formulation. The relative BA results bridged Formulation C to mirabegron granules Formulation B, the formulation used in Study 178-CL-203 (the single ascending dose study in pediatric patients).*

- *A meal decreased the AUC and C_{max} of mirabegron granules Formulation C by ~ 45% and ~ 63%, respectively. The magnitude of food effects on Formulation C is similar to that for mirabegron ER tablets observed in Study 178-CL-201 (57% and 60% decreases in AUC and C_{max}, respectively).*

4.2.3 Study 178-CL-202

Title: A Multicentre, Open-label, Single Ascending Dose Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Mirabegron OCAS Tablets in Pediatric Subjects from 5 to Less than 18 Years of Age with Neurogenic Detrusor Overactivity (NDO) or Overactive Bladder (OAB)
Objectives:
To evaluate the pharmacokinetics, safety and tolerability of mirabegron prolonged-release tablets after single-dose administration at different dose levels in children and adolescents with NDO or OAB

Study Design:
This was a multicenter, open-label, single-ascending-dose study in the pediatric NDO/OAB population. The following 5 cohorts of at least 6 subjects per cohort were planned and completed:

- Cohort 1: male and female adolescents (12 to less than 18 years); low dose (fed conditions)
- Cohort 2: male and female children (5 to less than 12 years); low dose (fed conditions)
- Cohort 3: male and female adolescents (12 to less than 18 years); high dose (fed conditions)
- Cohort 4: male and female children (5 to less than 12 years); high dose (fed conditions)
- Cohort 5: male and female children (5 to less than 12 years); high dose (fasted conditions)

Subjects of cohorts 1 to 4 were dosed within 1 h after completion of the light breakfast and were allowed to have a light lunch > 2 h after dosing. Subjects in cohort 5 remained fasted from at least midnight before until 4 h after dosing.

Table 4.2.3-1. Dosing regimen of Study 178-CL-202

Low: Cohort 1 (Adolescents) and Cohort 2 (Children)	
Body weight	**Tablet dose**
20.0 to < 55.0 kg	25 mg tablet
≥ 55.0 kg	50 mg tablet
High: Cohort 3 (Adolescents), Cohorts 4 and 5 (Children)	
Body weight	**Tablet dose**
20.0 to < 40.0 kg	50 mg tablet
≥ 40.0 kg	75 mg (1 x 25 mg tablet and 1 x 50 mg tablet)

PK Results:
A total of 34 pediatric patients (19 children and 15 adolescents) were enrolled. All the 34 patients completed the study and were included in PK analysis. Plasma mirabegron concentration data was analyzed using non-compartmental analysis. Descriptive statistics for mirabegron PK parameters following a single dose of mirabegron are summarized in Table 4.2.3-2.

The median AUC values were similar within each dose group between children and adolescents in the cohorts under fed conditions. Median C_{max} was lower in adolescents than children. The results from Cohort 4 and Cohort 5 show that the effect of food on the exposure observed in children is consistent with the effect of food observed in adults, where food intake resulted in a decrease in exposure of approximately 50 - 60%. The median T_{max} values were similar across all cohorts at approximately 4 to 5 h. The mean elimination half-life was in the range of 26 – 31 hours across all cohorts. The median values of CL/F and Vz/F were higher in adolescents than children. The values of these 2 parameters decreased in the higher dose groups due to an increase in bioavailability. The median AUC_{0-24} values in

Cohort 3 and Cohort 4 receiving high dose under fed conditions were slightly higher than the median steady-state AUC_{0-t} (188 ng*h/mL) in adult patients receiving mirabegron ER tablets QD.

Table 4.2.3-2. Summary of Plasma Pharmacokinetic Parameters of Mirabegron in Study178-CL-202

Parameter Statistics	Cohort 1 Adolescents Low Dose Fed (n = 7)	Cohort 2 Children Low Dose Fed (n = 7)	Cohort 3 Adolescents High Dose Fed (n = 8)	Cohort 4 Children High Dose Fed (n = 6)	Cohort 5 Children High Dose Fasted (n = 6)
AUC_{inf} (ng·h/mL)					
Mean (SD)	90.83 (25.56)	128.8 (65.48)	394.9 (205.5)	596.5 (385.5)	830.4 (384.8)
%CV	28.1	50.8	52.0	64.6	46.3
Median	89.44	103.7	420.1	417.9	745.2
Min-Max	56.4 - 116	53.1 - 204	124 - 713	245 - 1209	459 - 1526
N	5	7	8	5	6
C_{max} (ng/mL)					
Mean (SD)	4.730 (2.717)	6.909 (4.670)	31.98 (26.10)	43.99 (31.93)	56.42 (17.73)
%CV	57.4	67.6	81.6	72.6	31.4
Median	3.850	5.240	29.66	38.06	58.36
Min-Max	2.45 - 10.5	2.45 - 14.9	3.40 - 80.4	14.1 - 98.2	28.6 - 79.2
N	7	7	8	6	6
t_{max} (h)					
Mean (SD)	4.867 (0.6683)	4.534 (1.328)	4.995 (1.802)	4.227 (0.1909)	3.960 (0.2945)
%CV	13.7	29.3	36.1	4.5	7.4
Median	5.030	4.170	4.475	4.280	3.950
Min-Max	3.95 - 5.75	2.55 - 6.37	3.08 - 7.08	3.88 - 4.42	3.47 - 4.27
N	7	7	8	6	6
$t_{1/2}$ (h)					
Mean (SD)	27.16 (6.664)	30.76 (8.119)	29.20 (4.510)	28.97 (6.076)	26.16 (2.931)
%CV	24.5	26.4	15.4	21.0	11.2
Median	25.74	34.76	29.05	28.89	24.97
Min-Max	19.9 - 34.7	19.4 - 38.5	21.1 - 36.4	20.6 - 37.0	23.7 - 30.8
N	5	7	8	5	6
CL/F (L/h)					
Mean (SD)	339.1 (97.54)	248.7 (132.5)	230.1 (137.4)	113.0 (62.89)	79.08 (45.64)
%CV	28.8	53.3	59.7	55.7	57.7
Median	325.0	241.1	160.6	119.7	69.71
Min-Max	217 - 443	123 - 471	105 - 460	41.4 - 204	32.8 - 163
N	5	7	8	5	6
V_z/F (L)					
Mean (SD)	13063 (4569)	9959 (3639)	9918 (6702)	4895 (2921)	2866 (1438)
%CV	35.0	36.5	67.6	59.7	50.2
Median	12070	8705	6658	4603	2569
Min-Max	8894 - 20813	6156 - 15830	4401 - 21123	1227 - 8518	1455 - 5581
N	5	7	8	5	6
AUC_{24} (ng·h/mL)					
Mean (SD)	47.90 (14.24)	66.33 (31.66)	230.7 (132.5)	336.0 (225.4)	508.6 (190.2)
%CV	29.7	47.7	57.4	67.1	37.4
Median	49.03	53.63	254.0	247.1	474.2
Min-Max	31.8 - 66.3	26.8 - 116	50.0 - 423	159 - 743	272 - 831
N	7	7	8	6	6

Source: Study 178-CL-202 report, Table 12

4.2.4 Study 178-CL-203

Title: A Multicentre, Open-label, Single Dose, Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Mirabegron Oral Suspension in Pediatric Subjects from 3 to Less than 12 Years of Age with Neurogenic Detrusor Overactivity (NDO) or Overactive Bladder (OAB)

Objectives:
To evaluate the pharmacokinetics, safety, tolerability, palatability and acceptability of mirabegron oral suspension after single dose administration in children with NDO or OAB

Study Design:
The study was a multicenter, open-label, single-dose study in children with NDO from 3 to less than 12 years of age and in children with OAB from 5 to less than 12 years of age. A single dose of mirabegron ER granules for oral suspension was administered within 1 h after completion of a light breakfast, targeted to obtain equivalent exposure to administration of once-daily 50 mg of mirabegron ER tablets in adults at steady state under undefined food conditions. Body weight-based dosing regimen is shown in Table 4.2.4-1.

Table 4.2.4-1. Dosing regimen of Formulation B in Study 178-CL-203

Weight Range (kg body weight)	Oral Suspension Dose (mL)†	Corresponding Dose of Mirabegron (mg)
15 - 19 kg	40 mL	80 mg
20 – 29 kg	50 mL	100 mg
30 – 39 kg	55 mL	110 mg
> 40 kg	65 mL	130 mg

† Strength: 2 mg mirabegron/mL suspension

PK Results:
A total of 9 pediatric patients (3 with OAB and 6 with NDO) was enrolled. All the 9 patients completed the study and were included in PK analysis. Descriptive statistics for mirabegron PK parameters following a single dose of mirabegron granules are summarized in Table 4.2.4-2. The median AUC_{0-24} (222 ng*h/mL) in pediatric patients receiving a single dose of mirabegron oral suspension under fed conditions was slightly higher than the median steady-state AUC_{0-t} (188 ng*h/mL) in adult patients receiving mirabegron ER tablets QD.

Table 4.2.4-2. Summary of Plasma Pharmacokinetic Parameters of Mirabegron in Study178-CL-203

Parameter Statistic	Total (n = 9)
AUC_{inf} (ng•h/mL)	
Mean (SD)	464.1 (288.9)
%CV	62.3
Median	431.5
Min – Max	99.7 – 1005
C_{max} (ng/mL)	
Mean (SD)	18.41 (11.72)
%CV	63.7
Median	16.70
Min – Max	2.56 – 42.4
$t_{1/2}$ (h)	
Mean (SD)	25.99 (5.800)
%CV	22.3
Median	23.92
Min – Max	16.2 – 33.4
t_{max} (h)	
Median	3.930
Min – Max	1.25 – 6.50
AUC_{24} (ng•h/mL)	
Mean (SD)	226.9 (136.2)
%CV	60.0
Median	222.2
Min – Max	39.7 – 467
AUC_{last} (ng•h/mL)	
Mean (SD)	414.3 (263.6)
%CV	63.6
Median	375.9
Min – Max	62.8 – 936
CL/F (L/h)	
Mean (SD)	338.0 (281.5)
%CV	83.3
Median	231.7
Min – Max	109 – 1003
V_Z/F (L)	
Mean (SD)	13726 (14036)
%CV	102.3
Median	9591
Min – Max	2561 – 48272

Source: Study 178-CL-203 report, Table 14

4.3 Population PK Analyses

4.3.1 Review Summary

In general, the applicant's population PK (PopPK) analysis is considered acceptable for the purpose of characterizing the PK profile of mirabegron in pediatric subjects with neurogenic detrusor overactivity (NDO) aged 3 years and older. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in **Error! Reference source not found.**.

Table 1. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements (b) (4)	(b) (4)		

(b) (4)

[redacted]

Predict exposures at alternative dosing regimen

Table 1: Once Daily Recommended Oral Suspension Dose According to Patient Body Weight

Recommended Dose	Body Weight Range	Tablet Dose	Suspension Volume[1]
Recommended Starting Dose	11 kg to less than 22 kg	--	3 mL
	22 kg to less than 35 kg	--	4 mL
	greater than or equal to 35 kg	25 mg	6 mL[2]
Recommended Maximum Dose	11 kg to less than 22 kg	--	6 mL
	22 kg to less than 35 kg	--	8 mL
	greater than or equal to 35 kg	50 mg	10 mL[2]

--: not applicable; NDO: neurogenic detrusor overactivity.

1. MYRBETRIQ LS Granules for oral suspension formulation (granules were reconstituted with water to prepare a suspension with a concentration of 8 mg/mL suspension).
2. Patients ≥ 35 kg who cannot swallow tablets may take a suspension dose.

The proposed dosing regimen is acceptable.

PopPK analysis using data in Study No. 178-CL-206A suggests the recommended starting dose and maximum dose for mirabegron oral suspension provide similar exposure in pediatric patient with body weight less than 35 kg as mirabegron ER tablet in adult. (Figure 5 and 6)

Simulation using PopPK model suggests the proposed dose provide similar exposure in pediatric patients with body weight

		greater than or equal to 35 kg as mirabegron ER tablet in adult. (Figure 7)

4.3.2 Introduction

The primary objectives of applicant's analysis were to:

- Characterize the structural pharmacokinetic (PK) model and quantify the population variability in the PK parameters of mirabegron.
- Describe the effects of intrinsic and/or extrinsic factors on mirabegron exposure.
- Assess whether the proposed dosing regimen for mirabegron oral suspension can provide similar exposure in pediatric patients as mirabegron ER tablet in adult.

4.3.3 Model development

Data

The analyses were based on PK data from 3 studies. The study design, study population, and timing of blood samples varied among the 3 clinical studies. Brief descriptions of the studies included are presented in Table 1.

The final NONMEM data file for analysis contained 542 PK observations from 114 subjects.

Table 2 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 1. Summary of Studies with PK Sampling Included in Population PK Analysis

Study # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject Type and Food Status	Dose(s) [mg]

178-CL-202 A Multicentre, Open label, Single Ascending Dose Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Mirabegron OCAS Tablets in Pediatric Subjects from 5 to Less than 18 Years of Age with Neurogenic Detrusor Overactivity (NDO) or Overactive Bladder (OAB)	Low Dose: Body weight < 55 kg = 25 mg Body weight ⩾ 55 kg = 50 mg High Dose: Body weight < 40 kg = 50 mg Body weight ⩾ 40 kg = 75 mg Cohort 1: Adolescents Low Dose Fed Cohort 2: Children Low Dose Fed Cohort 3: Adolescents High Dose Fed Cohort 4: Children High Dose Fed Cohort 5: Children High Dose Fasted	Male and female children (5 to < 12 years) and adolescents (12 to <18 years) with NDO or OAB N=34 Fasting and Fed	25 and 50 mg (low dose), 50 mg and 75 mg (high dose) tablets
178-CL-203 A Multicentre, Open-label, Single Dose, Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Mirabegron Oral Suspension in Pediatric Subjects from 3 to Less than 12 Years of Age with NDO or OAB	Body weight-based Dosing: 15-19 kg = 80 mg Fed 20-29 kg = 100 mg Fed 30-39 kg = 110 mg Fed > 40 kg = 130 mg Fed	Male and female children with NDO or OAB N=9 Fed	80, 100, 110, 130 mg oral suspension (2 mg/mL)

178-CL-206A An Open-label Baseline controlled, Multicenter, Phase 3 Dose-titration Study Followed by a Fixed-dose Observation Period to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Children and Adolescents From 3 to Less Than 18 Years of Age with NDO on Clean Intermittent Catheterization (CIC)	Patients started on Low Dose with potential titration to High Dose at Weeks 2, 4, and 8. <u>Formulation Selection:</u> Body weight < 35 kg: oral suspension Body weight ⩾ 35 kg: tablets <u>Low Dose Selection:</u> Body weight 11 to < 22 kg: 24 mg oral suspension Body weight 22 to < 35 kg: 32 mg oral suspension Body weight ⩾ 35 kg: 48 mg oral suspension or 25 mg tablet <u>High Dose Selection:</u> Body weight 11 to < 22 kg: 48 mg oral suspension Body weight 22 to < 35 kg: 64 mg oral suspension Body weight ⩾ 35 kg: 88 mg oral suspension or 50 mg	Male and Female Children and adolescents with NDO N=86 Fed	Tablet: 25 mg (low dose) and 50 mg (high dose) Oral suspension (8 mg/mL): 24 mg, 32 mg, 48 mg (low dose); 48 mg, 64 mg and 88 mg (high dose)

Table adapted from Applicant's Population PK report No. 178-pk-206, Table. 1

Table 2. Summary of Baseline Demographic Covariates for Analysis

Covariate	Statistic	Total
Body Weight (kg)	N Mean (SD) Median (min,max)	114 37.3 (16.2) 35.0 [12.6, 80.0]
Age (yr)	N Mean (SD) Median (min,max)	114 10.1 (3.68) 10.0 (3.00, 17.0)
Sex Male Female	 N (%) N (%)	 49 (43.0%) 65 (57.0%)
Formulation Tablet Suspension	 N (%) N (%)	 72 (63.2%) 42 (36.8%)
Food Status Fasting Fed	 N (%) N (%)	 6 (5.3%) 108 (94.7%)
Population OAB NDO	 N (%) N (%)	 26 (22.8%) 88 (77.2%)

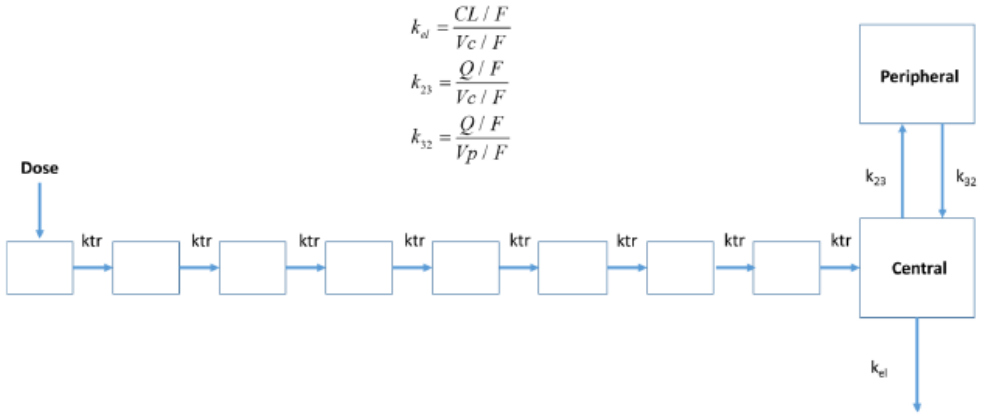
Abbreviations: N=Number of subjects, SD=Standard deviation; OAB = overactive bladder, NDO = neurogenic detrusor overactivity

Base model

The final base model was a two-compartment model with transit compartment absorption and first-order elimination. Eight transit compartments using the Erlang distribution were added to the two-compartment model and the speed with which drug progressed through the series of transit compartments was controlled by a first-order transit rate constant (ktr). The effect of weight was included as a fixed allometric exponent on CL/F, Vc/F, Vp/F, and Q/F and the effects of food, formulation (suspension or tablet), and dose were included on F1. (Figure 1)

Inter-individual variability (IIV) was modelled assuming a log-normal distribution for patient level random effects. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Figure 1. Scheme of Model Structure



The base structural model was expressed mathematically using the following equations:

$$ktr_i = \theta_1 \cdot \exp(\eta_{1,i}) \quad [3]$$

$$CL/F_i = \theta_2 \cdot \left(\frac{WT_i}{70}\right)^{0.75} \cdot \exp(\eta_{2,i}) \quad [4]$$

$$Vc/F_i = \theta_3 \cdot \left(\frac{WT_i}{70}\right)^{1.00} \cdot \exp(\eta_{3,i}) \quad [5]$$

$$Q/F_i = \theta_5 \cdot \left(\frac{WT_i}{70}\right)^{0.75} \quad [6]$$

$$Vp/F_i = \theta_4 \cdot \left(\frac{WT_i}{70}\right)^{1.00} \quad [7]$$

$$F_{ij} = 1 \cdot \exp(\theta_7 \cdot I_{FORM-SUSP}) \cdot \exp(\theta_8 \cdot I_{MEAL-FAST}) \cdot \left(\frac{DOSE_{ij}}{50}\right)^{\theta_{11}} \quad [8]$$

where $\theta(\cdot)$ represent fixed effect parameters, $\eta(\cdot)$ represent subject-specific random effects, WT_i is the body weight in kg for the i^{th} patient, $I_{FORM=SUSP}$ is an indicator variable equal to 1 for doses administered as the suspension formulation and 0 otherwise, $I_{MEAL=FAST}$ is an indicator variable equal to 1 for doses administered without a meal and 0 otherwise, and $DOSE_{ij}$ represents the dose administered in the i^{th} patient on the j^{th} day.

Source: 178-pk-206 PopPK report, Figure 1

Covariate analysis

Covariate parameters, including gender, population and age on CL/F and Vc/F; and gender, population and age on F were added to the base model and tested in univariate manner. Food and formulation effects were evaluated on absorption rate and bioavailability components of the model. Continuous covariate effects were added using power models. Categorical covariate effects were modeled using exponential models for the test effect versus the reference condition. A single univariate forward selection step, in which one model was prepared for each relevant parameter-covariate relationship, was implemented to identify covariates for inclusion. Covariates producing a 6.63-unit reduction in the objective function relative to the model without the covariate effect were included in the model (α=0.01).

4.3.4 Final Model

The parameter estimates for the final covariate model are listed in Table 3. The goodness-of-fit plots for the final covariate model for all data are shown in Figure . The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in Figure . Eta shrinkage was 33.0%, 4.65%, and 19.9% for ktr, CL, and Vc, respectively.

Table 3. Parameter Estimates (RSE) and Median (95% CI) for the Final Model

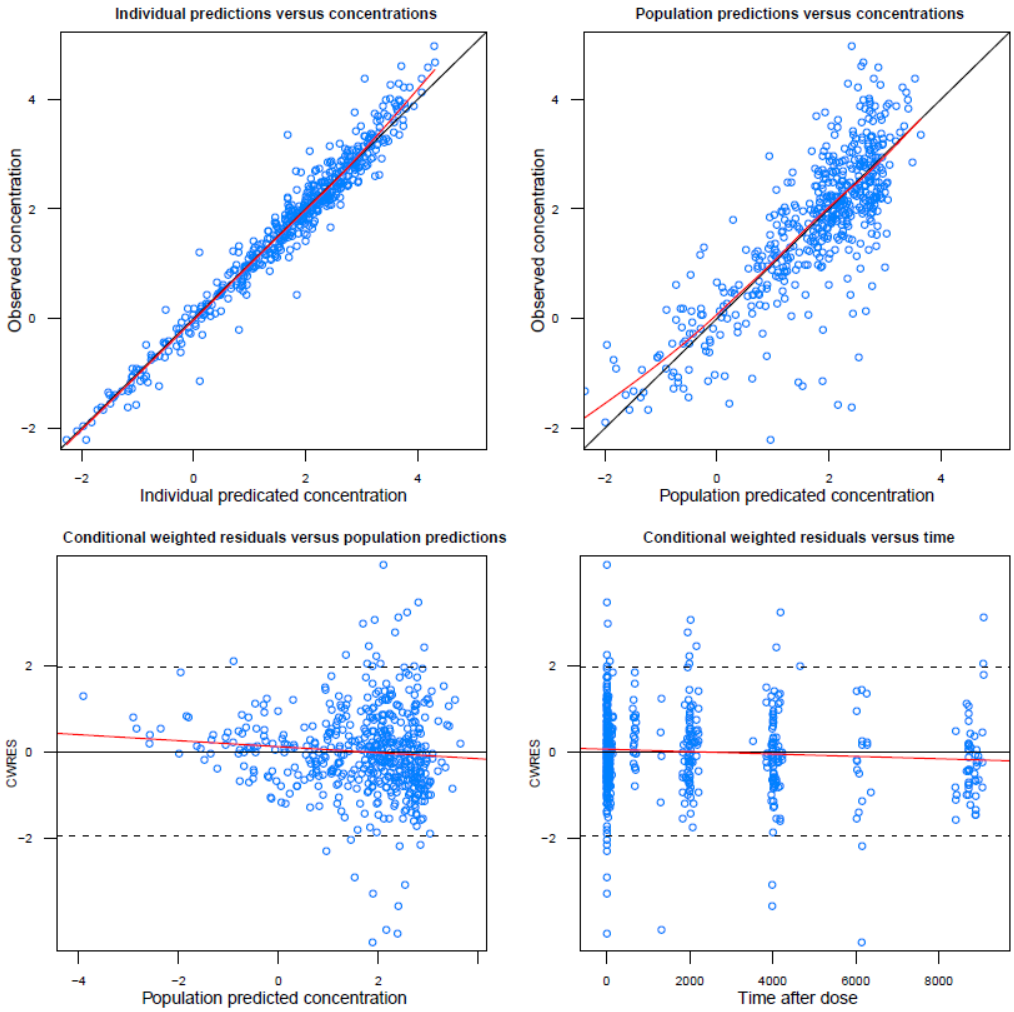
Parameter	Notation	Estimate	Standard Error
Fixed Effects			
Transit Rate Constant (ktr) [1/hr]	θ_1	4.10	0.341
Apparent Clearance (CL/F) [L/hr]	θ_2	234	197
Apparent Central Volume of Distribution (Vc/F) [L]	θ_3	7240	977
Apparent Peripheral Volume of Distribution (Vp/F) [L]	θ_4	6060	890
Apparent Intercompartmental Clearance (Q/F) [L/hr]	θ_5	273	81.7
Suspension Formulation on F	θ_7	-0.846	0.122
Fasted Meal Status on F	θ_8	0.806	0.215
Dose on F	θ_{11}	0.459	FIXED
Population = OAB on CL/F	θ_{12}	0.367	0.105
Table continued on next page			

Parameter	Notation	Estimate	Standard Error
Interindividual Variability			
IIV ktr	ω_1^2	0.178	0.0491
Covariance (IIV ktr, IIV CL/F)	Cov (ω_1, ω_2)	0.00622	0.0341
IIV CL/F	ω_2^2	0.302	0.0470
Covariance (IIV ktr, IIV Vc/F)	Cov (ω_1, ω_3)	0.218	0.104
Covariance (IIV CL/F, IIV Vc/F)	Cov (ω_2, ω_3)	0.342	0.0751
IIV Vc/F	ω_3^2	0.965	0.255
Residual Variability			
Residual Error [approximate CV]	θ_6	0.366	0.0165

IIV = interindividual variability, CV = coefficient of variation, F = relative bioavailability
Source: MSTask01/model/mod038.lst

Source: 178-pk-206 PopPK report, Table 9

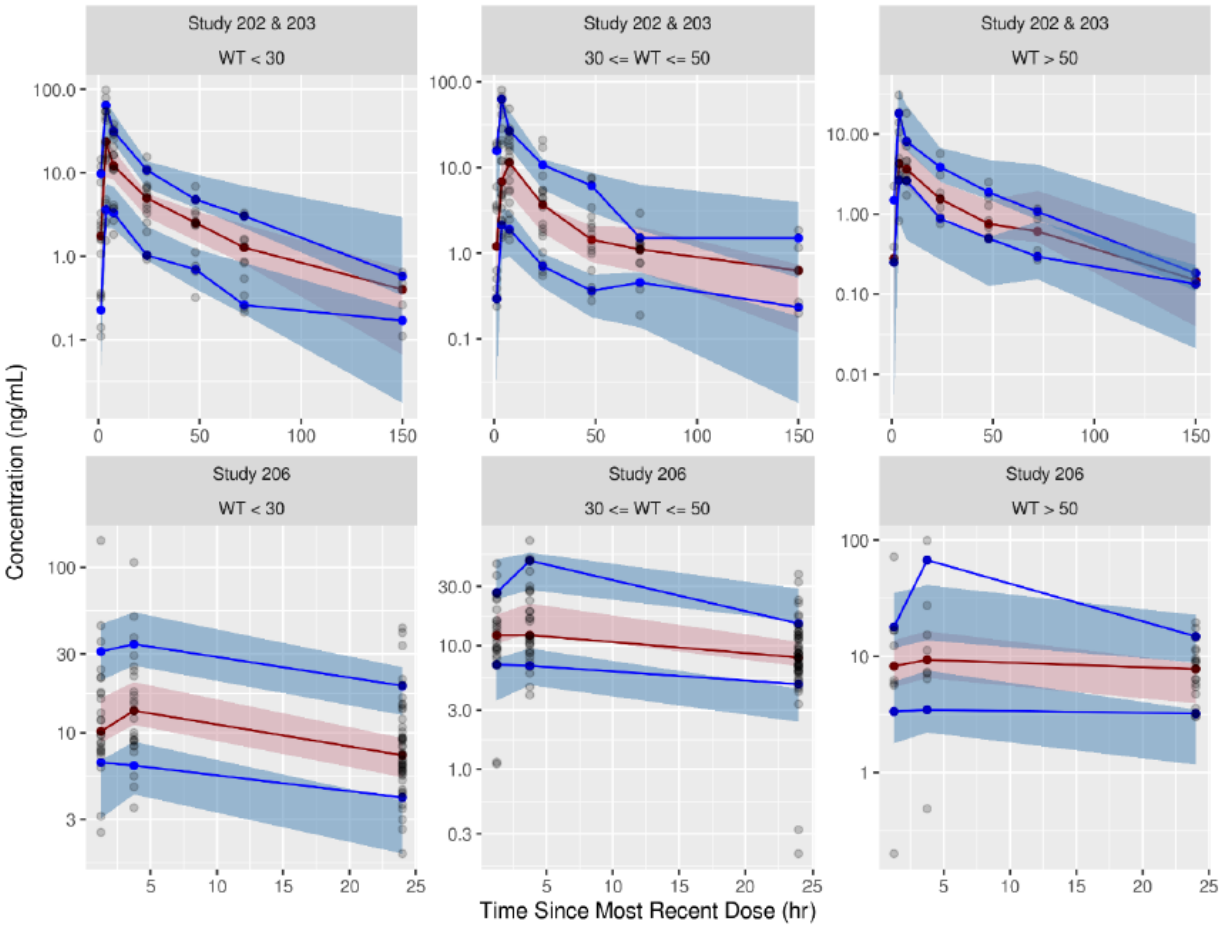
Figure 2. Goodness-of-fit plots for final covariate model



The black line in the DV vs PRED/IPRED plots represents the line of unity (y=x). The black line in the CWRES vs PRED/TIME plots represents the horizontal line (y=0). The red line represents a smooth regression line.

Source: Reviewer's independent analysis

Figure 3. VPC plots for final covariate model



The Solid red line (pink shaded region) is the observed median (90% prediction interval). The solid blue lines (blue shaded region) are the observed 10th and 90th percentiles (90% prediction intervals).

Source: 178-pk-206 PopPK report, Figure 3

The effects of body weight, formulation, meal status, and patient population (OAB or NDO patient) on steady state C_{max} and $AUC_{0\text{-}tau}$ relative to the reference subject are summarized in Error! Reference source not found.. The reference subject was a 50 kg NDO patient that received a 50 mg once-daily mirabegron tablet with food. Patients receiving the suspension formulation were predicted to have 42.9% of the relative bioavailability compared to those subjects receiving the tablet formulation. Patients receiving mirabegron with food were predicted to have 44.7% of the relative bioavailability compared to subjects receiving mirabegron without food. Patients with OAB were predicted to have 44.3% increase in CL/F compared to patients with NDO. Finally, patients receiving a 25 mg dose of mirabegron were predicted to have a 27.3% reduction in relative bioavailability compared to a patient receiving the 50 mg dose while a patient receiving an 80 mg dose was predicted to have a 24.1% increase in relative bioavailability compared to a patient receiving the 50 mg dose.

Table 4. Numerical Comparison of Covariate Effects on Steady-State C_{max} and $AUC_{(0\text{-}tau)}$

Condition	Steady-State C_{max} (ng/mL)		Steady-State $AUC_{(0\text{-}tau)}$ (ng*h/mL)	
	Test/Reference Ratio (90% CI)	Percentage Difference (90% CI)	Test/Reference Ratio (90% CI)	Percentage Difference (90% CI)
Reference [a]	1 (1, 1)	0 (0, 0)	1 (1, 1)	0 (0, 0)
Body Weight = 15 kg	2.74 (2.71, 2.77)	174 (171, 177)	2.47 (2.47,2.47)	147 (147, 147)
Body Weight = 35 kg	1.35 (1.34, 1.35)	34.5 (34.0, 34.9)	1.31 (1.31, 1.31)	30.7 (30.7, 30.7)
Body Weight = 70 kg	0.757 (0.755, 0.760)	-24.3 (-24.5, -24.0)	0.777 (0.777, 0.777)	-22.3 (-22.3, -22.3)
Formulation = Suspension	0.429 (0.353, 0.528)	-57.1 (-64.7, -47.2)	0.429 (0.353, 0.528)	-57.1 (-64.7, -47.2)
Food = Fasted	2.24 (1.56, 3.18)	124 (56.2, 218)	2.24 (1.56, 3.18)	124 (56.2, 218)
Population = OAB	0.788 (0.709, 0.878)	-21.2 (-29.1, -12.2)	0.693 (0.584, 0.822)	-30.7 (-41.6, -17.8)

[a] Reference subject = 50 kg NDO patient receiving a 50 mg once-daily dose in the fed state

Source: 178-pk-206 PopPK report, Table 10

4.4 Additional Analysis (Issue-based analysis)

4.4.1 Introduction

The reviewer evaluated whether the proposed dosing regimen for mirabegron oral suspension is acceptable in pediatric patients with NDO.

4.4.2 Objectives

Analysis objective is:

- To evaluate the appropriateness of the proposed dose for mirabegron suspension (8 mg/mL) in pediatric NDO patients.

4.4.3 Methods

Sparse PK samples from three clinical studies in children and adolescent patients with NDO or OAB, which include two Phase 1 studies in NDO and OAB patients (Nos. 178-CL-202 and 178-CL-203) and one Phase 3 study in patients with NDO (No. 178-CL-206A) were pooled into one dataset to conduct PopPK analysis.

Table 4. Analysis Data Sets

Study Number	Name	Link to EDR
PPK178.xpt; mod038.mod	Data and final best model file for PopPK report 178-PK-206	\\CDSESUB1\evsprod\NDA213801\0003\m5\datasets\178-pk-206\analysis\adam\datasets;

		\\CDSESUB1\evsprod\nda213801\0001\m5\datasets\178-pk-206\analysis\programs\mod038-mod.txt
Nm201.xpt; Model34.mod	Data and final best model file for PopPK report 178-PK-204	\\CDSESUB1\evsprod\NDA213801\0003\m5\datasets\178-pk-204\analysis\adam\datasets; \\CDSESUB1\evsprod\nda213801\0001\m5\datasets\178-pk-204\analysis\programs\model34-mod.txt
Dose-estimation-206-sup; 201ppk_AS_orig;	Simulation file, dataset, and parameter file to estimate the dose for study 206A using virtual pediatric patients.	\\CDSESUB1\evsprod\nda213801\0011\m5\datasets\178-pk-204\analysis\programs\dose-estimation-206-susp.r; \\CDSESUB1\evsprod\nda213801\0011\m5\datasets\178-pk-204\analysis\adam\datasets\201ppk-as-orig.lst;

Data preparation was conducted using SAS 9.4 for Windows. NONMEM version VII was used for population PK analysis. The diagnostic and other plots were generated with SAS and R.

The base model provided by the applicant (a two-compartment model with transit compartment absorption and first-order elimination, combined with a log-normal residual error model) were utilized. Graphical analysis of the base model output (goodness-of-fit plots and Eta-covariate plots) was used to evaluate the adequacy of the model and selection of covariates for further evaluation. The AUC predicted from the best model was used to compare the exposure of proposed starting dose and maximum dose in pediatric patients with body weight less than 35 kg to the target exposure in adult patients. These target exposures were defined as the median steady state AUC after administration of 25 and 50 mg doses of mirabegron tablets in adult OAB patients, which are 69 and 188 ng*h/mL, respectively.

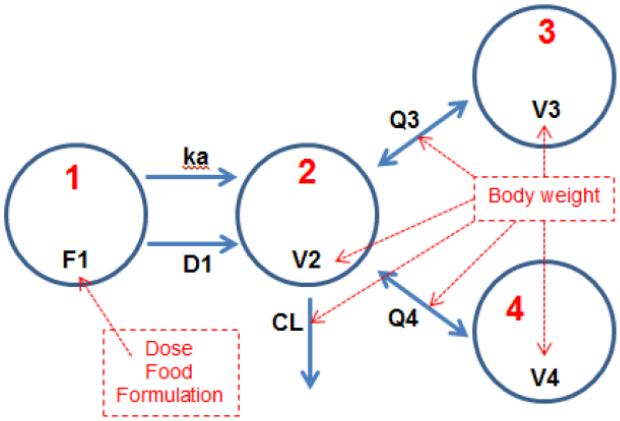
Because there is only one patient with body weight 35 kg administered with oral suspension in Study 178-CL-206A, PK simulation using virtual pediatric population was used to determine the appropriateness of the proposed dose for oral suspension for patients with body weight greater than or equal to 35 kg. Data from two studies were used in the modeling and validation. First, the data from Study No. 178-CL-201 was used for model development following administration of tablets and oral suspension in young adults under fasted and fed conditions. Second, the data from Study No. 178-CL-202 was used to evaluate model predictions in children following administration of tablets in both fasted and fed conditions. In both studies the fed condition comprises a light meal. PK simulation was performed in 5000 virtual pediatric patients sampled from age 2 to less than 18 years in National Health and Nutrition Examination Survey (NHANES) database to predict the doses for study 178-CL-206A . Body weights outside the 3rd and 97th percentiles of the body weight-height proportionality as defined by World Health Organization (WHO) were excluded from the database prior to sampling. An additional 500 subjects <20 kg were also sampled to increase the smaller number of subjects with lower weights.

A systematic multi-step approach to model development is described as below: 1. Base model development including structural and stochastic effects; 2. Covariate model development; 3. Best model selection; 4. Predictive performance and robustness. The model components were selected and assembled based on a combination of prior knowledge and data-driven decision-making guided by statistical and heuristic rules. Throughout model development, the estimation method used to analyze the data was the first order conditional estimation (FOCE)

with the INTERACTION option. All models in which fixed effects were added/removed were compared following a χ^2-distribution with degrees of freedom equal to the number of additional parameters (p). Significance for added/removed variance components was based on a 50:50 mixture of χ^2-distributions with p and p+1 degrees of freedom. Stochastic models assumed log-distribution, and a proportional variance model was used to describe residual error.

The best PopPK model to describe data for study No. 178-CL-201 was a 3-compartment model with a combination of first and zero order absorption (Figure 4). Food and formulation were included in the model as covariates on F1, and dose was retained on F1 (although the parameters for dose-dependency were fixed since there was one dose in the study). Body weight was included through allometric scaling with fixed parameters on all clearance and volume terms. The model was validated by comparing model-estimated PK parameters to those calculated using non-compartmental analysis (NCA), an internal validation using visual predictive check, and an external validation through simulation of pediatric patient profiles and comparing to the observed data from study 178-CL-202.

Figure 4. Schematic for Best PopPK Model for Study No. 178-CL-201



Impactful covariates are in red and connected by arrows to the corresponding parameters

CL: clearance; V2/V3/V4: volumes of distribution; Q3/Q4: inter-compartmental clearances; F1: bioavailability; ka: absorption rate constant; D1: duration of zero-order absorption

The model equations are:

$CL=\theta1\cdot(WT/70)^{0.75}\cdot e^{\eta1}$

$V2=\theta2\cdot(WT/70)\cdot e^{\eta2}$

$Q3=\theta3\cdot(WT/70)^{0.75}* e^{\eta6}$

$V3=\theta4\cdot(WT/70)$

$Q4=\theta13\cdot(WT/70)^{0.75}$

$V4=\theta12\cdot(WT/70)$

$ka=\theta5\cdot e^{\eta4}$

$D1=\theta6\cdot e^{\eta5}$

$FD50=\theta7$

$COVD=\theta8$

Source: 178-pk-204 PopPK report, Figure 4

Table 6. Final Parameter Estimates

Parameter (units)	Estimate	SE	CV (%)	Shrinkage (%)
CL (L/h)	29.1	1.52	5.23	
V2 (L)	140	14.8	10.6	
Q3 (L/h)	13.5	1.89	14.0	
V3 (L)	3290	317	9.64	
Q4 (L/h)	128	8.44	6.59	
V4 (L)	1380	40.6	2.94	
ka (/h)	0.356	0.0231	6.49	
D1	3.64	FIXED		
SWF1 (food)	0.380	0.0302	7.95	
SWF2 (formulation)	0.462	0.00337	7.29	
FD50	0.228	FIXED		
COVD	0.459	FIXED		
Stochastic Model (IIV and Residual Error)				
IIV CL	0.0548 (23.7%)	0.0335	61.2	18.9
IIV CL, V2	0.0943 (50.1%)	0.0761	80.7	
IIV V2	0.648 (95.5%)	0.334	51.6	11.0
IIV F1	0.265 (55.1%)	0.0987	37.3	4.08
Proportional error	0.553	0.0168	3.04	1.69

CL (clearance), V (volume of distribution), Q (intercompartmental clearance), ka (first order absorption rate constant), D1 (zero-order infusion duration), SWF1 (fasted/fed switch), SWF2 (tablet/suspension switch), FD50: absolute bioavailability for the dose of 50 mg of mirabegron; COVD: exponent for dose effect on bioavailability; IIV: interindividual variability

Source: ~ED178\YM178-Pediatrics\03_Phase 1 Studies\02_178CL201\PopPK\ 03_Formalanalysis\02_Final models\Model34

Source: 178-pk-204 PopPK report, Table 7

Simulations were performed using the best model as described above in order to determine the dose of oral suspension or tablet to be administered in children under fed conditions that would result in steady state exposure similar to that of the approved tablet doses in adults. The target exposures were defined to be 69 and 188 ng*h/mL for the 25 and 50 mg doses, respectively. The exact suspension dose for every virtual pediatric patient to reach target exposure were calculated using the following equation. In the equations above, FD_{50} and *COVD* are model parameters characterizing the dose dependency on bioavailability ($F1_i$), and $SWF_{1,i}$ and $SWF_{2,i}$ are switch factors for the food and formulation effects, respectively.

$$Dose_i = \left(\frac{AUC_{target} \cdot CL_{children,i} \cdot 50^{COVD}}{FD_{50} \cdot SWF_{1,i} \cdot SWF_{2,i} \cdot 1000}\right)^{1/(1+COVD)}$$

which was obtained by combining the following 2 equations:

$$Dose_i = \frac{AUC_{target} \cdot CL_{children,i}}{F1_i \cdot 1000}$$

$$F1_i = FD_{50}\left(\frac{Dose_i}{50}\right)^{COVD} \cdot SWF_{1,i} \cdot SWF_{2,i}$$

$CL_{children,i}$ is the clearance for each virtual pediatric patient which was predicted using the following equation:

$$CL_{children,i} = CL_{adults}\left(\frac{weight_{children,i}}{70}\right)^{0.75} \cdot \exp(\eta_i)$$

Individual virtual patient values for the between subject variability on clearance (η_i) are sampled from a normal distribution with mean 0 and the variance estimated by the 178-CL-201 model, and used to modify the model-estimated value of CL_{adults}. These clearance values are then scaled based on $weight_{children,i}$, each virtual pediatric patient's body weight.

The virtual patients were then divided into three weight categories, and the median exact dose is calculated for each weight category. Finally, the AUC is calculated for each subject at the median exact dose within corresponding weight category using the following equation. Individual patient values for the between subject variability on bioavailability ($\eta_{2,i}$) are sampled from a normal distribution with mean 0 and the variance estimated by the 178-CL-201 model. The weight categories were adjusted by visual inspection using plots of calculated AUC_{24h} versus body weight with respect to their accuracy to reach the target exposure. The first scenario split the body weight starting with approximately equal ranges, and the median exact doses rounded to the nearest 8 mg (e.g., 1 mL of 8 mg/mL oral suspension). Then the body weight ranges were adjusted incrementally until there was a reasonable variance in each group around the target at the rounded doses. The processes were repeated for each set of new weight categories until a best scenario was obtained.

Target AUC for 178-CL-206: $\frac{MDose \cdot F1_i \cdot 1000}{CL_{children,i}}$

$$AA = FD_{50}\left(\frac{MDose}{50}\right)^{COVD}$$

$$BB = \log\left(\frac{AA}{1-AA}\right)$$

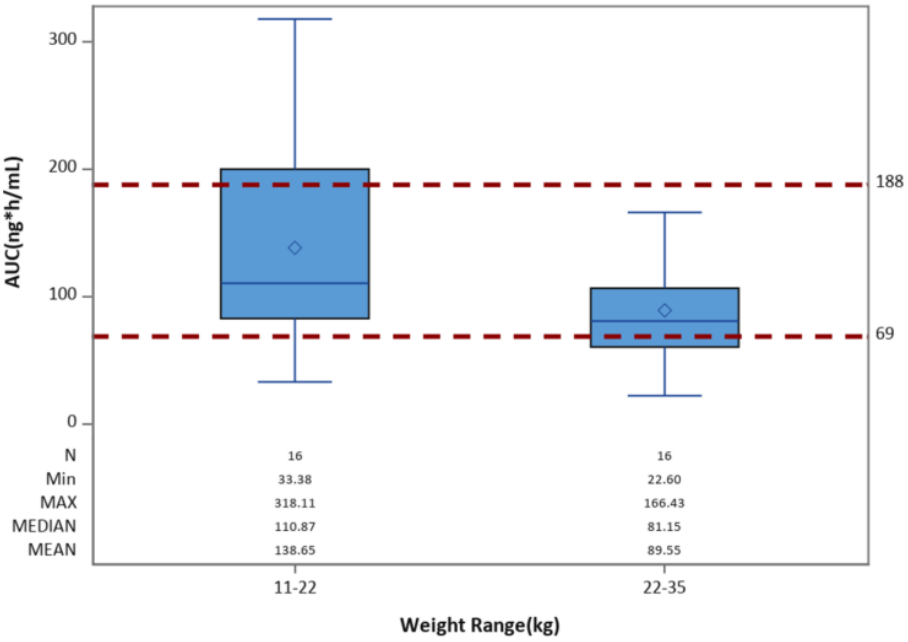
$$F1_i = \left(\frac{\exp(BB + \eta_{2,i})}{1+\exp(BB + \eta_{2,i})}\right) \cdot SWF_{1,i} \cdot SWF_{2,i}$$

NONMEM 7.3 was used in nonlinear mixed effect modeling, and R was used for data management and model post-processing and simulations.

4.4.4 Results

Based on this reviewer's analysis, the proposed starting doses (3 ml as starting dose for body weight range 11 kg to less than 22 kg; 4 ml as starting dose for body weight range 22 kg to less than 35 kg) give similar exposure as the starting dose (25 mg) and maximum dose (50 mg) in adults (Figure 5 and 7).

Figure 5. AUC comparison for starting dose of mirabegron oral suspension in NDO patient body weight less than 35 kg*



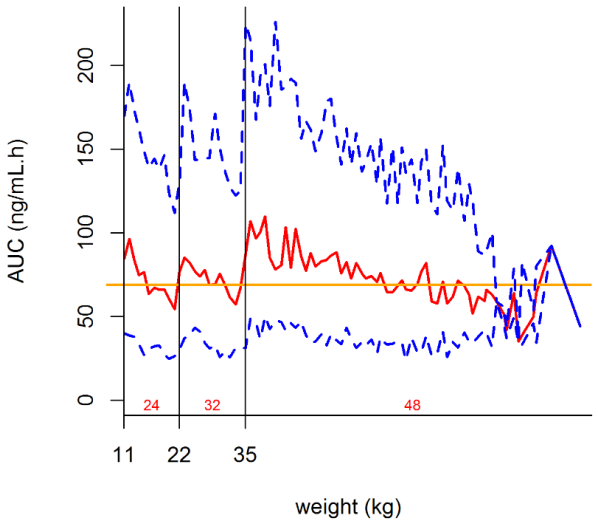
* The red dash line corresponding to the targeted AUC exposure in adults, which is 69 and 188 ng*h/mL for starting and maximum dose, respectively.

The reviewer verified the best model selected for the simulation and deems it is acceptable. Based on the simulation, the final body weight categories were determined to be 11-< 22 kg, 22 -<35 kg and >=35 kg. For each body weight in the population, the median and 5th and 95th percentiles for these predicted AUCs were calculated and plotted versus body weight. The median exact suspension doses for each of the 3 weight groups were 24, 31 and 44 mg for pediatric equivalent dose to 25 mg ER tablet (PED25) and 47, 61, and 87 mg for pediatric equivalent dose to 50 mg ER tablet (PED50). Rounding to the nearest 8 mg (i.e., 1 mL) led to final doses of 24, 32, and 48 mg for PED25, and 48, 64, and 88 mg (6, 8, and 11 mL) for PED50 for the three weight groups. The applicant decided to round up the doses for evaluation in Study 178-CL-206A because underdosing is particularly important to avoid in NDO population. In the NDA submission, 80 mg (10 mL) was proposed as the maximum dose for the ≥ 35 kg weight group due to the ability to dose the oral suspension with a single dosing device

administration. The simulation result is shown in Figure 6. Based on the simulation data, the exposure from the proposed oral suspension dose of 80 mg in pediatric patients with body weight ≥ 35 kg is expected to be comparable to that from the approved maximum dose of tablets 50 mg in adult patients.

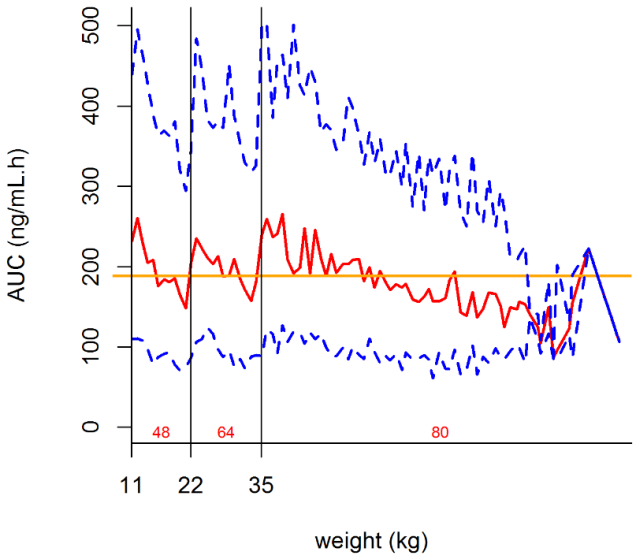
Figure 6. Result of the optimization of the oral suspension (8 mg/mL) dose in children in study 178-CL-206A *

Starting Dose (PED25)



*The orange line is the target AUC level (69 ng*h/mL) which is determined from adult study data in approved tablet formulation. The red curve is the median simulated AUC, and the two blue curves represent the 5th and 95th percentiles of predicted AUCs.

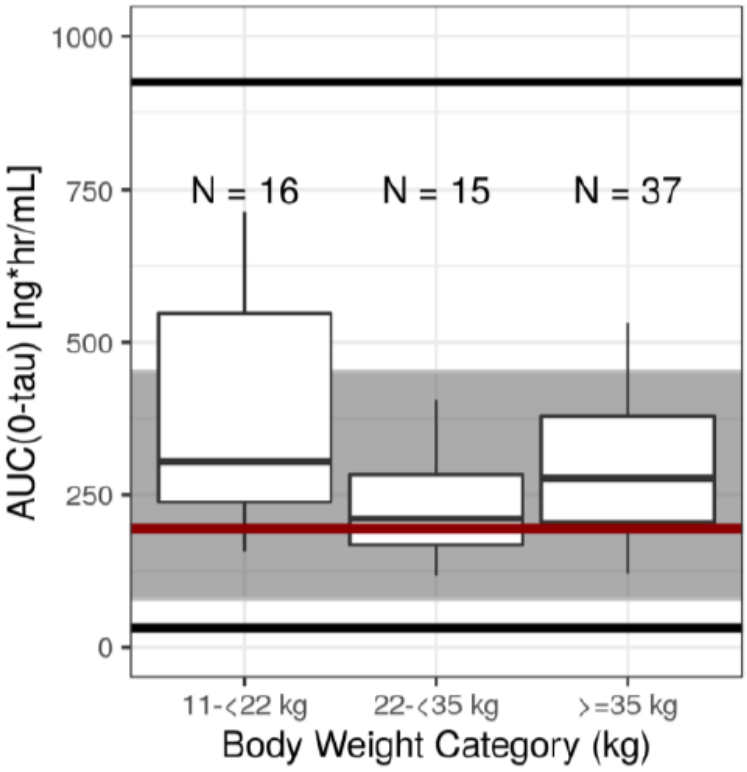
Maximum Dose (PED50)



*The orange line is the target AUC level (188 ng*h/mL) which is determined from adult study data in approved tablet formulation. The red curve is the median simulated AUC, and the two blue curves represent the 5th and 95th percentiles of predicted AUCs.

The steady-state exposure range (5%, 25%, 50%, 75%, and 95%) of patients who took either mirabegron oral suspension or ER tablet in study 178-CL-206A was also compared to that of mirabegron in adults at approved dose (Figure 7). All pediatric subjects' exposure in study 178-CL-206A fall within the range of adult exposures, and the majority fall within the 5th-95th percentile of adult data.

Figure 7. Steady State AUC at PED50 for pediatric patients in 178-CL-206A compared to adult exposure at 50 mg*



*The boxplots represent the requested percentiles for the pediatric subgroups: the box shows the 25th, 50th, and 75th percentiles, and the ends of the whiskers are the 5th and 95th percentile in each category. The distribution of adult exposures is shown as annotations on the plots: solid black lines represent the minimum and maximum, the solid red line is the median, and the gray shaded band is the 5th-95th percentile of adult exposures. The adult exposure distribution was based on individual predicted exposures from the final population PK model in adults [Study No. 178-PK-015 in approved mirabegron ER tablet].

Source: IR response 2020-dec-14, Figure 1

4.4.5 Listing of analyses codes and output files

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for the final model	PPK178.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Mirabegron_NDA213801_YW\PPK Analysis
NONMEM code for the final model	Run5.mod	
Simulation code	Dose-estimation-206-susp-max80.r	
Virtual pediatric patient dataset	NHANES_demo.csv	
Simulation parameter file	201ppk_AS_orig.lst	

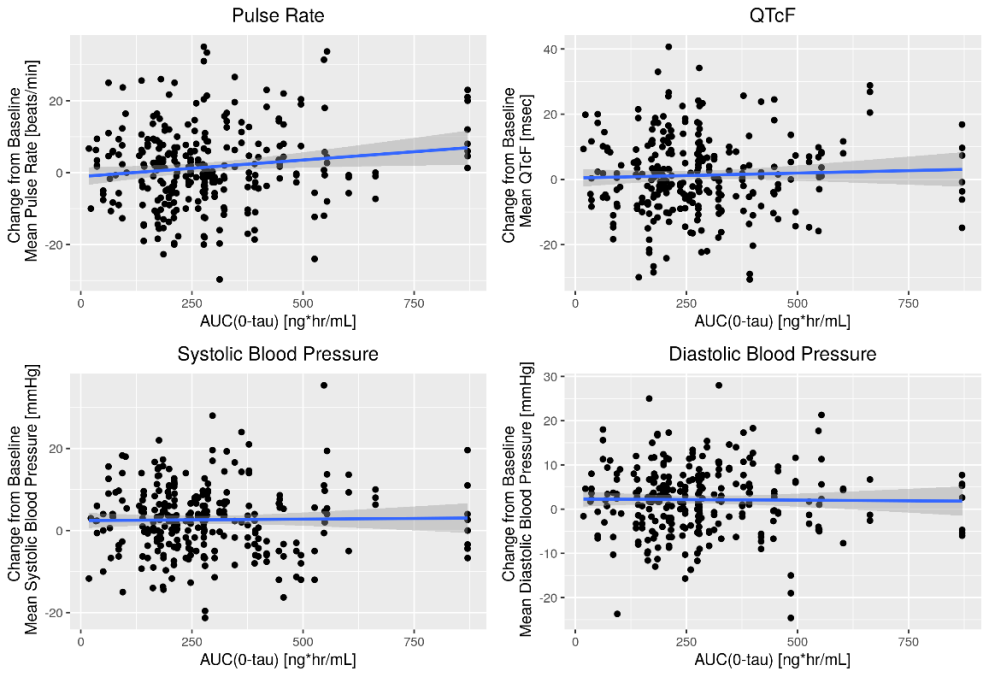
4.5 Exposure-Response Analyses

Review Summary

In the current application, the applicant did not conduct E-R analysis for efficacy. They provided E-R analysis for safety to address potential risks if a patient takes mirabegron oral suspension or mirabegron tablets on an empty stomach in their response to the FDA's information request letter dated Dec 3, 2020. The reviewer deems it is acceptable to not conduct E-R analysis for efficacy because the dose is titrated to achieve efficacy in study No. 178-CL-206A.

For NDO patients in study 178-CL-206A, safety data of mirabegron including pulse rate, clinically measured blood pressure and QTcF interval were obtained at weeks 4, 12, 24, and 52. Individual predicted steady-state exposures based on actual mirabegron doses administered on the day of the observation of each safety endpoint were used in the analysis. No clear trends were observed for systolic blood pressure, diastolic blood pressure, or QTcF for either AUC_{tau} (Figure 9) or C_{max} (Figure 3.3.2-5 as shown in Section 3.3 Clinical Pharmacology Review Questions). Similar findings were observed when the data were plotted separately for each visit (data not shown). However, a positive trend is noted for pulse rate in the pediatric patients. If the patients continually received mirabegron under fasting conditions, the steady state exposure is predicted to increase by approximately 2.2 fold (Table 4 in Section 4.3.4). The pulse rate is predicted to increase by approximately 4 beats/min in fasting state comparing to fed state at the median C_{max} for the PED50 dose (Figure 10). As a result, the Applicant proposed to administer mirabegron oral suspension with food to minimize the heart rate effect. The reviewer deems the Applicant's proposal acceptable.

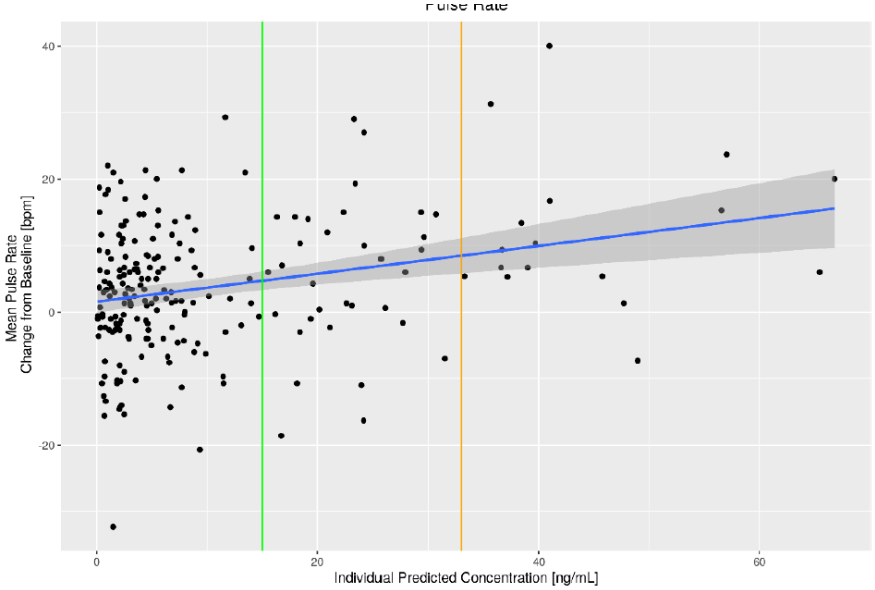
Figure 9. Key Safety Endpoints (all visits) versus individual predicted steady-state AUC_{tau} for patients in Study 178-CL-206A*



*Solid blue line (grey shaded region) represents prediction (95% confidence interval) from a linear regression. Steady-state AUC_{tau} calculated based on the dose administered on the day of observation.

Source: IR response 2020-dec-3, Figure 4

Figure 10. Mean Change from Baseline Pulse Rate vs Individual Predicated Mirabegraon Concentration



Solid blue line (grey shaded region) represents prediction (95% confidence interval) from a linear regression. Green vertical line represents median predicted C_{max} value for patients in Study 178-CL-206A (16 ng/mL) and the orange vertical line represents extrapolated median C_{max} value for patients receiving mirabegron under persistent fasted meal conditions (35 ng/mL).

Source: IR response 2020-dec-3, Figure 7

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/s/

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