CLINICAL REVIEW

<table>
<tr><td>Application Type</td><td>NDA and sNDA</td></tr>
<tr><td>Application Number(s)</td><td>NDA 213801 and sNDA 202622/s-017</td></tr>
<tr><td>Priority or Standard</td><td>Priority</td></tr>
<tr><td>Submit Date(s)</td><td>September 28, 2020</td></tr>
<tr><td>Received Date(s)</td><td>September 28, 2020</td></tr>
<tr><td>PDUFA Goal Date</td><td>March 28, 2021</td></tr>
<tr><td>Division/Office</td><td>DUOG/ORPURM</td></tr>
<tr><td>Reviewer Name(s)</td><td>Elena Boley</td></tr>
<tr><td>Review Completion Date</td><td>March 18, 2021</td></tr>
<tr><td>Established/Proper Name</td><td>Mirabegron for extended-release oral suspension
Mirabegron extended-release tablets</td></tr>
<tr><td>(Proposed) Trade Name</td><td>MYRBETRIQ® Granules
MYRBETRIQ®</td></tr>
<tr><td>Applicant</td><td>Astellas Pharma Global Development, Inc.</td></tr>
<tr><td>Dosage Form(s)</td><td>Extended-release oral suspension 8mg/mL
Extended-release tablets 25mg and 50mg</td></tr>
<tr><td>Applicant Proposed Dosing Regimen(s)</td><td><u>Mirabegron for extended-release oral suspension</u>:
The recommended dose of MYRBETRIQ® Granules is determined based on patient weight. Treatment should be initiated at the recommended starting dose (see Table). After 4 to 8 weeks, based on individual efficacy and safety, dosage may be increased to the lowest effective dose, but should not exceed the maximum recommended dose.

<table>
<tr><th>Body Weight Range</th><th>Starting Dose[1]</th><th>Maximum Volume[1]</th></tr>
<tr><td>11 kg to less than 22 kg</td><td>3 mL (24 mg)</td><td>6 mL (48 mg)</td></tr>
<tr><td>22 kg to less than 35 kg</td><td>4 mL (32 mg)</td><td>8 mL (64 mg)</td></tr>
<tr><td>Greater than or equal to 35 kg[2]</td><td>6 mL (48 mg)</td><td>10 mL (80 mg)</td></tr>
</table>
[1]MYRBETRIQ 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.

<u>Mirabegron extended-release tablets</u>:
For Pediatric Patients ≥ 35 kg, the recommended starting dose of MYRBETRIQ is 25 mg once daily. Based on individual patient efficacy and tolerability, the dose may be increased to 50 mg once daily after 4 to 8 weeks.</td></tr>
<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>Oral suspension: Neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 years and older
Tablets: NDO in pediatric patients aged 3 years and older and weighing 35 kg or more.</td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Approval</td></tr>
</table>

Recommended Indication(s)/Population(s) (if applicable)	

Table of Contents

Glossary 9
1. Executive Summary 12
1.1. Product Introduction 12
1.2. Conclusions on the Substantial Evidence of Effectiveness 12
1.3. Benefit-Risk Assessment 12
1.4. Patient Experience Data 20
2. Therapeutic Context 20
2.1. Analysis of Condition 20
2.2. Analysis of Current Treatment Options 21
3. Regulatory Background 22
3.1. U.S. Regulatory Actions and Marketing History 22
3.2. Summary of Presubmission/Submission Regulatory Activity 23
3.3. Foreign Regulatory Actions and Marketing History 25
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 25
4.1. Office of Scientific Investigations (OSI) 25
4.2. Office of Product Quality (OPQ) 25
4.3. Clinical Microbiology 26
4.4. Nonclinical Pharmacology/Toxicology 26
4.5. Clinical Pharmacology 26
4.6. Devices and Companion Diagnostic Issues 27
4.7. Consumer Study Reviews 27
4.8. Division of Medication Error Prevention and Analysis (DMEPA) 27
4.9. Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) 28
4.10. Division of Epidemiology (DEPI) 28
4.11. Division of Risk Management (DRISK) 28
4.12. Division of Pharmacovigilance (DPV) 28
5. Sources of Clinical Data and Review Strategy 28
5.1. Table of Clinical Studies 28
5.2. Review Strategy 35
6. Review of Relevant Individual Trials Used to Support Efficacy 35
6.1. Study 178-CL-206A 35
6.1.1. Study Design 35
6.1.2. Study Results 46
7. Integrated Review of Effectiveness 75
7.1. Assessment of Efficacy Across Trials 75
7.2. Additional Efficacy Considerations 76
7.2.1. Considerations on Benefit in the Postmarket Setting 76
7.2.2. Other Relevant Benefits 76
7.3. Integrated Assessment of Effectiveness 76
8. Review of Safety 77
8.1. Safety Review Approach 77

8.2. Review of the Safety Database 77
8.2.1. Overall Exposure 78
8.2.2. Relevant characteristics of the safety population 79
8.2.3. Adequacy of the safety database 79
8.3. Adequacy of Applicant's Clinical Safety Assessments 79
8.3.1. Issues Regarding Data Integrity and Submission Quality 79
8.3.2. Categorization of Adverse Events 80
8.3.3. Routine Clinical Tests 80
8.4. Safety Results 80
8.4.1. Serious Adverse Events 82
8.4.2. Dropouts and/or Discontinuations Due to Adverse Effects 96
8.4.3. Adverse Events 97
8.4.4. Treatment Emergent Adverse Events and Adverse Reactions 98
8.4.5. Laboratory Findings 109
8.4.6. Vital Signs 110
8.4.7. Electrocardiograms (ECGs) 123
8.4.8. QT 125
8.4.9. Immunogenicity 125
8.4.10. Urinary Tract Ultrasound and PVR 125
8.5. Analysis of Submission-Specific Safety Issues 127
8.5.1. Submission-Specific Safety Issues 127
8.6. Safety Analyses by Demographic Subgroups 128
8.7. Specific Safety Studies/Clinical Trials 129
8.7.1. Interdisciplinary Review Team for QT Studies Consult 129
8.7.2. DPMH Consult 129
8.8. Additional Safety Explorations 129
8.8.1. Human Carcinogenicity or Tumor Development 129
8.8.2. Human Reproduction and Pregnancy 129
8.8.3. Pediatrics and Assessment of Effects on Growth 129
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound 131
8.9. Safety in the Postmarket Setting 131
8.9.1. Safety Concerns Identified Through Postmarket Experience 131
8.9.2. Expectations on Safety in the Postmarket Setting 137
8.10. Integrated Assessment of Safety 137
9. Advisory Committee Meeting and Other External Consultations 139
10. Labeling Recommendations 139
10.1. Prescription Drug Labeling 139
10.2. Nonprescription Drug Labeling 140
11. Risk Evaluation and Mitigation Strategies (REMS) 140
12. Postmarketing Requirements and Commitments 140
13. Appendices 140
13.1. References 140
13.2. Financial Disclosure 140

Table of Tables

Table 1 Available Treatments for Pediatric Neurogenic Detrusor Overactivity (NDO) 22
Table 2 Listing of Clinical Trials Relevant to this NDA/sNDA 30
Table 3 Weight-based Doses for Mirabegron Tablets or Oral Suspension 37
Table 4 Study Flow Chart 38
Table 5 Schedule of Assessments 41
Table 6 Summary of Patient Disposition and Analysis Sets, Study 178-CL-206A 47
Table 7 Protocol Deviations in Patients who Received ≥ 1 Dose of Mirabegron (All Allocated Set) for Study 178-CL-206A 48
Table 8 Summary of Demographics and Baseline Characteristics for Study 178-CL-206A (SAF) 49
Table 9 Neurogenic Detrusor Overactivity Diagnosis and History (SAF); Study 178-CL-206A. 51
Table 10 Overview of NDO Therapies Prior to Study Drug Administration in Study 178-CL-206A (SAF) 52
Table 11 Summary of Study Drug Dosing; Study 178-CL-206A (SAF) 53
Table 12 Summary of Study Drug Compliance and Exposure over the Whole Treatment Period; Study 178-CL-206A (SAF) 53
Table 13 Change from Baseline in Maximum Cystometric Capacity* (mL) at Week 24 – LOCF (FAS); Study 178-CL-206A 54
Table 14 Summary of Maximum Cystometric Capacity (mL) by Study Week (FAS); Study 178-CL-206A 55
Table 15 Results of Secondary Analyses of Change from Baseline in MCC at 24 weeks using different statistical approaches (without and with LOCF, BOCF) for different populations; Study 178-CL-206A 56
Table 16 Secondary Analyses of Change from Baseline to Week 24 in MCC (mL): Repeated Measures Analysis (FAS and PPS), Study 178-CL-206A 57
Table 17 Secondary Analysis of Change from Baseline to Week 24 (With and Without LOCF) in MCC (mL): Wilcoxon Signed-rank Test (FAS), Study 178-CL-206A 58
Table 18 Sensitivity Analysis of the Primary Estimand in MCC (mL): Repeated Measures Analysis (FAS), Study 178-CL-206A 58
Table 19 Change from Baseline in Urodynamic Endpoints at Week 4 and Week 24 (FAS); Study 178-CL-206A 60
Table 20 Change From Baseline in Secondary Efficacy Endpoints based on Urodynamic Studies for each Age Group at 4 and 24 Weeks (FAS); 178-CL-206A 62
Table 21 Change From Baseline to Weeks 4, 24, and 52 in Average Catheterized Volume per Catheterization (mL) (FAS); Study 178-CL-206A 63
Table 22 Change From Baseline to Weeks 4, 24, and 52 in Maximum Catheterized Volume per Catheterization (mL) (FAS); Study 178-CL-206A 63
Table 23 Change From Baseline to Weeks 4, 24, and 52 in Maximum Catheterized Daytime Volume (mL) (FAS); Study 178-CL-206A 64
Table 24 Change From Baseline to Weeks 4, 24 and 52 in Average Morning Catheterized Volume (mL) (FAS); Study 178-CL-206A 65

Table 25 Change From Baseline to Weeks 4, 24 and 52 in Mean Number of Leakage Episodes per Day (Day and Night Time): Ad-hoc Analysis With Imputation (FAS); Study 178-CL-206A 66
Table 26 Change From Baseline to Weeks 4, 24 and 52 in Mean Number of Leakage Episodes per Day (Day and Night Time): Ad-hoc Analysis With Imputation and Excluding 1 Child's Data (FAS); Study 178-CL-206A 67
Table 27 Change From Baseline at Each Visit in Mean Number of Leakage Episodes per Day (Day and Night Time): Ad-hoc Analysis (new algorithm, version 2), excluding data from Subject (b) (6) Study 178-CL-206A..... 68
Table 28 Change From Baseline to Weeks 4, 24 and 52 in Number of Dry (Leakage-free) Days per 7 Days (Day and Night Time) (FAS), Study 178-CL-206A..... 69
Table 29 Change From Baseline to Weeks 24 and 52 in Total Patient Global Impression of Severity Scale Score (FAS), Study 178-CL-206A 70
Table 30 Total Clinician Global Impression of Change at Weeks 24 and 52 (FAS), Study 178-CL-206A 71
Table 31 Subgroup Analysis of Change from Baseline to Week 24 (LOCF) in Maximum Cystometric Capacity (mL): Effect of Sex (FAS), Study 178-CL-206A 72
Table 32 Subgroup Analysis of Maximum Cystometric Capacity (mL) at Week 24 (LOCF) by Race (FAS), Study 178-CL-206A..... 73
Table 33 Subgroup Analysis of Change from Baseline to Week 24 (LOCF) in Maximum Cystometric Capacity (mL) by Formulation (FAS)..... 73
Table 34 Pediatric Studies Safety Population in the Mirabegron Pediatric NDO Development Program..... 78
Table 35 Overview of Treatment-emergent Adverse Events (SAF); Study 178-CL-206A 80
Table 36 Overview of TEAEs and Death (SAF); Studies 178-CL-202 and 178-CL-203..... 81
Table 37 Serious TEAEs (SAF); Study 178-CL-206A..... 82
Table 38 Serious Treatment-emergent Adverse Events (SAF)..... 83
Table 39 Treatment-emergent Adverse Events Leading to Permanent Discontinuation (SAF).. 96
Table 40 Treatment-Emergent Adverse Events by Severity (SAF)..... 98
Table 41 TEAEs in at Least 2% of All Patients (SAF); Study 178-CL-206A 98
Table 42 Percentages of Patients with Adverse Reactions Reported in ≥ 2% of Patients in Study 178-CL-206A (SAF)..... 100
Table 43 Drug-related* TEAEs in Study 178-CL-206A (SAF) 100
Table 44 TEAEs in at Least 2% of All Patients (SAF); Study 178-CL-202 and 128-CL-203... 101
Table 45 Overview of Incidence of TEAEs of Special Interest (SAF); Study 178-CL-206A .. 102
Table 46 Cardiovascular TEAEs of Special Interest (SAF); Study 178-CL-206A 103
Table 47 TEAEs of Special Interest: Hypersensitivity Reactions (SAF); Study 178-CL-206A 104
Table 48 TEAEs of Special Interest: Urinary Tract Infection (SAF); Study 178-CL-206A..... 104
Table 49 TEAEs by Time Intervals in Study 178-CL-206A (SAF) 108
Table 50 TEAEs by Sex, Race, Drug Formulation, and NDO Medication Use at Baseline in Study 178-CL-206A (SAF)..... 108
Table 51 Vital Signs: Changes From Baseline in Blood Pressure (Percentiles) and Pulse Rate - Clinic Measurement (Clinical Practice Guidelines, 2017) (SAF) 114
Table 52 Potentially Clinically Relevant Values in Vital Signs – Clinic Measurements (SAF)115

Table 53 Changes in Blood Pressure Relative to Mirabegron Exposure from Clinic Visits in Study 178-CL-206A 117
Table 54 Summary of BP at Baseline and Shifts to Stage I and Stage II Hypertension†, 178-CL-206A 120
Table 55 Changes in Heart Rate from Study Clinic Visits in Children and Adolescents in Study 178-CL-206A 121
Table 56 Heart Rate Parameters from Study Clinic Visits in Children and Adolescents in Study 178-CL-206A 122
Table 57 Interpretation of Upper Urinary Tract Results (SAF); Study 178-CL-206A 126
Table 58 Serious Adverse Events Received for Pediatric Patients until 30 Jun 2019 132
Table 59 SAEs reported in the 120-Day Safety Update 136

Table of Figures

No table of figures entries found.

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BE/BA	bioequivalence/bioavailability
BLA	biologics license application
BMI	body mass index
BOCF	baseline observation carried forward
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFB	change from baseline
CFR	Code of Federal Regulations
CGI-C	Clinician Global Impression of Change
CI	confidence interval
CIC	continuous intermittent catheterization
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DEPI	Division of Epidemiology
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DPV	Division of Pharmacovigilance
DRISK	Division of Risk Management
EBC	expected bladder capacity
ECG	electrocardiogram
EoS	end of study
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration

FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
ICCS	International Children's Continence Society
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LOCF	last observation carried forward
MAH	Marketing Authorization Holder
MCC	maximum cystometric capacity
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NDO	neurogenic detrusor overactivity
NME	new molecular entity
OAB	overactive bladder
OCS	Office of Computational Science
OPDP	Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
PIN-Q	Pediatric Incontinence Questionnaire
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics or protocol deviation
PGI-S	Patient Global Impression of Severity Scale
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPS	per protocol set
PPI	patient package insert
PPSR	Proposed Pediatric Study Request
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PVR	post void residual
QTc	corrected QT interval
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAF	safety analysis set

SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care or system organ class
TEAE	treatment emergent adverse event
UTI	urinary tract infection
WR	Written Request

1. Executive Summary

1.1. Product Introduction

Mirabegron (MYRBETRIQ®) is a selective human beta-3 adrenoceptor agonist. Activation of the beta-3 adrenergic receptors residing on the bladder (detrusor smooth muscle) inhibits involuntary detrusor muscle contractions and increases of bladder capacity. Mirabegron, 25 mg and 50 mg tablets, was originally approved on June 28, 2012 under NDA 202611 for the treatment of adults with overactive bladder (OAB), with symptoms of urge incontinence, urgency and urinary frequency. In this NDA and sNDA, data for the pediatric population is presented to support the safety and efficacy of mirabegron oral suspension and mirabegron tablet, respectively, for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 3 to less than 18 years.

Treatment with mirabegron for extended-release oral suspension in children should be initiated at the recommended starting dose based on the patient's weight. Thereafter, based on individual efficacy and safety, the dose may be increased to the maximum oral suspension dose (appropriate to the patient's weight range) once daily after 4 to 8 weeks. The maximum dose for each weight range should not be exceeded. Mirabegron for extended-release oral suspension should be administered with food.

Treatment with mirabegron extended-release tablets in children ≥ 35 kg should be initiated at 25 mg once daily with food. Based on individual patient efficacy and tolerability, the dose may be increased to 50 mg once daily after 4 to 8 weeks.

MYRBETRIQ Granules for extended-release oral suspension: 8.3 g of granules (830 mg of mirabegron) are yellowish white granules. After reconstitution with water, 8 mg/mL oral suspension is a pale yellow to brownish yellow suspension.

MYRBETRIQ extended-release tablets are marketed in the US as MYRBETRIQ 25 mg and 50 mg tablets. The 25 mg tablet is oval, brown, film coated, and debossed with the Astellas logo and "325." The 50 mg tablet is yellow, film coated, and debossed with the Astellas logo and "355."

1.2. Conclusions on the Substantial Evidence of Effectiveness

From the Clinical perspective, the evidence presented in this NDA and sNDA is adequate to support the effectiveness of these products in the treatment of pediatric patients with NDO.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

MYRBETRIQ (mirabegron tablets) and MYRBETRIQ Granules (oral suspension) will be indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients. Neurogenic detrusor overactivity is defined as detrusor overactivity that develops as a result of a neurologic lesion. Tablets are appropriate for children ≥ 35 kg who are capable of swallowing them. An oral suspension, which facilitates swallowing for younger children and allows accurate dose titration, is intended to provide another treatment option for younger NDO pediatric patients and older NDO patients who cannot or desire not to swallow tablets. The goal of treatment is to preserve renal function and minimize symptoms of incontinence by increasing bladder capacity and the duration of time between incontinence episodes.

At this time, the Clinical review team recommends that this NDA and sNDA should be APPROVED.

NDO results from neurological lesions often related to congenital anomaly and injury to the spinal cord. In this special pediatric patient population, NDO poses a meaningful burden both physically and socially/emotionally. Physical consequences of untreated NDO are bladder wall injury and renal damage. Interference in social and emotional development results from the limited lifestyle and decreased level of engagement caused by frequent incontinence episodes.

Current oral pharmacologic treatment options for NDO are limited and include only three approved options: oxybutynin (tablets and syrup) and solifenacin (oral suspension), each in combination with clean intermittent catheterization (CIC), and onabotulinumtoxin A (intradetrusor injection). Oxybutynin's side effect profile includes potential central nervous system adverse effects which raises concerns about learning and school performance, as well as more typical side effects associated with anticholinergic medications such as headaches, blurred vision, constipation, altered behavior, dry mouth, and flushed cheeks. Solifenacin's anticholinergic side effects consist primarily of constipation and dry mouth. Side effects of onabotulinumtoxin A intradetrusor injection include bacteruria, UTI, leukocyturia, and hematuria. There is a need for alternative options for treatment of this patient population that are safe and effective.

Mirabegron, a beta-3 adrenergic agonist, works by activating the beta-3 adrenergic receptors residing on the bladder (detrusor) smooth muscle, thereby inhibiting involuntary detrusor muscle contractions and increasing bladder capacity. The efficacy of mirabegron tablets and oral suspension has been demonstrated through clinically meaningful increases in maximum cystometric capacity and supported by improvement in many urodynamic parameters and e-diary recorded bladder volume and leakage measurements. The magnitude of treatment effect was similar across age groups. The efficacy of mirabegron tablets and oral suspension does not appear to be associated with any new safety issues.

The safety profile of mirabegron tablets and oral suspension is consistent with the known risks of mirabegron tablets for the treatment of OAB in

adults. There were no deaths in the development program, and none of the SAEs appeared to be drug-related. Discontinuations (n=3) were due to AST increased, urinary incontinence, and dermatitis allergic, and none was related to the study drug. The most commonly reported adverse reactions were UTI (24.4%, which includes *E.coli* urinary tract infection, UTI bacterial, UTI, and UTI Pseudomonal), nasopharyngitis (5.8%), constipation (4.7%), and headache (3.5%). UTI TEAEs were thought to reflect, at least in part, the high annual incidence of UTI in pediatric patients with NDO practicing CIC and not all associated with mirabegron treatment. Other TEAEs of special interest were not drug related and included bradycardia, QT prolongation, neoplasm, and seizure, each reported in a single patient; hypersensitivity reactions (n=5); and fetal disorder after exposure during pregnancy (n=1), which was erroneously coded. Vital signs data showed an increase from baseline in blood pressure (not related to exposure) for patients <12 years of age of 4.3 mm Hg in mean systolic blood pressure and 1.7 mm Hg in mean diastolic blood pressure, with larger increases for patients < 8 years of age. Overall, TEAEs were reported with similar frequency in the pediatric NDO patients as they were in clinical trials of adults with OAB. Postmarket experience SAE cases lacked information or were confounded.

The benefit-risk analysis takes into account that NDO in the pediatric population is a serious condition that is associated with bladder wall changes and renal damage, as well as social and emotional distress that greatly interferes with the development of these children. Mirabegron tablets and oral suspension provide an alternative treatment to the currently approved options, is efficacious, and has a different side effect profile. Additionally, mirabegron tablets and oral suspension offer a convenient once daily dosing regimen and data to support safety and efficacy for pediatric patients as young as 3 years old.

These benefits compare favorably against the safety profile which reflects the known risks apparent in the premarket and postmarket experience with mirabegron tablets to date. The clinical trials of mirabegron tablets and oral suspension provided no safety signals beyond those known for mirabegron tablets in adults with OAB. Labelling is adequate to address the known risks of mirabegron. The safety data submitted supports the use of mirabegron tablets and oral suspension as an additional first line therapy, coupled with CIC, for the treatment of pediatric patients aged 3 to < 18 years with NDO.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• NDO is defined by the International Children's Continence Society (ICCS) as detrusor overactivity when there is a relevant neurological condition. NDO is a urodynamic observation characterized by involuntary detrusor contractions that are spontaneous or provoked during the filling phase,	This condition is important because of the irreversible kidney damage it can cause without treatment as well as the severe limitations on daily living and the resulting social and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	involving a detrusor pressure increase of greater than 15 cm H_2O above baseline. • NDO can develop as a result of a lesion at any level in the nervous system. The most prevalent cause of NDO in children is myelodysplasia, which includes such conditions as myelomeningocele, meningocele, and occult spinal dysraphism/spina bifida occulta, and results from neural tube closure defects during fetal development. The most common acquired cause for NDO is cerebral palsy. An injury in the perinatal period (e.g. perinatal infection, anoxia) can produce a neuromuscular disability or a specific cerebral dysfunction. Less common acquired causes include spinal tumors, trauma, or sequalae of transverse myelitis. Because NDO results from a number of different conditions, prevalence is not easily quantifiable. • If untreated, NDO can cause bladder wall changes and renal damage due to hydronephrosis. • Chronic incontinence in children with NDO leads to limited social participation, embarrassment and shame, and decreased independence. These consequences adversely affect the social and emotional development of children and also of adolescents transitioning into adulthood.	emotional harm it causes during the critical childhood developmental life stage.
Current Treatment Options	• The current first line treatment option is antimuscarinics coupled with CIC (4-5 times a day). The only approved oral medications are oxybutynin and solifenacin. Oxybutynin comes in tablets or syrup, is approved for patients with NDO aged 5 years and older and is dosed 2-3 times a day. Solifenacin oral suspension is approved for patients with NDO aged 2 years and older and is dosed once daily. Onabotulinumtoxin A is approved for intradetrusor injection, a more invasive route of administration requiring anesthesia, in pediatric patients aged 5 and older who have been inadequately managed with anticholinergics. Even more invasive treatment options for those who fail treatment with oral medication and CIC or intradetrusor injection	There is a need for an additional pharmacotherapy option that offers effective therapy with a different side effect profile for a broad range of ages. Such an alternative may improve patient adherence (and be more convenient for caregivers), may be more effective and well tolerated than current therapy in some patients, and may delay or obviate the use of invasive therapies in the future.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	include incontinent urinary diversion or reconstructive bladder surgery with augmentation cystoplasty. • Current approved pharmacotherapy increases mean MCC at 24 weeks by 49 mL (oxybutynin) and 53 mL (solifenacin) compared to baseline. Onabotulinumtoxin A intradetrusor injections decreased daily urinary incontinence episodes and increased MCC by 64 mL after 6 weeks of treatment. • The safety profile for oxybutynin includes typical anticholinergic side effects such as headaches, blurred vision, constipation, altered behavior, dry mouth, and flushed cheeks. There are also potential CNS adverse effects that raise concerns for cognitive effects that could affect learning and school performance in the pediatric demographic. The safety profile of solifenacin includes primarily the typical anticholinergic side effects of constipation and dry mouth.	
Benefit	• The Phase 3 trial that supported the findings of efficacy in this application was an open-label, baseline-controlled, multicenter, dose-titration study in pediatric patients aged 3 to < 18 years with NDO who had been practicing CIC technique. The study was 52 weeks in total and was composed of a 24 week dose titration period followed by a 28 week fixed dose period. Two dosage forms were studied: oral suspension (in patients < 35 kg) and tablets (in patients ≥ 35 kg). • The primary endpoint was change from baseline to 24 weeks in mean maximum cystometric capacity (MCC). The secondary endpoints were based on urodynamics, patient e-diary responses (bladder volume and leakage measures), and PROs and included: ○ Change from baseline to week 4 in MCC and change from baseline to weeks 4 and 24 in bladder compliance, number of overactive detrusor contractions (> 15 cm H_2O) until end of filling, detrusor pressure at end	Baseline-controlled, open label studies have demonstrated the efficacy of mirabegron oral suspension in pediatric patients with NDO, aged 3 and older, and tablets in pediatric patients with NDO, aged < 18 years old and weighing ≥ 35 kg. Overall, the magnitude of the benefit in children (3 to < 12 years of age) and in adolescents (12 to < 18 years of age) was comparable. The duration of this efficacy was present at one year. The clinical meaningfulness of the changes in the primary endpoint is supported by secondary endpoint analyses. • The evidence provided meets the evidentiary standard for benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of filling, and filling volume until first overactive detrusor contraction (> 15 cm H_20). ○ Change from baseline to weeks 2, 4, 8, 12, 24, 36, and 52 in average catheterized volume per catheterization, maximum catheterized volume, maximum catheterized daytime volume, average morning catheterized volume (based on first catheterization after patient woke up), mean number of leakage episodes per day (day and night time), and number of dry (leakage-free) days/7 days (day and night time). ○ Change from baseline to weeks 24 and 52 in Pediatric Incontinence Questionnaire (PIN-Q), Patient Global Impression of Severity Scale (PGI-S), Clinician Global Impression of Change (CGI-C), and Acceptability (also at week 4). • In the Phase 3 study, the overall mean change from baseline to week 24 was 87 mL (95% CI 66, 108 mL, $p < 0.001$). The mean increase for pediatric patients aged 3 to < 12 years (72 mL [95% CI 45, 99, $p < 0.001$]) was smaller than the increase for pediatric patients aged 12 to < 18 (113 mL [95% CI, 79, 147, $p < 0.001$]); the difference was expected to be due to the different age-related bladder volumes and baseline MCCs between the 2 groups. This endpoint is deemed appropriate based on prior use as a primary efficacy endpoint in the clinical studies that supported approval of oxybutynin and solifenacin for the same indication and its routine use in clinical practice as a marker of bladder filling capacity. • Secondary endpoints support the primary efficacy results with improved urodynamic measurements and improvement in e-diary reported bladder volume and leakage measurements that reflect clinical meaningfulness. There were meaningful increases in all secondary endpoints. • PRO data showed that adolescents, all patients, and clinicians recognized improvement at week 24 which was maintained at week 52 for the Patient Global Impression of Severity Scale and the Total Clinician Global	• The quality of the evidence is supported by analysis of secondary endpoints which also demonstrate the clinical relevance of the findings. Mirabegron, in tablet or oral suspension forms, may provide benefit to patients by providing highly effective therapy with a different side effect profile than current therapies and with convenient daily dosing in patients as young as 3 years old.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Impression of Change. Patients also appeared to find the tablets and oral solution acceptable in terms of taste and swallowability. • The treatment effect measured at 24 weeks appeared to be similar to the treatment effect over the longer-term (52 weeks), demonstrating persistence of efficacy. • The magnitude of treatment effect was similar across age groups, with qualitative differences in effect explained by the anatomical changes that occur with physical growth during maturation in the age group of the patient population studied. • Mirabegron oral suspension provides an option in a wide pediatric age group (includes children as young as 3), requires convenient once daily dosing, and has a safety profile distinct from the currently approved anticholinergic treatment options. • The study drug was not studied in all races and ethnicities, nor was it studied in the United States, but there is no reason to expect differences in efficacy based on race or ethnicity or geographic region.	
Risk and Risk Management	• The extent of exposure and overall safety assessment in this application includes primarily pediatric NDO patients and small numbers of generally healthy pediatric patients with OAB symptoms. The product's safety profile is informed by one Phase 3 trial in pediatric NDO patients and two Phase 1 pharmacokinetic trials in pediatric NDO and generally healthy pediatric patients with OAB symptoms. The overall understanding of this product's safety profile is also based on 9 years of post-approval experience with mirabegron in adults with OAB. • The safety database population consisted mainly of White and Asian pediatric patients. While an overall diverse population is expected to use the product, there is no reason to presume differences in efficacy or safety based on race or ethnicity. The study populations for other racial groups	The safety results from the Phase 3 study and the two Phase 1 studies demonstrated the expected adverse reactions to mirabegron, with no new safety signals identified. Mirabegron in oral suspension and tablet form was generally well tolerated in pediatric NDO patients. The safety profile of mirabegron oral suspension and tablets in the pediatric NDO population was fully consistent with the safety profile of approved mirabegron tablets in adults with OAB. There were no new or unresolved safety issues.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	were too small to assess for differences in drug effect. • Mirabegron is intended for chronic use, which was reflected in the 52-week study duration. • Safety concerns were investigated extensively. Mirabegron increased mean blood pressure by 4.3 mm Hg for systolic blood pressure and 1.7 mm Hg for diastolic blood pressure in patients < 12 years old, with larger increases in children < 8 years old. This finding was not exposure-related. Aside from common expected safety concerns of constipation and headache, there were no additional signals for drug-related increases in ECG QT prolonged, UTI, urinary retention, or heart rate. No SAEs in the clinical trials were drug-related. • There are no specific concerns for mirabegron oral suspension or tablets in the post-market setting in the indicated pediatric NDO population. If mirabegron oral suspension were to be used off-label in adult or geriatric patients unable to swallow tablets, potential risk is mitigated by comparable mirabegron doses and lower exposures.	

1.4. Patient Experience Data

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

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	X Patient reported outcome (PRO) PIN-Q, PGI-S, and acceptability Questionnaire	6.1.1. Study Design 6.1.2. Study Results
	X Observer reported outcome (ObsRO) PIN-Q, PGI-S, and acceptability Questionnaire	6.1.1. Study Design 6.1.2. Study Results
	X Clinician reported outcome (ClinRO) CGI-C	6.1.1. Study Design 6.1.2. Study Results
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

NDO is defined by the International Children's Continence Society (ICCS) as detrusor overactivity when there is a relevant neurological condition. NDO is a urodynamic observation characterized by involuntary detrusor contractions that are spontaneous or provoked during the filling phase, involving a detrusor pressure increase of greater than 15 cm H_2O above baseline. A subset of patients with NDO also experience external urethral sphincter contraction, instead of relaxation, that occurs during detrusor contraction. This pathologic dyssynergia may lead to high pressure incontinence with the risk of diminished bladder capacity and compliance as well as increased risk of recurrent urinary tract infections, high pressure voiding, and resultant renal parenchymal and upper urinary tract injury.

NDO can develop as a result of a lesion at any level in the nervous system, including the cerebral cortex, spinal cord, or peripheral nervous system. The most prevalent cause of NDO in children is myelodysplasia, a group of developmental abnormalities that results from defects that occur during neural tube closure such as myelomeningocele, meningocele, and occult spinal dysraphism (spina bifida occulta). The most common acquired cause for NDO is cerebral palsy. An injury in the perinatal period (e.g. perinatal infection, anoxia) can produce a neuromuscular disability or a specific cerebral dysfunction. Less common acquired causes include spinal tumors, trauma, or sequalae of transverse myelitis.

Early management of NDO is focused on optimizing bladder function to prevent hydronephrotic renal damage and secondary bladder wall changes that result from high-pressure detrusor contractions and elevated bladder pressure during filling. The most common pharmacologic treatment for NDO is the antimuscarinic oxybutynin (oral or intravesical), which suppresses detrusor overactivity. Clean intermittent catheterization (CIC), typically performed 4-5 times per day, improves bladder drainage and reduces bladder pressure during filling. To date, the vast majority of patients are treated successfully with oxybutynin treatment coupled with CIC. Experience with pharmacologic therapies other than oxybutynin is still limited in children with NDO.

NDO is a condition that significantly impacts a child's social participation due to the frequency of CIC and the occurrence of incontinence episodes. Optimizing quality of life throughout early childhood and in the adolescent years improves social and emotional health and physical development and contributes to a successful transition to adulthood. Better management of incontinence related to neurogenic bladder dysfunction improves quality of life by allowing greater independence and opportunities for social participation.

2.2. Analysis of Current Treatment Options

The first-line treatment for pediatric NDO is the combination of continuous intermittent catheterization (CIC) and antimuscarinic drugs. The three currently approved treatments for NDO in pediatric patients are oxybutynin chloride, available as immediate-release tablets, extended-release tablets, and syrup; solifenacin succinate, available as an oral suspension; and onabotulinumtoxin A, available as an intradetrusor injection.

Oxybutynin used in the pediatric population (for patients aged 5 years to less than 18 years) has been associated with side effects such as headaches, blurred vision, constipation, altered behavior, dry mouth, flushed cheeks, and potential effects on the CNS, which are of particular concern as they can

lead to impaired school performance. Intravesical oxybutynin, which has a reduced first pass metabolism in the liver compared to oral anticholinergic therapy and has high systemic efficacy and bioavailability, has been evaluated for its potential to be effective with a more tolerable side effect profile.

Solifencin succinate, in oral suspension form for the treatment of NDO in pediatric patients aged 2 years to less than 18 years, was approved on May 28, 2020. Its side effect profile did not include evidence of effects on the CNS but included typical antimuscarinic effects such as constipation and dry mouth.

Onabotulinumtoxin A intradetrusor injection was recently approved on February 9, 2021 for the treatment of NDO in pediatric patients aged 5 and older who have an inadequate response to or are intolerant of anticholinergic medication. This invasive treatment requires injection under anesthesia and is intended as a second-line treatment for patients inadequately managed by the currently approved oral treatment options.

Table 1 below summarizes the currently available treatments for pediatric NDO including approved treatments and medications approved or OAB in adults that have been used off-label to treat pediatric patients with NDO.

Table 1 Available Treatments for Pediatric Neurogenic Detrusor Overactivity (NDO)

Oral antimuscarinic drugs	Oral β-3 adrenergic agonists	Intradetrusor injection
Approved for NDO in pediatric patients		
Ditropan (oxybutynin chloride) Syrup (5 mg/5 mL) Tablets, immediate-release and extended-release		Botox (onabotulinumtoxin A)
VESIcare (solifenacin succinate) LS Oral suspension (1 mg/mL)		
Available (approved for OAB in adults)		
VESIcare (solifenacin tablets)	MYRBETRIQ (mirabegron tablets)	
Enablex (darifenacin tablets)	GEMTESA (vibegron tablets)	
Trosec (trospium tablets)		
Detrol, Detrol LA (tolterodine tablets)		
Toviaz (fesoterodine tabets)		
Propiverine tablets		

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The reader is referred to Section 3.2 of this review for the specific regulatory history and activity for this NDA and sNDA. The reader is referred to the original NDA Clinical review of mirabegron tablets for additional regulatory history.

3.2. Summary of Presubmission/Submission Regulatory Activity

On June 28, 2012, NDA 202611 was approved for MYRBETRIQ for the treatment of OAB in adults. The NDA approval letter included the following two PREA postmarketing requirements (PMRs) for deferred pediatric studies:

1) PMR-1 (1898-1): An 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 less than 18 years of age with NDO or OAB.
2) PMR-2 (1898-2): An open label, baseline-controlled, multicenter, 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 less than 18 years of age with NDO.

On July 18, 2014, a Type C meeting was held to discuss the progress of the mirabegron pediatric drug development program, including 1) results from completed Study 178-CL-202 (a Phase 1 study in pediatric patients with NDO and OAB symptoms), and 2) design of planned Study 178-CL-203 (another Phase 1 study in pediatric patients with NDO and OAB symptoms).

On February 20, 2015, the Sponsor submitted their Proposed Pediatric Study Request (PPSR).

On May 21, 2015, FDA issued a letter stating that the PPSR was inadequate and recommended that the Sponsor resubmit the PPSR after addressing several issues.

On March 12, 2015, the Sponsor submitted the complete study report (CSR) for completed Phase 1 Study 178-CL-202.

On November 13, 2015, a Type C meeting was held to discuss the PPSR.

On December 2, 2015, the PPSR was resubmitted along with the final draft protocol for the planned Phase 1 Study 178-CL-203.

On December 11, 2015, a teleconference was held with the Sponsor to discuss the logistics of Studies 178-CL-206A and 178-CL-206, the two planned Phase 3 pediatric studies that together were intended to fulfill PMR-2 (1898-2).

On March 18, 2016, FDA issued a pediatric Written Request (WR). The WR requested studies to fulfill the two PREA PMRs but lowered the minimum patient age for eligibility for the PMR studies from 5 years to 3 years. Additionally, the WR specified that the planned Phase 3 Studies 178-CL-206A (outside US) and 178-CL-206 (US) were to be considered a single study (referred to as "Study 2").

On June 17, 2016, non-IND Study 178-CL-206A was initiated.

On August 22, 2016, the Sponsor submitted their Acceptance of FDA's WR. and committed to:

- completing the requested "Study 1" (Study 178-CL-203, also meant to fulfill PMR 1898-1) and
- initiating "Study 2" (Study 178-CL-206, also meant to fulfill PMR 1989-2) after FDA review and agreement on the interim results from the epidemiology safety study of neoplasm events, Study 178-CL-113.

On March 31, 2017, the Sponsor submitted results from the second completed Phase 1 Study 178-CL-203 in pediatric patients, and results from a second completed Phase 1 Study 178-CL-208 in adults, that comprised part of the supporting information required prior to initiating planned Phase 3 Study 178-CL-206 in pediatric patients. The remaining information needed prior to initiating Study 178-CL-206 was the interim results report from the ongoing PMR epidemiology study in adults intended to evaluate the potential risk of mirabegron in neoplasm events.

On October 30, 2017, the Sponsor submitted the interim report for study 178-CL-113 (entitled "*Post-authorization Safety Study Evaluation of Neoplasm Events in Users of Mirabegron and Other Treatments for Overactive Bladder*"), which served both as PMR 1898-4 for NDA 202611 and as a third piece of information required by the WR prior to initiating the Phase 3 pediatric study (referred to in the WR as "Study 2"). FDA issued an additional IR regarding the interim report analysis, and the Sponsor responded on March 2, 2018.

On July 20, 2018, FDA confirmed agreement with the interim report for Study 178-CL-113. The results of Study 178-CL-113 did not identify a risk of mirabegron in adult neoplasm events. The Sponsor had now completed all requirements for initiating their US-based Phase 3 study, Study 178-CL-206.

On April 28, 2018, mirabegron 25 mg or 50 mg in combination with solifenacin succinate 5 mg was approved for the treatment of OAB in adults.

On August 15, 2019, the Sponsor requested a pre-NDA meeting to discuss the planned NDA 213801 and sNDA 202611, the overall completed clinical pediatric drug development program, and the pediatric data package to fulfill PREA requirements as well as the terms of the WR. Among their concerns was whether the required Study 2 (PMR 1898-2) would be satisfied solely by the completed Phase 3 study, the non-US, non-IND Study 178-CL-206A, without additional data from the US based Study 178-CL-206, which the Sponsor intended not to conduct.

On November 6, 2019, the Division provided Type B Pre-NDA Meeting Preliminary Comments to Sponsor. In those comments, the Division agreed that the pediatric development program to date appeared sufficient to determine fulfillment of the WR requirements. Additionally, the Division agreed that the planned submission of NDA 213801 and sNDA 202611, containing the results of Study 178-CL206A, appeared sufficient to support filing applications for mirabegron tablets and granules for oral suspension for the proposed pediatric indication. Finally, the Division confirmed that the planned NDA and sNDA appeared sufficient to support a

determination regarding Pediatric Exclusivity, and to satisfy PREA requirements. After receiving the Division's preliminary comments, the Sponsor opted to cancel the pre-NDA meeting.

On September 28, 2020, the Sponsor submitted for review a new NDA and a supplemental NDA to market the granules for oral suspension and the tablets, respectively. The Sponsor also submitted these two applications to fulfill the PREA-related PMRs and to be granted pediatric exclusivity.

3.3. Foreign Regulatory Actions and Marketing History

On July 1, 2011, mirabegron tablets received approval in Japan for the treatment of OAB with symptoms of urge, urinary incontinence, urgency and urinary frequency in adults. Marketing approval for the same indication was granted in the US on June 28, 2012 and in Europe on December 20, 2012. Mirabegron is now approved in 83 countries and marketed in 65 countries.

Mirabegron is not yet marketed for use in pediatric patients. However, information from the clinical trials comprising the global pediatric development program for pediatric use for both the tablets and the oral suspension was included in the Periodic Safety Update Report.

According to the Periodic Safety Update Report for mirabegron (film-coated, prolonged-release tablets and oral suspension) for the time period July 1, 2019 to June 30, 2020, no actions were taken for safety reasons by the Sponsor, acting as both Marketing Authorization Holder (MAH) and the Sponsor of clinical trials. In addition, no actions were taken by regulatory authorities, data and safety monitoring boards, or independent ethics committees. There were no restrictions on distribution, no clinical study suspensions, no dosage modifications, and no changes in target population, indications, or formulation.

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

4.1. Office of Scientific Investigations (OSI)

DUOG consulted OSI requesting routine good clinical practice (GCP) inspections of the Sponsor and two of the clinical investigators, Dr. David Bolong (Philippines) and Dr. Sang Won Han (Korea). However, due to the ongoing COVID-19 global pandemic and the resulting challenges in completing on-site GCP inspections before the application's action due date, DUOG determined that the application could proceed without inspections. As a result, the planned inspections were cancelled. No irregularities were observed in the data that would require for-cause inspections, and there was no reason to be concerned about study conduct or data quality.

4.2. Office of Product Quality (OPQ)

There are no outstanding CMC issues. The CMC team recommended the application be approved.

4.3 Clinical Microbiology

There were no clinical Microbiology issues.

4.4 Nonclinical Pharmacology/Toxicology

The juvenile rat study identified no toxicities at the same exposure levels observed in the Phase 1 and 3 pediatric populations. No revisions to the nonclinical-related sections of the original label or the new parts of the label were recommended by the Pharm/Tox review team.

4.5 Clinical Pharmacology

There were several Clinical Pharmacology review issues, and for a comprehensive review, the reader is referred to the Clinical Pharmacology review.

In response to Clinical Pharmacology requests conveyed in the 74-day letter, the Sponsor provided an exposure-response (E-R) analysis of safety to address potential risks if a patient were to take mirabegron oral suspension or mirabegron tablets on an empty stomach. The rationale for Clinical Pharmacology's request was that dosing in the Phase 3 study was conducted under fed conditions, while dosing under fasting conditions is expected to increase exposure by up to 2-fold (for area-under-the-curve).

To address the concern, the Sponsor conducted the requested E-R analysis. Individual predicted steady-state exposures (AUC_{tau} or C_{max}) based on actual mirabegron doses administered on the day of the observation were compared to systolic blood pressure, diastolic blood pressure, HR, and QTcF. A trend was only evident for HR, where continuous treatment with mirabegron PED50 dose under fasting conditions was predicted to result in an increase in exposure of approximately 2.2 times, corresponding to an increase of approximately 4 bpm in heart rate compared with treatment under a fed state. The Sponsor proposed that mirabegron oral suspension should be administered with food. The clinical pharmacology team found this proposal acceptable.

Additionally, a simulation to determine the optimal dose of mirabegron oral suspension in pediatric patients weighing ≥ 35 kg was performed so that exposures in this weight group would be comparable to adult exposures. The Sponsor ran their simulation using 88 mg (11ml) not 80 mg (10 ml). The repeat simulation using 80 mg (10 mL), which the Sponsor performed in response to an FDA IR, was determined to be acceptable.

The Clinical Pharmacology review team concluded that the application was acceptable from the Clinical Pharmacology perspective. The ClinPharm review team had some comments and recommendations for labeling pertaining to dosing in specific population (e.g., renal impairment

and moderate hepatic impairment), and those labeling recommendations were accepted by the Sponsor. There were no outstanding Clinical Pharmacology issues for this application.

4.6 Devices and Companion Diagnostic Issues

There were no devices and no companion diagnostics included in this application.

4.7 Consumer Study Reviews

Mirabegron is available by prescription only. Therefore, over-the-counter, pre-marketing consumer behavior studies are not relevant to this application.

4.8 Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA made an IR to Spon(b) (4)on December 18, 2020, regarding the Sponsor's proposed proprietary name, Myrbetriq(b) (4)Granules, under NDA 213801. In the IR, DMEPA requested that the Sponsor provide a rationale to support the use of two modifiers, (b) (4) and "Granules." The Sponsor responded on December 22, 2020 by submitting a Proprietary Name Review amendment that amended their proposed proprietary name to include only one modifier, as follows: Mybetriq Granules. DMEPA considered this name acceptable.

DMEPA also evaluated the proposed pouch label, container label, carton labeling, Prescribing Information (PI), and Patient Information and identified areas of vulnerability that may lead to medication errors. DMEPA also participated fully in the labeling review process that led to final agreed-upon labeling.

DMEPA made a number of recommendations for revisions to the overall PI and also, to the container label, carton labeling, and the pouch label. Recommended revisions to the PI included corrections and clarifications intended to improve accuracy and optimize the information presented. Recommended revisions to the container label and carton labeling were intended to clarify and simplify information and instructions, remove clutter, and create consistency with PI. For the pouch, DMEPA made recommendations to the Sponsor to use language that clearly reflects its purpose.

The Sponsor resubmitted revised carton labeling on March 4, 2021 (for Myrbetriq Granules) and March 15, 2021 (for Myrbetriq) to address the concerns stated by DMEPA. At the time this Clinical review was finalized, while the final carton labeling had not been agreed-upon, labeling discussions with Sponsor were ongoing, and final agreement regarding the acceptability of the labels, from a medication errors perspective, was forthcoming.

4.9 Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP)

On March 4, 2021, DMPP and OPDP provided proposed edits to the Sponsor-proposed Patient Information (PPI) labeling.
Separately, OPDP also provided comments and recommendations on the PI related to issues of potential product promotion.

The DMPP/OPDP edits to the PPI, and OPDP edits to the PI, were all either instituted by discussion with the Sponsor or resolved by discussion among the FDA review team.

4.10 Division of Epidemiology (DEPI)

There were no issues and no comments from the Epidemiology (DEPI) perspective.

4.11 Division of Risk Management (DRISK)

There were no issues and no comments from the Risk Management (DRISK) perspective.

4.12 Division of Pharmacovigilance (DPV)

There were no issues and no comments from the Pharmacovigilance (DPV) perspective.

5 Sources of Clinical Data and Review Strategy

5.4 Table of Clinical Studies

The principal analyses of efficacy and safety included in this NDA and sNDA include data from one Phase 3 efficacy and safety clinical study. Supportive exposure and safety data were obtained from two Phase 1 single dose PK studies in pediatric patients with NDO and OAB symptoms and two Phase 1 BE/BA studies in healthy adults.

- Efficacy and safety clinical studies (N = 1): 178-CL-206A (open-label, baseline-controlled, dose titration Phase 3 study),
- Supportive exposure and safety studies (N = 4):
  - Phase 1 clinical pharmacology studies (N=2): 178-CL-202 (open-label, single ascending dose study) and 178-CL-203 (open-label single dose study)
  - Phase 1 bioequivalence and bioavalability studies (N=2): 178-CL-201 (open-label, randomized, single dose, 4-period crossover clinical study) and 178-CL-208 (open-label, randomized, single dose, 3-period crossover clinical study)

Reviewer's Comment: The Phase 1 studies 178-CL-202 and 178-CL-203 enrolled subjects with NDO and OAB symptoms. For this review, only the data from the patients with NDO has been

included in the analyses. Data from the BE/BA studies was performed in healthy adults and supports the various formulations studied.

Table 2 Listing of Clinical Trials Relevant to this NDA/sNDA

Study ID NCT # Phase #	Objective/Study Endpoints	Study Design and Type of Control, Study Duration	Test Product(s); Dosage Regimen; Schedule; Route of Administration	Number of Subjects	Study Population	Numbers of Countries
Controlled Studies to Support Efficacy and Safety						
178-CL-206A EudraCT#2015-002876-25	**Objectives** Primary: Evaluate the efficacy of mirabegron after multiple doses in the pediatric population with NDO. Secondary: Evaluate the safety and tolerability of mirabegron after multiple doses in the pediatric population and to evaluate the PK of mirabegron after multiple doses in the pediatric population with NDO. **Endpoints** Primary: • Change from baseline in maximum cystometric capacity (MCC) after 24 weeks of treatment (based on filling urodynamics). Secondary: • Change from baseline in urodynamic measures: o MCC (week 4) o Bladder compliance (week 4 and 24) o No. of overactive detrusor contractions (>15 cm H_2O) until end of filling (week 4 and 24) o Detrusor pressure at end of filling (weeks 4 and 24) o Filling volume until first overactive detrusor contraction (>15 cm H_2O) (weeks 4 and 24) • Change from baseline at weeks 2, 4, 8, 12, 24, 36 and 52 in electronic diary recorded bladder volume and leakage measures: o Average catheterized volume per catheterization	Phase 3, multicenter, open-label, baseline controlled dose-titration study in pediatric patients with NDO on clean intermittent catheterization. Study treatment duration: 52 weeks • 24-week dose titration efficacy treatment period • 28-week fixed dose long term safety period	mirabegron tablets, 25 mg and 50 mg. Mirabegron oral suspension formulation C (8 mg/mL). The initial dose of mirabegron was based on the patient's weight and was targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 25 mg tablet once daily (PED25). At week 2, 4 or 8, patients were up-titrated to PED50 based on given dose titration criteria.	Enrolled: 91 (56 children and 35 adolescents) Treated: 86 (55 children and 31 adolescents) Completed: 70 (43 children and 27 adolescents)	Male and female children aged 3 to less than 12 years with NDO on clean intermittent catheterization. Male and female adolescents aged 12 to less than 18 years with NDO on clean intermittent catheterization.	32 sites in 19 countries in 4 geographic regions (Europe, North America, Middle East, and Asia-Pacific): Belgium, Croatia, Denmark, Latvia, Lithuania, Norway, Poland, Romania, Serbia, Slovakia, Australia, Malaysia, Philippines, South Korea, Taiwan, Israel, Jordan, Turkey and Mexico

	○ Maximum catheterized volume ○ Maximum catheterizes daytime volume ○ Average morning catheterizes volume (first cath in the morning after awakening) ○ Mean number of leakage episodes per day (day and night time) ○ Number of dry (leakage-free) days/7 days (day and night time) • Change from baseline in patient and clinician reported Questionnaire endpoints: ○ Pediatric Incontinence Questionnaire (PIN-Q) (week 24 and 52) ○ Patient Global Impression of Severity Scale (PGI-S) (week 24 and 52) ○ Clinical Global Impression of Change (CGI-C) (week 24 and 52) ○ Acceptability (week 4, 24, and 52) • Pharmacokinetic endpoints: ○ C_{max}. T_{max}, AUC_{24}, C_{trough}, CL/F, and V_z/F					
Controlled Studies to Support Safety						
178-CL-202 NCT Phase 1	**Objectives** Primary: Evaluate the PK of mirabegron prolonged-release tablets after single doses at different dose levels in pediatric patients with NDO or OAB symptoms. Secondary: Evaluate the safety and tolerability of mirabegron prolonged-release tablets after single-dose at different dose levels in pediatric patients with NDO or OAB symptoms. **Endpoints** Primary: Pharmacokinetic variables: AUC_{inf}, C_{max}, t_{max}, $t_{1/2}$, CL/F, V_z/F, AUC_{24} Secondary: • Safety variables: AEs, clinical laboratory evluations, vital signs, ECGs, physical examination, PVR	Phase 1, multicenter, open-label, single ascending dose study in pediatric patients with NDO/OAB symptoms. 1 day (single dose)	mirabegron tablets doses at 25 mg, 50 mg and 75 mg. Cohort 1: adolescents (12 to less than 18 years); low dose, fed. Cohort 2: children (5 to less than 12 years); low dose, fed. Cohort 3: adolescents (12 to less than 18 years); high dose, fed Cohort 4: children (5 to less than 12 years); high dose, fed Cohort 5: children (5 to less than 12 years); high dose, fasted	Enrolled: 34 (15 adolescents and 19 children) Treated: 34 (15 adolescents and 19 children) Completed: 34 (15 adolescents and 19 children)	Male and female adolescents aged 12 to less than 18 years with NDO or OAB symptoms. Male and female children aged 5 to less than 12 years with NDO or OAB symptoms.	Belgium, Denmark, Norway and Poland

	• Palatability and Acceptability Questionnaire		Low dose: • 25 mg tablet (body weight 20.0 to < 55.0 kg) • 50 mg tablet (body weight ≥ 55.0 kg) High dose: • 50 mg tablet (body weight 20.0 to < 40.0 kg) • 75 mg tablet (body weight ≥ 40.0 kg)			
178-CL-203 NCT Phase 1	**Objectives** Primary: Evaluate the PK of oral suspension (Formulation B) after single doses in children with NDO or OAB symptoms. Secondary: • Evaluate the safety and tolerability of single doses of oral suspension in children with NDO or OAB symptoms. • Evaluate the palatability and acceptability of a single dose of oral suspension in children with NDO or OAB symptoms. **Endpoints** Primary: Mirabegron in plasma: C_{max}, AUC_{inf}, t_{max}, $t_{1/2}$, AUC_{24}, AUC_{last}, CL/F, V_z/F Secondary: • Safety endpoints: AEs, clinical laboratory evaluations, vital signs, ECGs, physical examinations, PVR • Acceptability and palatability assessments	Phase 1, multicenter, open-label, single-dose study in pediatric patients with NDO or OAB symptoms. 1 day (single dose)	mirabegron oral suspension formulation B (2 mg/mL). Single doses were administered according to each patient's weight, to achieve a target exposure equivalent to that following 50 mg prolonged release tablets given once daily to adults at steady state.	Enrolled: 9 children Treated: 9 children Completed: 9 children	Male and female children aged 3 to less than 12 years with NDO or OAB symptoms.	Denmark and Poland
Relative bioavailability studies (PK studies)						
178-CL-201 Phase 1	**Objectives** Primary Objective: Determine relative BA and PK profile of 50 mg oral suspension (Formulation A) in comparison to the 50 mg tablet in the fasted state.	Phase 1, open-label, randomized, single dose, 4-period crossover clinical	mirabegron 50 mg tablet or 50 mg oral suspension (2mg/mL) **Treatment groups**	Enrolled: 25 adults Treated:	Healthy adult subjects (young male and female subjects aged 18	Germany

	Secondary Objective: • Evaluate the food effect on the PK of a single dose 50 mg oral suspension • Evaluate the safety and tolerability of single doses of 50 mg mirabegron oral suspension under fed and fasted conditions. **Endpoints** Primary: • Mirabegron in plasma: AUC_{inf}, AUC_{last} and C_{max}. Secondary: • Mirabegron in plasma: AUC(%extrap), CL/F, λz, MRTinf, t½, tlag, tmax and Vz/F. • Safety endpoints: AEs, clinical laboratory evaluations, vital signs, ECGs, physical examinations • Palatability assessment	study. 1 day (single doses)	Treatment A: oral suspension (fasting) Treatment B: oral suspension (fed) Treatment C: tablets (fasting) Treatment D: tablets (fed)	25 adults Completed: 22 adults	to less than 26 years)	
178-CL-208 Phase 1	**Objectives** Primary Objective: Determine relative BA of 88 mg oral suspension (Formulation C) in comparison to the 88 mg oral suspension (Formulation B) in the fasted state Secondary Objectives: • Evaluate the food effect on the PK of a single dose 88 mg oral suspension (Formulation C). • To evaluate the safety and tolerability of single doses of 88 mg mirabegron oral suspension. **Endpoints** Primary: • Mirabegron in plasma: AUC_{inf}, AUC_{last} and C_{max}. Secondary: • Mirabegron in plasma: AUC_{inf}(%extrap), CL/F, MRT_{inf}, $t_{½}$, t_{lag}, t_{max} and V_z/F, $λ_z$ • Safety Endpoints: AEs, vital signs, clinical laboratory tests, ECG • Palatability	Phase 1, open-label, randomized, single dose, 3-period crossover clinical study. 1 day (single doses)	mirabegron oral suspension (2 mg/mL) Formulation B or mirabegron oral suspension (8mg/mL) Formulation C **Treatment groups** Treatment A: 88 mg Formulation C, fasting Treatment B: 88 mg Formulation B, fasting Treatment C: 88 mg Formulation C, fed	Enrolled: 24 adults Treated: 24 adults Completed: 24 adults	Healthy adult subjects (male and female subjects aged 18 to 45 years)	Germany

NDO: neurogenic detrusor overactivity; OAB: overactive bladder; 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.

5.5 Review Strategy

This review examines the results from the Phase 3 study, 178-CL-206A, the pivotal study to support the efficacy, safety, and tolerability of mirabegron in pediatric patients aged 3 and older with NDO. Data collected from the NDO patients included in the two Phase 1 studies, studies 178-CL-202 and 178-CL-203, was also analyzed to support mirabegron's safety profile. Finally, to support the comparative bioavailability and bioequivalence of the new granule formulation and the tablet formulation in pediatric patients to the approved tablet formulation in adults, we considered data from the two Phase 1 BE/BA studies performed in healthy adults.

Of note, three formulations of mirabegron granules for oral suspension were evaluated over the course of the drug development program. The first formulation, Formulation A (extended-release granules reconstituted with an extemporaneously prepared vehicle), was developed and supplied for Study 178-CL-201, which determined the relative bioavailability of Formulation A compared to the tablet. Then Formulation B (extended-release granules, reconstituted with water) was created and used in PK Study 178-CL-203. Formulations A and B, when prepared, each had a concentration of 2 mg/mL. Formulation C, which was developed to be a more concentrated version of Formulation B, was reconstituted with water for a concentration of 8 mg/mL. This higher concentration Formula C was developed to achieve smaller, more acceptable dosing volumes for administration to small children. Formulation B and C were studied in the Phase 1 relative bioavailability Study 178-CL-208, which showed that Formulation B and Formulation C were bioequivalent under fasting conditions and that both formulations were safe and well-tolerated. Formulation C was the formulation administered in the Phase 3 efficacy and safety study 178-CL-206A and is the proposed formulation for commercialization. Unless otherwise stated, mirabegron granules for oral suspension refers to the to-be-marketed Formulation C.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.4 Study 178-CL-206A

6.4.1 Study Design

Overview and Objective
The primary objective of the Phase 3 study 178-CL-206A was to evaluate the efficacy of mirabegron after multiple-dose administration in the treatment of pediatric patients with NDO.

The secondary objectives were two-fold: 1) to evaluate the safety and tolerability of mirabegron after multiple-dose administration in the treatment of pediatric patients with NDO and 2) to evaluate the pharmacokinetics of mirabegron after multiple-dose administration in the treatment of pediatric patients with NDO.

Trial Design

Study 178-CL-206A was a Phase 3, open-label, baseline-controlled, multicenter study in children and adolescents from 3 to <18 years of age with NDO practicing CIC. The study included 26 patient-enrolling sites in 19 countries and 4 geographic regions.

The study consisted of 3 investigational periods:

- Pre-treatment period: a maximum of 28 days before baseline, including screening, washout (if applicable) and baseline
- Efficacy treatment period: beginning the day after baseline and continuing to week 24
- Long-term safety period: beginning after week 24 and continuing to week 52 (end of study/treatment).

After completing informed consent and screening (visit 1), all patients completed a 2-day weekend e-diary. At visit 2, patients were divided into two groups according to their current NDO therapy and other medications. Group A patients were those who were not receiving any prohibited medication including any oral drug treatment to manage their NDO, or those for whom enough time had passed that previous treatment with botulinum toxin was no longer considered effective. Group B patients were those who were receiving oral drug treatment to manage their NDO or any other prohibited medication and underwent a 2-week washout period. During the final visit of the pretreatment period (visit 3), patients completed a 7-day baseline e-diary.

Selection of Dose and Formulation in Study 178-CL-206A

Patients received the appropriate dosage form based on their weight and in some circumstances, their clinical needs and personal preference. Patients weighing <35 kg were administered mirabegron oral suspension 8mg/mL, and patients weighing ≥35 kg were administered mirabegron tablets. Patients weighing ≥35 kg who were unable or unwilling to take tablets could choose to take the suspension. The initial dose of mirabegron was selected to achieve plasma concentrations equivalent to the steady-state exposures expected with 25 mg mirabegron administered once daily in adults (PED25). This dose could be up-titrated to PED50 (the pediatric dose targeted to achieve steady-state exposures similar to those of adults administered the mirabegron 50 mg tablet once daily).

In order to define pediatric exposures that correlated with the approved daily adult doses of mirabegron (25 mg and 50 mg), the Sponsor developed a population pharmacokinetic model based on the adult Phase 3 data from the clinical trials from the original NDA 202611 for treatment of adults with OAB. Weight-based (allometric) scaling was added to the clearance and volume terms so the pharmacokinetics could be scaled to pediatric patients. Using the mean steady-state AUC_{tau} values following administration of 25 and 50 mg mirabegron tablets once daily in the adult Phase 3 program as target values, simulations were performed to determine the pediatric equivalent doses (PED25 and PED50). The simulations accounted for the lower relative bioavailability of the oral suspension compared with the tablet. The model was then validated on the pediatric data from the single ascending dose Study 178-CL-202, which showed that the model predicted the pharmacokinetics of mirabegron in pediatric patients.

Additional simulations showed that the lowest body weight at which children had comparable steady-state exposures to adults from the 25 mg and 50 mg mirabegron tablets was 35 kg. Children weighing <35 kg were recommended to take the mirabegron oral suspension because dosing with the 25 mg or 50 mg tablet would result in exposures higher than exposures in adults.

The Sponsor determined that the average age at which a pediatric patient with NDO weighs 35 kg is 11 years old by leveraging its experience in the pediatric NDO development program for VESIcare LS (solifenacin succinate). Because the tablet formulation was intended for use by pediatric patients weighing ≥35 kg, patients were expected to be old enough to routinely tolerate swallowing a tablet, but if not, mirabegron granules would be available for those patients too. The Sponsor then chose 11 kg as the lower weight limit based on the approximate body weight of a 3-year old child (per the National Health and Nutrition Examination Survey database). The simulation resulted in the three body weight categories shown in Table 3.

Table 3 below provides the final weight-base starting (PED25) and maximum (PED50) doses for mirabegron tablets or oral suspension.

Table 3 Weight-based Doses for Mirabegron Tablets or Oral Suspension

Recommended Dose	Body Weight Range	Tablet Dose	Suspension Volume[1]
PED25 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]
PED50 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]

[1]suspension concentration of 8 mg/mL
[2]Patients ≥ 35 kg who were unable or unwilling to swallow tablets could choose to take the suspension.
PED25: pediatric equivalent dose 25 mg; PED50: pediatric equivalent dose 50 mg.
Source: derived from 178-CL-206A CSR, Table 1, p. 30.

Patients who weighed <35 kg at the initiation of treatment who then achieved a weight of ≥ 35 kg at week 24 were permitted to switch to the tablet form of mirabegron. Requests from patients to switch formulations for acceptability reasons were considered by the Sponsor on a case-by-case basis.

Dose up-titration from PED25 to PED50 was performed at week 2, 4, or 8 unless:

- based on urodynamics and the e-diary, the investigator considered the patient to be effectively treated with PED25;
- the patient experienced safety or tolerability issues with PED25.

A dose of PED50 could be down-titrated at any time for safety concerns.

At week 24, the primary efficacy endpoint (change from baseline in MCC) was assessed.

Table 4 below provides an overview of the study design.

Table 4 Study Flow Chart

Study Period (56 weeks)									
Pre-treatment Period (4 weeks)			Treatment Period (52 weeks)						
			Efficacy Treatment Period (24 weeks)					Long-term Safety Period (28 weeks)	
Visit 1	Visit 2/ TC 1	Visit 3	Visit 4 TC 2 Week 2	Visit 5 Week 4	Visit 6 TC 3 Week 8	Visit 7 Week 12	Visit 8 Week 24	Visit 9 TC 4 Week 36	Visit 10/ EoS Week
Screening	Groups A and B: Review of 2-day e-diary Group B: Start washout on day -15	Baseline	1st possibility for up-titration	2nd possibility for up-titration	3rd possibility for up-titration	Fixed dose	Fixed dose	Fixed dose	End of Study

TC: telephone contact
Source: Modified from 178-CL-206A CSR, Figure 1, p. 23.

Key inclusion criteria for the study were:

1. IEC-/IRB-approved written informed consent and privacy language, as per national regulations, obtained from the patient and/or from the patient's parent(s) or legal guardian(s) prior to any study-related procedures (including discontinuation of prohibited medication, if applicable); assent by the patient was given as required by local law.
2. Age from 3 to < 18 years of age
3. Body weight of ≥ 11 kg
4. A diagnosis of NDO confirmed by urodynamic investigation at baseline by the presence of ≥ 1 involuntary detrusor contraction > 15 cm H_2O from baseline detrusor pressure, and/or a decrease in bladder compliance leading to an increase in baseline detrusor pressure of > 20 cm H_2O
5. Use of CIC for ≥ 4 weeks prior to screening
6. Current indication for drug therapy to manage NDO
7. Female patient had to be either:
   - of nonchildbearing potential:
     - Clearly premenarchal or in the judgment of the investigator was premenarchal
     - Documented surgically sterile
   - or, if of childbearing potential:
     - Agreed not to try to become pregnant during the study and for 28 days after the final study drug administration
     - And had a negative pregnancy test at screening and at baseline
     - And, if sexually active, agreed to use a highly effective method of birth control, which included established use of oral, injected or implanted hormonal methods of contraception, OR placement of an intrauterine device

or system. Birth control had to be practiced from screening and continuing throughout the study period, and for 28 days after the final study drug administration.

8. Male patients and their female spouse/partner who were of childbearing potential had to use a highly effective method of birth control, which included established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device or system. Birth control had to be practiced from screening and continued throughout the study period, and for 28 days after the final study drug administration.
9. Female patients could not breastfeed from screening until 28 days after last study drug administration.

Key exclusion criteria for the study were:

1. Any known genitourinary condition (other than NDO) that could cause overactive contractions or incontinence (e.g., bladder exstrophy, urinary tract obstruction, urethral diverticulum or fistula) or kidney/bladder stones or another persistent local pathology that may cause urinary symptoms
2. Any of the following gastrointestinal problems: partial or complete obstruction, decreased motility such as paralytic ileus, patients at risk of gastric retention
3. Urinary indwelling catheter within 4 weeks prior to screening
4. History of surgically treated underactive urethral sphincter
5. Vesico-ureteral reflux grade 3 to 5
6. History of bladder augmentation surgery
7. History of electrostimulation therapy, if started within 30 days before screening or was expected to start during the study period. Patients who were on an established regimen were allowed to remain on this for the duration of the study.
8. Symptomatic UTI at baseline (symptomatic was defined as pain, fever, hematuria, new onset foul-smelling urine). If present at screening or diagnosed between screening and baseline, the UTI should have been treated successfully (clinical recovery) prior to baseline. If a symptomatic UTI was present at baseline, all baseline assessments were allowed to be postponed for a maximum of 7 days until the UTI was successfully treated (clinical recovery).
9. Mean resting pulse rate > 99th percentile
10. Established hypertension (HTN) and an SBP or DBP greater than the 99th percentile of the normal range determined by sex, age and height, plus 5 mm Hg
11. Increased risk of QT prolongation (e.g., hypokalemia, long QT syndrome; or family history of long QT syndrome, exercise-induced syncope)
12. Severe renal impairment (eGFR according to Larsson equation < 30 mL/min)
13. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2 x the upper limit of normal (ULN) or total bilirubin (TBL) ≥ 1.5 x ULN according to age and sex
14. Current or past history of any malignancy
15. Known or suspected hypersensitivity to mirabegron, any of the excipients used in the current formulations or previous severe hypersensitivity to any drug.
16. Participation in another clinical study (and/or had taken an investigational drug) within 30 days (or 5 half-lives of the drug, or the limit set by national law, whichever

was longer) prior to screening.

17. Use of any of the following prohibited medications (after start of washout):
    - Any medication, other than the study drug used, for the management of NDO
    - Any drugs that are sensitive cytochrome P450 (CYP) 2D6 substrates with a narrow therapeutic index or sensitive P-glycoprotein substrates
    - Any strong CYP3A4 inhibitors if the patient had a mild to moderate renal impairment (eGFR 30 – 89 mL/min)
18. Past administration of intravesical botulinum toxin; except if given > 4 months prior to screening and the patient experienced symptoms comparable to those existing prior to the botulinum toxin injections.

Study Treatments

Table 5 below shows the study schedule of assessments.

Table 5 Schedule of Assessments

Assessments	Visit 1	Visit 2/ TC 1 †	Visit 3	Visit 4/ TC 2 †	Visit 5	Visit 6/ TC 3 †	Visit 7	Visit 8	Visit 9/ TC 4 †	Visit 10/ EoS ‡
	Screening	Start of Washout †††	Baseline	Week 2	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52
	Day -28 to Day -15	Day -15 to Day -8	Day -1	Day 14 (+3 days)	Day 28 (+3 days)	Day 56 (±7 days)	Day 84 (±7 days)	Day 168 (±7 days)	Day 252 (±14 days)	Day 364 (±14 days)
Signing informed consent form	X									
Inclusion/Exclusion criteria	X		X							
Demographics	X									
Height & weight	X		X					X		X
Medical history (including NDO)	X									
Current NDO medications	X	X								
Vital signs (triplicate) and body temperature (ear) §	X		X		X		X	X		X
Physical examination	X									X
12-lead ECG (triplicate) ¶	X		X		X		X	X		X
Hematology/Biochemistry/eGFR	X		(X) ††		(X) ††		X			X
Urinalysis	X		X		X		X	X		X
Pregnancy test ‡‡	X		X		X		X	X		X
Pharmacokinetics §§					(X)	(X)	(X)	(X)	(X)	(X)
Upper urinary tract ultrasound			X							X
Urodynamic assessments ¶¶			X		X			X		
Dose-titration assessment				X	X	X				
Dispense study drug †††			X		X		X	X	**(X)**	
Bladder diary and collection of catheterized volume ‡‡‡		X	X	X	X	X	X	X	X	X
SBPM (triplicate) §§§		X	X	X	X	X	X	X	X	X
PIN-Q, PGI-S			X					X		X
CGI-C								X		X
Acceptability questionnaires					X			X		X
Adverse events and previous and concomitant medication		●	—	—	—	—	—	—	—	●

DSMB: Data and Safety Monitoring Board; ECG: electrocardiogram; e-diary: electronic diary; EoS: end of study; CGI-C: Clinician Global Impression of Change scale; NDO: neurogenic detrusor overactivity; PGI-S: Patient Global Impression of Severity Scale; PIN-Q: Pediatric Incontinence Questionnaire; SBPM: self-blood pressure measurement; TC: telephone contact.

† For the visits where a TC was indicated, there was no need for the patient to visit the clinic, provided that the e-diary data was reviewed by the investigator prior to the TC and discussed and confirmed with the patient or the patient's parent(s)/caregiver(s) during the TC.
‡ Patients who withdrew early from the study after having received study drug had to complete the EoS visit. If the final dose was reached before the last possibility for up-titration at 8 weeks, the fixed-dose treatment period was extended to keep the entire treatment period 364 days as a minimum. The maximum is 378 days in order to allow for visit windows.
§ Triplicate vital signs with an interval of approximately 2 minutes in the sitting position (when possible, otherwise supine, but always in the same position). Preferably the right arm had to be used. Patient had to be calm and without distress for ≥ 5 minutes. Clinic measurements were used to assess eligibility. Single measurements for body temperature had to be performed with an ear thermometer.
¶ Triplicate 12-lead ECG with an interval of about 30 seconds to 5 minutes in the supine position (when possible, but always in the same position). Patient had to be calm and without distress for ≥ 5 minutes.
†† Additional hematology/biochemistry taken at baseline only if an AE related to hematology/biochemistry parameters occurred between visit 1/screening and visit 3/baseline. The first group of patients (minimum of 5, maximum of 10) who reached study visit 5/week 4 had an additional blood draw for a DSMB-mandated interim safety check at this visit. For sampling, preferably the left arm had to be used. Blood sampling had to occur after vital signs and ECG measurements.
‡‡ Pregnancy test in female patients of childbearing potential in serum (if blood is drawn) or urine (at other visits).
§§ A total of 4 pharmacokinetic samples had to be collected, divided over 2 sampling days. Sampling day 1: 1 trough sample; Sampling day 2: 1 trough and 2 post-dose samples between 2 and 5 hours post-dose, with ≥ 1 hour in between the samples. These 2 sampling days were not in a specific order and could be selected from the given options. To allow for an early assessment of the dose-response relationship by the DSMB, it was preferred the pharmacokinetic sampling took place as early in the study as possible. Dosing on a sampling day with post-dose samples had to occur within 1 hour after completion of breakfast. On days where a pharmacokinetic visit was planned in the clinic, breakfast and dosing had to occur in the clinic. Blood sampling had to occur after vital signs and ECG measurements.
¶¶ Additional urodynamic assessments at other visits could be performed if deemed necessary by the investigator.
††† Daily study drug administration began on day 1 (the day after visit 3/baseline). Due to shelf-life limitations, an additional dispensing visit was foreseen at visit 9/week 36 for patients receiving mirabegron oral suspension. This dispensing visit did not need to be accompanied by the patient.
‡‡‡ After a successful screening visit, all patients started with the completion of a 2-day weekend e-diary visit to get acquainted with the e-diary and the assessments. Completion of this diary had to start in the weekend prior to visit 2. Completion of subsequent bladder diaries had to start approximately 7 days prior to the indicated visit (or TC). If successful completion of the 2-day weekend e-diary was confirmed at visit 2, patients from group A started with collection of the 7-day baseline e-diary, followed by the baseline visit. Patients in group B started with a 14-day washout. In the second week of the washout period, collection of their 7-day baseline e-diary started, followed by the baseline visit.
§§§ Triplicate SBPM had to be performed in the morning and evening during the 2-day weekend e-diary collection period and on 2 consecutive days at around 1 and 2 weeks after start of dosing with PED25 (day 1) and after up-titration to PED50, if not already covered by the scheduled SBPM. Measurements were to be taken with an interval of approximately 2 minutes in the sitting position (when possible, otherwise supine, but always in the same position). Preferably the right arm had to be used. Morning measurements had to be taken after waking-up, before breakfast and before study drug intake, evening measurements before bedtime. Patient had to be calm and without distress for ≥ 5 minutes.
Source: 178-CL-206A CSR, Table 2, p. 32.

Study Endpoints

The primary efficacy endpoint was the change from baseline in maximum cystometric capacity (MCC) after 24 weeks of treatment (based on filling urodynamics) using LOCF.

MCC was defined as the maximum bladder capacity reached during filling cystometry before

- the patient experienced leakage or bladder pain/discomfort
- the patient's bladder capacity measured 135% of expected bladder capacity
- the patient's detrusor pressure became dangerously high

The primary efficacy estimand, which was defined using a hypothetical strategy, is described as having the following attributes:

- Target population: all patients who took ≥1 dose of the study drug and have a valid non-missing MCC measurement at baseline and after administration of the study drug
- Outcome measurement: MCC at week 24
- Intercurrent event: all patients who had not discontinued the study drug (for any reason)
- Population-based summary: change from baseline in MCC at week 24 (or before if the study drug was discontinued)

The secondary efficacy endpoints included urodynamic measures, bladder volume and leakage measures, and patient or clinician-reported questionnaire findings.

For urodynamic measures, secondary endpoints included change from baseline at weeks 4 and 24:

- MCC (week 4 only)
- Bladder compliance (change in volume/change in pressure)
- Number of overactive detrusor contractions (> 15 cm H_2O) until end of filling
- Detrusor pressure at end of filling
- Filling volume until first overactive detrusor contraction (> 15 cm H_2O)

Bladder volume and leakage measures were obtained from the electronic (e-diary). Endpoints were change from baseline at weeks 2, 4, 8, 12, 24, 36, and 52 in the following measures:

- Average catheterized volume per catheterization
- Maximum catheterized volume
- Maximum catheterized daytime volume
- Average morning catheterized volume (based on first catheterization after patient woke up)
- Mean number of leakage episodes per day (day and night time)
- Number of dry (leakage-free) days/7 days (day and night time)

Urine volume was weighed (with 1g equivalent to 1mL) and the results were recorded in the e-dairy.

Patient- or Clinician-reported questionnaires were used to obtain the following endpoints at

weeks 24 and 52:

- Change from baseline in the Pediatric Incontinence Questionnaire (PIN-Q)
- Change from baseline in the Patient Global Impression of Severity Scale (PGI-S)
- Clinician Global Impression of Change (CGI-C)
- Acceptability (also at week 4)

The following pharmacokinetic parameters, determined for each patient, served as the pharmacokinetic endpoints:

- C_{max}, t_{max}, AUC_{24}, C_{trough}, CL/F, and V_z/F

Safety endpoints included the following:

- Incidence, relationship and severity of treatment-emergent adverse events (TEAEs)
- Change from baseline in vital signs (clinic measurements): systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate and temperature at weeks 4, 12, 24, and 52
- Change from baseline in vital signs (self-blood pressure measurement [SBPM]): SBP, DBP, pulse rate at weeks 2, 4, 8, 12, 24, 36, and 52 and on 2 consecutive days at around 1 and 2 weeks after start of dosing with the pediatric equivalent dose to mirabegron 25 mg (PED25) (day 1) and after up-titration to the pediatric equivalent dose to mirabegron 50 mg (PED50) (weeks 2, 4, or 8), if not already covered by the scheduled week 2 and/or week 4 SBPM.
- Change from baseline in hematology and biochemistry tests at weeks 12 and 52 and urinalysis tests at weeks 4, 12, 24, and 52
- Change from baseline in 12-lead electrocardiogram (ECG) parameters at weeks 4, 12, 24, and 52
- Change from baseline to week 52 (EoT/EoS) in upper urinary tract ultrasound assessment
- Change from baseline in estimated glomerular filtration rate (eGFR) at weeks 12 and 52

The following exploratory efficacy endpoints were examined:

- Change from baseline at weeks 4 and 24 in filling volume at 20 cm, 30 cm, and at 40 cm H_2O detrusor pressure, if those pressures were reached during the examination
- Change from baseline at weeks 4 and 24 in MCC expressed as percentage of expected bladder capacity (EBC)
- Change from baseline at weeks 2, 4, 8, 12, 24, 36, and 52 as determined from the e-diary entries in:
    - Mean grade of leakage
    - Total catheterized volume per day
    - Number of CICs/day
    - Responder in respect to leakage (complete, partial, no response)

The following exploratory safety endpoints were examined:

- Change from baseline in body height and weight at weeks 24 and 52

Statistical Analysis Plan

Change from baseline in MCC after 24 weeks of treatment (based on filling urodynamics) was analyzed using a paired t-test to test the hypothesis that the change from baseline in MCC is not equal to zero with a 2-sided alpha level of 0.05. A 95% CI was calculated for mean change from baseline. It was assessed whether the estimated lower bound of the 95% CI excluded 0 mL. No adjustment for multiplicity was made. Missing MCC observations at visit 8/week 24 were imputed using the last observation carried forward method (LOCF). The data were summarized with descriptive statistics as a continuous variable (n, mean, SD, SEM, 95% CI, minimum, median, maximum). The SAP described the estimand of primary interest including sensitivity analysis of the primary estimand. The SAP also pre-specified analysis methods to account for missing data for the primary efficacy analyses.

Pharmacokinetic parameters were summarized for the PKAS using descriptive statistics in the Population Pharmacokinetic Modeling Report.

Safety endpoints were summarized for the SAF using descriptive statistics. Safety parameters such as vital signs, height and weight were also be summarized with respect to age-, height- and sex-specific percentiles. Additional AEs of special interests (increased blood pressure, increased heart rate/tachycardia/atrial fibrillation/palpitations, QT prolongation, hypersensitivity reactions, urinary retention, neoplasm, urinary tract infection (UTI), nervous system (seizures, syncope), fetal disorders after exposure during pregnancy, and concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated) were summarized.

Reviewer's Comment: The Sponsor performed paired t-tests to test the null hypothesis. While appropriate to present data as mean changes from baseline, including 95% confidence intervals, presentations of P values are not supportable in this open-label, baseline-controlled study. For this reason, statistical significance can be nominal only. Determinations of treatment effects will be based on numerical changes in efficacy endpoint values, including 95% CI, not P values.

Protocol Amendments

The original protocol for Study 178-CL-206A (dated December 2015) underwent one substantial amendment (dated November 2, 2016). The amended protocol contained the following revisions:

- The lower limit of the age range for the study population was decreased from 5 years of age to 3 years of age. The original protocol was designed to fulfill EMA and FDA pediatric study requirements; however, the Written Request specified the study should include patients as young as 3. The Sponsor made the appropriate revisions.
- Mirabegron oral suspension (Formulation C, 8 mg/mL), a second study drug formulation in addition to the tablet formulation, was added to the protocol to enable dosing of the younger patients.
- The lower limit of the weight range for the study population was decreased to ≥ 11 kg.
- Additional monitoring of the systolic blood pressure was included at weeks 1 and 2 after the initial dose and dose escalation per EMA and FDA comments.

Thirty-eight patients had already been enrolled when the changes in this protocol amendment

were implemented.

Reviewer's Comment: Although 38 patients had already enrolled when the amended protocol was implemented, the nature of the revisions in this protocol amendment are unlikely to affect the overall assessment of mirabegron in Study 178-CL-206A.

6.4.2 Study Results

Compliance with Good Clinical Practices

Study 178-CL-206A was conducted in compliance with good clinical practices. A description of the efficacy and safety study results can be found in sections 7 and 8 of this review.

Financial Disclosure
Form FDA 3454 (3/16) ("Certification: Financial Interests and Arrangements of Clinical Investigators"), dated September 18, 2020, and signed by Carol Soo, Director of Regulatory Affairs - Astellas Pharma Global Development, Inc., was included in this submission. Form 3454 was submitted with an attached list of investigators and certifies that the Sponsor does not have any financial arrangements whereby the value of compensation to the investigator could be affected by the outcome of the study; that the investigators were required to disclose whether they had a propriety interest in the product or a significant equity in the Sponsor and did not disclose such interests; and that none of the investigators in the list of investigators were the recipient of significant payments.

Reviewer's Comment: The Sponsor has adequately disclosed the absence of investigator proprietary interest in this product or investigator participation in financial arrangements with the Sponsor, in compliance with 21 CFR Part 54.

Patient Disposition
In the Phase 3 study 178-CL-206A, a total of 113 pediatric patients were screened, 22 were screen failures, and 91 enrolled. Eighty-six (86) patients (55 children and 31 adolescents) entered the 24-week dose-titration period and received ≥ 1 dose of mirabegron (included in the safety analysis set [SAF]), while 71 patients (44 [80.0%] children and 27 [87.1%] adolescents) entered the 28-week fixed dose assessment period. Seventy (43 [78.2%] children and 27 [87.1%] adolescents) completed treatment.

Sixteen (16) patients discontinued study drug: 12 (21.8%) children and 4 (12.9%) adolescents. Fifteen (15) of those discontinued during the 24-week dose-titration period, and one patient discontinued during the 28-week fixed-dose assessment period. Only 3 patients, all children, discontinued due to AEs. The 13 other patients discontinued for the following reasons: no signs of NDO on baseline urodynamic assessment (4 patients), technical issues with baseline urodynamic assessment (7 patients), and QTcB prolongation at baseline (2 patients). There were no discontinuations due to death, lack of efficacy, lost to follow-up, protocol deviation, withdrawal by patient or parent/guardian, or noncompliance with the study drug.

Of the 5 patients who were successfully screened and enrolled but who did not take the study drug, 3 showed no signs of NDO on baseline urodynamic assessment as per central review, 1 did not meeting inclusion/exclusion criteria (registered in error), and 1 did not meet inclusion criteria #12 (they were not able to comply with the study requirements).

Of the 86 who were included in the SAF, 68 had valid baseline and valid postbaseline measurements for the primary endpoint and were included in the full analysis set (FAS). A total of 60 (65.9%) patients were included in the per-protocol set (PPS).

Table 6 below provides a summary of patient disposition and contributions to each analysis set by age group.

Table 6 Summary of Patient Disposition and Analysis Sets, Study 178-CL-206A

Parameter	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Disposition [n (%)] (SAF)			
Completed treatment	43 (78.2%)	27 (87.1%)	70 (81.4%)
Study drug discontinuation†	12 (21.8%)	4 (12.9%)	16 (18.6%)
Adverse event	3 (5.5%)	0	3 (3.5%)
Death	0	0	0
Lack of efficacy	0	0	0
Lost to follow-up	0	0	0
Protocol deviation	0	0	0
Withdrawal by patient	0	0	0
Withdrawal by parent/guardian	0	0	0
Noncompliance with study drug	0	0	0
Other	9 (16.4%)	4 (12.9%)	13 (15.1%)
Analysis Set [n (%)] (All Allocated Set)			
All allocated set‡	56 (100.0%)	35 (100.0%)	91 (100.0%)
Safety analysis set§	55 (98.2%)	31 (88.6%)	86 (94.5%)
Full analysis set¶	43 (76.8%)	25 (71.4%)	68 (74.7%)
Per protocol set††	38 (67.9%)	22 (62.9%)	60 (65.9%)
Pharmacokinetics analysis set‡‡	43 (76.8%)	23 (65.7%)	66 (72.5%)

Note: Percentage of patients with non-missing registration date at baseline are shown. FAS: full analysis set; MCC: maximum cystometric capacity; SAF: safety analysis set.
† Only the primary reason for discontinuation was collected.
‡ All patients with a non-missing registration date at visit 3 (baseline).
§ All patients who received ≥ 1 dose of study drug.
¶ All patients of the SAF who had both a valid non-missing baseline measurement and ≥ 1 postbaseline measurement for the primary efficacy endpoint (maximum cystometric capacity, MCC).
†† All patients of the FAS who fulfilled the protocol in terms of their eligibility, interventions and outcome assessments, and for whom valid MCC measurements at baseline and at week 24 were observed.
‡‡ All patients of the SAF for whom plasma concentration data were available to facilitate derivation of ≥ 1 pharmacokinetic parameter and for whom the time of last dose prior to sampling was known.
Source: 178-CL-206A CSR, Table 3, p. 56.

Protocol Violations/Deviations

Protocol violations occurred in 3 of the 4 categories identified below in Table 7. The most common protocol violation occurred in 6 patients who received an excluded concomitant medication (PD4). For 3 of these patients, the excluded concomitant medication was a standard of care treatment to treat a serious TEAE: clarithromycin to treat bronchitis, dimethindene to treat rash generalized, and morphine to treat pain after a talipes correction (orthopedic surgery). The remaining 3 patients received triprolidine-pseudoephedrine, ethylmorphine, and morphine to treat rhinitis, a cold, and pain related to a scoliosis surgery, respectively.

The second most common protocol violations occurred in patients who were entered into the study without satisfying entry criteria (PD1). All 4 of these protocol violations were related to informed consent: in two cases, consent was not obtained prior to study-related procedures, in one case the wrong version was signed (so no consent was on record prior to completion of the e-diary), and in one case a verbal consent was given but the form was not signed (it was signed at a later visit). The Sponsor implemented a remediation process that included retraining the site team regarding the informed consent process. The remaining two PD1 deviations resulted from the patient's parent/legal guardian not complying with the study requirements (criteria 12): in one case, the catheterization volumes for the baseline-diary were not completed, and in the other case, e-diary entries were incorrect.

The single PD3 deviation reflected administration of a higher dose of the oral suspension formulation than was prescribed.

Table 7 Protocol Deviations in Patients who Received ≥ 1 Dose of Mirabegron (All Allocated Set) for Study 178-CL-206A

Deviation Criteria, n (%)	Children (3 to < 12 Years) n = 56	Adolescents (12 to < 18 Years) n = 35	All Patients (3 to < 18 Years) n = 91
PD1: Entered into the study even though they did not satisfy entry criteria	1 (1.8%)	3 (8.6%)	4 (4.4%)
PD2: Developed withdrawal criteria during the study and was not withdrawn	0	0	0
PD3: Received wrong treatment or incorrect dose	1 (1.8%)	0	1 (1.1%)
PD4: Received excluded concomitant treatment.	2 (3.6%)	4 (11.4%)	6 (6.6%)

All those patients with a non-missing registration date at baseline (all allocated set). If a patient had multiple deviations in a single category, they were only counted once for that category.
PD: protocol deviation
Source: 178-CL-206A CSR, Table 4, p. 58.

Demographic and Baseline Characteristics

Overall, of the 86 total patients age 3 to < 18 years, 45.3% were male and 54.7% were female. The mean patient age was 10.1 years (with 19 patients aged 3 to < 12 years and 76 patients aged 12 to < 18 years) and the mean weight was 37.45 kg. A majority of the patients (72.1%) were

White, 23% were Asian, 3.5% patients were Hispanic or Latino, and no patients were Black/African American.

Reviewer's Comment: No Black/African American patients were enrolled. There is no reason to believe that the study population, clinical treatment methods, or efficacy or safety of mirabegron differ by race. Additionally, it is noted that the demographic characteristics of the SAF and FAS were similar, except that the efficacy analysis (FAS population) included no Hispanic or Latino patients.

More children participated than did adolescents (55 and 31, respectively). Mean weight and height were higher in the adolescents, as expected. The groups were otherwise similar with respect to characteristics such as sex, race ethnicity, and BMI.

Table 8 below provides a summary of demographics and baseline characteristics for study 178-CL-206A (SAF).

Table 8 Summary of Demographics and Baseline Characteristics for Study 178-CL-206A (SAF)

Parameter Category/ Statistics	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Sex, n (%)			
Male	22 (40.0%)	17 (54.8%)	39 (45.3%)
Female	33 (60.0%)	14 (45.2%)	47 (54.7%)
Age, years†			
Mean (SD)	7.9 (2.5)	14.0 (1.7)	10.1 (3.7)
Median	9.0	14.0	10.0
Min - Max	3 - 11	12 - 17	3 – 17
Race, n (%)			
White	40 (72.7%)	22 (71.0%)	62 (72.1%)
Black/African American	0	0	0
Asian	13 (23.6%)	7 (22.6%)	20 (23.3%)
American Indian/Alaska Native	0	1 (3.2%)	1 (1.2%)
Native Hawaiian/Pacific Islander	0	0	0
Other	2 (3.6%)	1 (3.2%)	3 (3.5%)
Ethnicity, n (%)			
Hispanic or Latino	1 (1.8%)	2 (6.5%)	3 (3.5%)
Not Hispanic or Latino	54 (98.2%)	29 (93.5%)	83 (96.5%)
Weight, kg‡			
n	55	31	86
Mean (SD)	29.83 (13.41)	50.96 (13.78)	37.45 (16.90)
Median	28.00	47.50	35.85
Min – Max	12.6 – 69.7	28.2 – 78.5	12.6 – 78.5
Height, cm‡			
n	55	31	86

Mean (SD)	124.77 (18.69)	152.91 (12.06)	134.91 (21.40)
Median	128.00	152.00	138.75
Min – Max	92.1 – 160.0	120.0 – 178.0	92.1 – 178.0
BMI, kg/m^2‡			
n	55	31	86
Mean (SD)	18.18 (3.94)	21.96 (6.02)	19.55 (5.10)
Median	17.10	19.80	18.35
Min – Max	11.9 – 27.2	10.5 – 33.3	10.5 – 33.3

All patients who received ≥ 1 dose of study drug (SAF).
BMI: body mass index; eCRF: electronic case report form; Max: maximum; Min: minimum; SAF: safety analysis set.
† Age at screening was calculated as (date of last informed consent given at screening - date of birth +1)/365.25.
If the date of birth was not given, the age at screening was equal to the value recorded on the demographics page of the eCRF (an integer number of years) plus 0.5.
‡ BMI = weight (kg)/[height (m2)]. Height and weight were assessed at screening.
Source: 178-CL-206A CSR, Table 5, p. 59.

Geographic Region of Origin

None of the studies included in this review was conducted in the United States. Of the patients included in the SAF, 60.5% (52 patients) were from Europe, 24.4% (21 patients) were from Asia, 11.6% (10 patients) were from the Middle East, and 3.5% (3 patients) were from North America (Mexico). No patients were from Latin America. The countries that enrolled the most patients were Poland (15 [17.4%]), the Philippines (10 [11.6%]), and Croatia and Lithuania (7 [8.1%] patients each).

Reviewer's Comment: No patients were included from the US. The global program is acceptable because there is no reason to believe that the study population or clinical treatment methods differ by region.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Across all patients in the SAF, the medical history was most commonly categorized in the following SOCs: congenital, familial and genetic disorders (53.5%), nervous system disorders (38.4%) and musculoskeletal and connective tissue disorders (29.1%).

Table 9 provides an overview of the past medical history of the NDO study population. The average length of time that a patient had previously experienced NDO was approximately 7 years with adolescents having a longer duration of disease (commensurate with their age) than the children. The majority of patients had undergone surgery for closure of spina bifida (77.9%), and many patients had also undergone a shunting procedure for hydrocephalus (46.5%), both procedures had occurred with similar incidences across the age groups. Overall, 44.2% of patients were wheelchair bound, with a higher percentage in the adolescent group; 11.6% had intellectual disability (referred to in the report as retardation), with similar percentages across age groups; and urethral sphincter activity was overactive in approximately half (51.2%), normal in

27.9%, and underactive in 17.4% of patients. The mean time since surgery was approximately 56 months.

Table 9 Neurogenic Detrusor Overactivity Diagnosis and History (SAF); Study 178-CL-206A.

Parameter Category/ Statistics	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Duration of NDO Disease†, years			
Mean (SD)	5.80 (3.33)	9.44 (5.18)	7.11 (4.43)
Median	5.7	10.7	6.85
Min - Max	0.3 – 11.9	0.1 – 15.9	0.1 – 15.9
Closure of Spina Bifida, n (%)			
Yes	43 (78.2%)	24 (77.4%)	67 (77.9%)
No	12 (21.8%)	7 (22.6%)	19 (22.1%)
Shunt for Hydrocephalus, n (%)			
Yes	23 (41.8%)	17 (54.8%)	40 (46.5%)
Wheelchair Bound, n (%)			
Yes	19 (34.5%)	19 (61.3%)	38 (44.2%)
Retardation, n (%)			
Yes	6 (10.9%)	4 (12.9%)	10 (11.6%)
Urethral Sphincter Activity, n (%)			
Overactive Sphincter	31 (56.4%)	13 (41.9%)	44 (51.2%)
Underactive Sphincter	7 (12.7%)	8 (25.8%)	15 (17.4%)
Normal Sphincter	16 (29.1%)	8 (25.8%)	24 (27.9%)
Time Since Surgery‡, months			
n	45	19	64
Mean (SD)	73.91 (44.10)	90.82 (77.50)	78.93 (55.99)
Median	78.80	57.10	75.40
Min – Max	6.7 – 138.3	2.8 – 192.9	2.8 – 192.9

All patients who received ≥ 1 dose of study drug (SAF).
† Duration is calculated from date of diagnosis to date of first mirabegron dose.
‡ Time since surgery is calculated from date of historical surgical procedure for underlying condition and/or complications to date of first mirabegron dose.
Source: 178-CL-206A CSR, Table 6, p. 61.

Reviewer's Comment: Overall, baseline characteristics were similar to those of the overall NDO population studied in recent trials of other drugs to treat NDO patients. Some differences between age groups are a function of expected disease progression related to age. It does not appear that such differences impacted the study results.

All 86 patients were practicing CIC (consistent with entry criteria) or used other terms describing practice of CIC, 88.4% had previously taken medication for the treatment of NDO (with a majority taking either oxybutynin or solifenacin), and 79.1% had previously taken medication for non-NDO conditions. During the treatment period, only 1 patient took a medication for an NDO related issue. However, this medication (Lyspafen, which is a combination of difenoxin and

atropine sulfate) was taken for bowel motility, not NDO, and so was not considered a prohibited medication. Table 10 below provides an overview of NDO therapies prior to study drug administration in study 178-CL-206A.

Table 10 Overview of NDO Therapies Prior to Study Drug Administration in Study 178-CL-206A (SAF)

Parameter Category/Statistics	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
NDO Nonmedication Therapy, n (%)*			
Yes	55 (100.0%)	31 (100.0%)	86 (100.0%)
Duration of Nonmedication Therapy at Screening (Years)			
Mean (SD)	4.43 (3.47)	9.09 (5.32)	6.11 (4.77)
Any NDO Medication Therapy, n (%)			
Yes	48 (87.3%)	28 (90.3%)	76 (88.4%)
Most Frequently Used (> 5% patients in any age group)			
Botulinum Toxin Type A	1 (1.8%)	2 (6.5%)	3 (3.5%)
Fesoterodine	0	3 (9.7%)	3 (3.5%)
Mirabegron	3 (5.5%)	3 (9.7%)	6 (7.0%)
Oxybutynin	21 (38.2%)	7 (22.6%)	28 (32.6%)
Propiverine	3 (5.5%)	2 (6.5%)	5 (5.8%)
Solifenacin	11 (20.0%)	8 (25.8%)	19 (22.1%)
Tolterodine	3 (5.5%)	1 (3.2%)	4 (4.7%)
Trospium	3 (5.5%)	1 (3.2%)	4 (4.7%)

*NDO nonmedication therapy here is CIC. Terms used by patients to described CIC included "CIC", "intermittent catheterization", "urinary catheterization", as well as other verbatim terms for describing CIC.
CIC: clean intermittent catheterization; SAF: safety analysis set.
Source: Compiled from 178-CL-206A CSR, Table 7, p. 62.

Treatment Compliance and Study Drug Exposure

The design of the Phase 3 study 178-CL-206A required all patients to start at the pediatric dose intended to achieve exposures at steady state equivalent to those of adults administered mirabegron 25 mg once daily (PED25): 54.7% started on tablets and 45.3% started on oral suspension. By week 2, 51.2% of patients had increased to PED50, and 33.7% continued on PED25. By week 4, 77.9% of patients were taking PED50 and only 7.0% continued PED25. At week 8, only 4 (4.7%) of patients remained at PED25, and the rest (80.2%) were receiving PED50. After week 8, all patients who had titrated up to PED50 had done so -- there were no dose increases or decreases from week 8 onwards. Between weeks 8 and 52, dose interruptions due to TEAEs or dosing noncompliance were recorded in the clinical database for 12 patients. Sixteen (16) patients discontinued study drug: 12 (21.8%) children and 4 (12.9%) adolescents. Table 11 summarizes the progression of study drug dosing in Study 178-CL-206A SAF population.

Table 11 Summary of Study Drug Dosing; Study 178-CL-206A (SAF)

Parameter	Children (3 to < 12 Years) n = 55		Adolescents (12 to < 18 ears) n = 31		All Patients (3 to < 18 Years) n = 86	
	PED25	PED50	PED25	PED50	PED25	PED50
Baseline	55(100.0%)		31(100%)		86(100.0%)	
Week 2	18(32.7%)	28(50.9%)	11(35.5%)	16(51.6%)	29(33.7%)	44(51.2%)
Week 4	4(7.3%)	42(76.4%)	2(6.5%)	25(80.6%)	6(7.0%)	67(77.9%)
Week 8	2(3.6%)	44(80.0%)	2(6.5%)	25(80.6%)	4(4.7%)	69(80.2%)
Week 12	2(3.6%)	43(78.2%)	2(6.5%)	25(80.6%)	4(4.7%)	68(79.1%)
Week 24	2(3.6%)	42(76.4%)	2(6.5%)	25(80.6%)	4(4.7%)	67(77.9%)
Week 36	2(3.6%)	41(74.5%)	2(6.5%)	25(80.6%)	4(4.7%)	66(76.7%)
Week 52	2(3.6%)	41(74.5%)	2(6.5%)	24(77.4%)	4(4.7%)	65(75.6%)

Source: Compiled from 178-CL-206A CSR, Table 12.2.1.1 p. 276.

Reviewer's Comment: In this review, we often refer to two groups within a dosing regimen. The two dosing regimen groups are 1) patients who had been up-titrated to PED50 at least once ("25/50 group") and 2) patients who maintained PED25 for safety reasons until at least week 24 ("25 only").

The mean average daily dose for tablets and suspension was 41.6 mg and 50.1 mg, respectively. Compliance with treatment was similar across both age groups and both formulations with a median compliance of 99%. Study drug exposure was also similar across age groups with a median duration of treatment of 364 days with a range of mean drug exposure from 293.7 to 318.6 days. The table below provides a summary of study drug compliance and exposure.

Table 12 Summary of Study Drug Compliance and Exposure over the Whole Treatment Period; Study 178-CL-206A (SAF)

Category/ Statistics	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Duration† (Days)			
n	55	31	86
Mean (SD)	293.65 (140.98)	318.55 (122.94)	302.63 (134.55)
Median	364.00	364.00	364.00
Min - Max	2.0 – 390.0	1.0 – 382.0	1.0 – 390.0
n (%)			
< 84	10 (18.2%)	4 (12.9%)	14 (16.3%)
≥ 84 to < 168	1 (1.8%)	0	1 (1.2%)
≥ 168 to < 252	1 (1.8%)	0	1 (1.2%)
≥ 252 to < 364	7 (12.7%)	7 (22.6%)	14 (16.3%)
≥ 364	36 (65.5%)	20 (64.5%)	56 (65.1%)
Unknown	0	0	0
Treatment Compliance for Patients using Tablets‡ (%)			
n	18¶	28	46¶

Mean (SD)	97.45 (3.78)	95.46 (13.36)	96.24 (10.65)
Median	99.87	99.73	99.73
Min - Max	89.9 – 101.6	32.1 – 103.6	32.1 – 103.6
Treatment Compliance for Patients using Oral Solution§ (%)			
n	36	3	39
Mean (SD)	97.00 (19.52)	101.35 (1.74)	97.33 (18.77)
Median	99.68	101.52	99.69
Min - Max	40.5 – 146.8	99.5 – 103.0	40.5 – 146.8

† Duration is defined as (date of last dose - date of first dose) + 1.
‡ Compliance = 100% x total number of tablets used/total number of expected tablets to be used.
§ Compliance = 100% x total dose of suspension used/total amount of expected dose of suspension to be used.
¶ Missing 1 child who was included in the SAF but was not evaluable for exposure as this child received tablets, discontinued early and never returned the blister.
Source: Compiled from 178-CL-206A CSR, Table 8, p. 63-64.

Efficacy Results – Primary Endpoint

Reviewer's Comment: Throughout the review of efficacy results, P values are shown for completeness and to convey the Sponsor's presentation of their analyses summaries. Although the Sponsor states in their submission that the results of the efficacy analyses showed statistical significance, we note that P values are not useful for decision-making, or data presentation in this open-label, baseline-controlled study. Any statement of statistical significance conveyed by P values is nominal only. Conclusions regarding treatment effects will be based on numerical changes in efficacy endpoint values, including mean changes from baseline and 95% confidence intervals.

The primary efficacy endpoint was the change from baseline in MCC after 24 weeks of treatment (based on filling urodynamics). Table 13 below provides a summary of the results for the primary endpoint. Overall for all patients, the mean change from baseline in MCC at 24 weeks was 87.20 mL ($P < 0.001$). Children and adolescents had mean increases in MCC at 24 weeks of 72.09 mL and 113.21 mL, respectively (both $P < 0.001$).

Reviewer's Comment: The numerically smaller increase in MCC in the younger pediatric patients was expected due to age-related bladder volumes and baseline MCC values. In light of this, we consider the increase in MCC in children and adolescents to be comparable.

Table 13 Change from Baseline in Maximum Cystometric Capacity* (mL) at Week 24 – LOCF (FAS); Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	43	158.64 (94.50)	25	238.92 (99.14)	68	188.16 (103.15)
Week 24 LOCF, n | Mean (SD)	43	230.73 (129.19)	25	352.13 (125.23)	68	275.36 (139.85)
Change from Baseline, n†	43		25		68	
Mean (SD)	72.09 (87.09)		113.21 (82.99)		87.20 (87.30)	

95% CI	(45.28, 98.89)§	(78.95, 147.47)§	(66.07, 108.33)§
P value‡	< 0.001	< 0.001	< 0.001

All patients who received ≥ 1 dose of study drug and had both a valid non-missing baseline measurement and ≥ 1 post-baseline measurement for the primary efficacy endpoint (maximum cystometric capacity) (FAS).
*Maximum Cystometric Capacity (MCC) is defined as the maximum bladder capacity reached during filling cystometry before either leakage or pain/discomfort was observed, or 135% of expected bladder capacity was reached, or a dangerously high detrusor pressure was reached.
† The number of patients with a non-missing change from baseline to week 24 LOCF.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
§ The lower bound of the 95% CI excluded zero.
Source: 178-Cl-206A CSR, Table 9, p.65.

The primary estimand followed a hypothetical strategy to address intercurrent events. The goal was to determine the treatment effect if the inevitable intercurrent events had not occurred. The attributes, noted earlier in this review (see section 6.1.1 Study design, study endpoints), include the target population (FAS), outcome (MCC at week 24), intercurrent event (patient had not discontinued treatment for any reason), and a population based summary (change from baseline in MCC at week 24 (or prior, due to study drug discontinuation). This definition was in line with the primary endpoint.

For the primary endpoint, the change from baseline in MCC at 24 weeks, the change was apparent as early as week 4. Table 14 below shows that after 4 weeks of treatment, patients in each age group realized all but approximately 30 mL of the change from baseline in MCC achieved at 24 weeks. Change from baseline results at week 24 with and without LOCF were concordant.

Table 14 Summary of Maximum Cystometric Capacity (mL) by Study Week (FAS); Study 178-CL-206A

	Visit			
Statistic	**Baseline**	**Week 4**	**Week 24**	**Week 24 LOCF**
Patients 3 to < 12 years of age				
n	43	41	38	43
Baseline Mean (SD)	158.64 (94.50)	203.94 (125.23)	225.66 (90.18)	230.73 (129.19)
CFB Mean (SD)	NA	41.36 (71.64)	71.05 (79.76)	72.09 (87.09)
95% CI		(18.75, 63.97)	(44.83, 97.27)	(45.28, 98.89)
P value		<0.001	<0.001	<0.001
Patients 12 to < 18 years of age				
n	25	23	24	25
Baseline Mean (SD)	238.92 (99.14)	311.04 (114.34)	346.76 (124.95)	352.13 (125.23)
CFB Mean (SD)	NA	80.78 (96.15)	113.38 (84.77)	113.21 (82.99)
95% CI		(39.20, 122.36)	(77.59, 149.18)	(78.95, 147.47)
P value		<0.001	<0.001	<0.001
Patients 3 to < 18 years of age				
n	68	64	62	68
Baseline Mean (SD)	188.16 (103.15)	242.43 (131.17)	272.53 (119.82)	275.36 (139.85)

CFB Mean (SD)	NA	55.53 (82.76)	87.44 (83.67)	87.20 (87.30)
95% CI		(34.85, 76.20)	(66.19, 108.69)	(66.07, 108.33)
P value		<0.001	<0.001	<0.001

LOCF: last observation carried forward; max: maximum; min: minimum; NA: not applicable.
Source: Compiled from 178-CL-206A CSR, Tables 12.3.1.1.1, 12.3.1.2.1, 12.3.1.3.1, and 12.3.2 and Table 10, p.66.

Reviewer's Comment: It is notable that treatment effect was observed as early as week 4. Knowledge of that result by caretakers could increase adherence to the treatment and improve efficacy.

Secondary and sensitivity analyses of the primary endpoint and the estimand in FAS and PPS
The Sponsor conducted several secondary and sensitivity analyses of the primary endpoint. For those, the analysis with LOCF for the PPS, the analysis without LOCF for the FAS and PPS, and the analysis using BOCF for all enrolled patients all showed clinically meaningful changes from baseline in MCC to week 24.

Table 15 below provides a summary of the results of these analyses.

Table 15 Results of Secondary Analyses of Change from Baseline in MCC at 24 weeks using different statistical approaches (without and with LOCF, BOCF) for different populations; Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 38	Adolescents (12 to < 18 Years) n = 22	All Patients (3 to < 18 Years) n = 60
Change from Baseline to Week 24 in MCC (mL) (LOCF) (PPS)			
Change from Baseline, n†	38	22	60
Mean (SD)	75.89 (89.20)	105.46 (85.65)	86.74 (88.36)
95% CI	(46.57, 105.21)	(67.49, 143.44)	(63.91, 109.56)
P value§	< 0.001	< 0.001	< 0.001
Change from Baseline to Week 24 in MCC (mL) (Without LOCF) (FAS)			
Change from Baseline, n*	38	24	62
Mean (SD)	71.05 (79.76)	113.38 (84.77)	87.44 (83.67)
95% CI	(44.83, 97.27)	(77.59, 149.18)	(66.19, 108.69)
P value§	< 0.001	< 0.001	< 0.001
Change from Baseline to Week 24 in MCC (mL) (Without LOCF) (PPS)			
Change from Baseline, n*	36	21	57
Mean (SD)	69.05 (81.53)	105.30 (87.76)	82.41 (84.95)
95% CI	(41.47, 96.64)	(65.35, 145.24)	(59.87, 104.95)
P value§	< 0.001	< 0.001	< 0.001
Change from Baseline to Week 24 in MCC (mL) (BOCF $^{\alpha}$) (SAF)			
Change from Baseline, n$^{\beta}$	52	29	81
Mean (SD)	51.92 (75.02)	93.83 (88.33)	66.93 (82.02)
95% CI	(31.04, 72.81)	(60.23, 127.43)	(48.79, 85.06)
P value§	< 0.001	< 0.001	< 0.001

The PPS included all patients from the full analysis set who fulfilled the protocol in terms of their eligibility, interventions and outcome assessments, and for whom valid MCC measurements at baseline and at week 24 were reported.
BOCF: baseline observation carried forward.
† The number of patients with a non-missing change from baseline to week 24 LOCF.
* The number of patients with a non-missing change from baseline to week 24.
[α] BOCF: the baseline value is imputed for the missing value at week 24.
[β] The number of patients with a non-missing change from baseline to week 24 BOCF.
§ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: Compiled from 178-CL-206A CSR, Table 11, p. 67; Table 12, p. 67; Table 13, p. 68; and Table 12.3.1.3.2, p. 448.

Additional sensitivity analyses using repeated measures ANCOVA in the FAS and PPS, summarized in Table 16, also showed clinically meaningful changes from baseline in MCC at 24 weeks for each age group as well as for all patients.

Table 16 Secondary Analyses of Change from Baseline to Week 24 in MCC (mL): Repeated Measures Analysis (FAS and PPS), Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
FAS Population						
Baseline, n | Mean (SD)	43	158.64 (94.50)	25	238.92 (99.14)	68	188.16 (103.15)
Week 4, n | Mean (SD)	41	203.94 (125.23)	23	311.04 (114.34)	64	242.43 (131.17)
Week 24, n | Mean (SD)	38	225.66 (90.18)	24	346.76 (124.95)	62	272.53 (119.82)
Adjusted Change from Baseline†						
Adjusted LS Mean (SE)	66.95 (13.36)		119.57 (16.93)		93.26 (10.56)	
95% CI	(40.2, 93.7)		(85.7,153.5)		(72.1, 114.4)	
P value‡	< 0.001		< 0.001		< 0.001	
PPS Population						
Baseline, n | Mean (SD)	38	167.00 (96.75)	22	254.23 (94.15)	60	198.98 (104.03)
Week 4, n | Mean (SD)	36	216.42 (128.00)	20	310.55 (117.02)	56	250.04 (131.26)
Week 24, n | Mean (SD)	36	226.16 (92.37)	21	353.91 (130.53)	57	273.23 (123.63)
Adjusted Change from Baseline†						
Adjusted LS Mean (SE)	65.54 (14.05)		110.38 (18.50)		87.96 (11.29)	
95% CI	(37.3, 93.7)		(73.3, 147.5)		(65.3, 110.6)	
P value‡	< 0.001		< 0.001		< 0.001	

ANCOVA: analysis of covariance; LS: least squares
† From a repeated measures ANCOVA of the change from baseline. The model included age group and visit (week 4, week 24) as fixed effects, age group by visit interaction, baseline as a covariate, and with visit repeated within patient. The LS mean for the visit by age group interaction was reported within age groups and the LS mean for the visit term was reported when both age groups were combined.
‡ P value from the same repeated measures ANCOVA model above, testing the null hypothesis that the adjusted change from baseline is equal to 0.
Source: Compiled from 178-CL-206A CSR Tables 12.3.1.5.1 and 12.3.1.5.2.

Additionally, a sensitivity analysis using the Wilcoxon signed-rank test (a summary is shown in the table below), with or without LOCF in the FAS, showed changes from baseline to week 24 in MCC that were also clinically meaningful.

Table 17 Secondary Analysis of Change from Baseline to Week 24 (With and Without LOCF) in MCC (mL): Wilcoxon Signed-rank Test (FAS), Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43	Adolescents (12 to < 18 Years) n = 25	All Patients (3 to < 18 Years) n = 68
Baseline, n	43	25	68
Median (Q1, Q3)	139.00 (97.00, 219.00)	243.00 (167.00, 296.0)	178.50 (110.00, 243.95)
Week 24, n†	38	24	62
Median (Q1, Q3)	72.50 (5.00, 108.00)	143.00 (33.50, 177.00)	76.50 (20.00, 157.00)
P value‡	< 0.001	< 0.001	< 0.001
Week 24 LOCF, n†	43	25	68
Median (Q1, Q3)	70.00 (1.00 108.00)	132.00 (43.00, 175.00)	76.50 (16.70 155.50)
P value‡	< 0.001	< 0.001	< 0.001

Q1: first quartile; Q3: third quartile.
† The number of patients with a non-missing change from baseline to week 24 or week 24 LOCF.
‡ From a Wilcoxon signed-rank test, which tests the null hypothesis that the medians at week 24 and week 24 LOCF are equal to the baseline median.
Source: 178-CL-206A CSR, Table 15, p. 69.

Finally, the sensitivity analysis of the primary estimand at week 24 confirmed the primary analysis of the primary estimand. Table 18 below shows the increases from baseline in MCC in each age group and overall.

Table 18 Sensitivity Analysis of the Primary Estimand in MCC (mL): Repeated Measures Analysis (FAS), Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	43	158.64 (94.50)	25	238.92 (99.14)	68	188.16 (103.15)
Week 4, n | Mean (SD)	41	203.94 (125.23)	23	311.04 (114.34)	64	242.43 (131.17)
Week 24, n | Mean (SD)	38	225.66 (90.18)	24	346.76 (124.95)	62	272.53 (119.82)
Adjusted Change from Baseline†						
Adjusted LS Mean (SE)	69.53 (11.94)		113.47 (18.39)		87.35 (10.62)	
90% CI	(49.4, 89.7)		(81.8, 145.1)		(69.6, 105.1)	
P value‡	< 0.001		< 0.001		< 0.001	

† From a repeated measures ANCOVA of the change from baseline. The model included age group and visit (week 4, week 24) as fixed effects, age group by visit interaction, baseline as a covariate, and with visit repeated within patient. The LS mean for the visit by age group interaction was reported within age groups and the LS mean for the visit term was reported when both age groups were combined.
‡ P value from the same repeated measures ANCOVA model above, testing the null hypothesis that the adjusted change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 12.3.1.9, p. 472-474.

Reviewer's Comment: The many secondary and sensitivity analyses of the primary endpoint support the primary efficacy results.

Data Quality and Integrity

To implement and maintain quality assurance and quality control systems, the Sponsor noted that standard operative procedures (SOPs) were written to ensure studies were conducted and data were generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

The Sponsor also performed one audit of Phase 3 Study 178-CL-206A clinical investigational sites in each of the following countries: Lithuania, Romania, and Croatia. Audits included on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents was required by the auditors. Audit certificates were submitted but the audit reports were not provided in this submission.

The Sponsor also conducted periodic monitoring site visits during which they reviewed data for accuracy and performed computer logic checks to identify potential errors. When errors were found, the errors were reviewed with study site personnel and the database was corrected accordingly. When clinical data were collected outside the clinical data management system, the vendor provided data in an agreed upon format. Outlier checks were performed regularly.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoints included urodynamic endpoints, patients e-diary endpoints of bladder volume and leakage measures, and patient- or clinician-reported endpoints derived from 4 questionnaires (Acceptability, CGI-C, PGI-S and PIN-Q).

Secondary endpoints based on urodynamic measures
The analyses of urodynamic endpoints, as summarized in Table 19 below, showed strong support for the primary endpoint. Analyses of change from baseline at 24 weeks were conducted to support the primary endpoint (also measured at 24 weeks), and analyses at the first measurable time point (4 weeks) were performed to show which endpoints (if any) showed early improvement.

- Maximum cystometric capacity improvement at week 4 was clinically meaningful in both age groups (41.4 mL and 80.8 mL in the child and adolescent groups, respectively), and in all patients (55.5 mL).
- Bladder compliance at week 4 showed improvement only in adolescents (15.2 mL/cm H_2O). However, week 24, bladder compliance was improved in children, adolescents, and all patients (14.6, 13.6, and 14.2 mL/cm H_2O, respectively). Bladder compliance was approximately doubled at week 24 compared with baseline.
- The number of overactive detrusor contractions (> 15 cm H_2O) until end of bladder filling did not show clinically meaningful improvement at week 4 compared to baseline in either age group. At week 24, however, there was a clinically meaningful decrease

from baseline in children (-1.9 contractions) and all patients (-1.45 contractions), with less of an effect in adolescents (-0.77 contractions).

- Detrusor pressure at end of bladder filling decreased meaningfully in all groups (-18.1, -13.2, and -16.2 cm H_2O in children, adolescents, and all patients, respectively). At week 4, children and all patients showed a clinically meaningful decrease in detrusor pressure at end of bladder filling compared with baseline; for adolescents, the decrease was less notable.
- Bladder volume until first detrusor contraction > 15 H_2O (FAS) increased at week 24 compared to baseline in both age groups (93 mL, 121 mL, and 104 mL in children, adolescents, and all patients, respectfully). At 4 weeks, the increase was clinically meaningful in children (56 mL), adolescents (73 mL), and all patients (62 mL).

The table below summarizes the change from baseline in all 5 of the secondary endpoints based on urodynamics.

Table 19 Change from Baseline in Urodynamic Endpoints at Week 4 and Week 24 (FAS); Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Maximum Cystometric Capacity (mL) at Week 4 (FAS)						
Baseline, n | Mean (SD)	43	158.64 (94.50)	25	238.92 (99.14)	68	188.16 (103.15)
Week 4, n | Mean (SD)	41	203.94 (125.23)	23	311.04 (114.34)	64	242.43 (131.17)
Change from Baseline, n†	41		23		64	
Mean (SD)	41.36 (71.64)		80.78 (96.15)		55.53 (82.76)	
95% CI	(18.75, 63.97)		(39.20, 122.36)		(34.85, 76.20)	
P value‡	< 0.001		< 0.001		< 0.001	
Bladder Compliance (mL/cm H_2O) at Weeks 4 and 24 (FAS)						
Baseline, n | Mean (SD)	40	14.53 (50.75)	24	11.02 (10.05)	64	13.21 (40.42)
Week 4, n | Mean (SD)	40	10.56 (6.47)	23	25.22 (27.73)	63	15.91 (18.70)
Change from Baseline, n†	39		22		61	
Mean (SD)	-4.09 (50.78)		15.16 (22.69)		2.85 (43.59)	
95% CI	(-20.55, 12.38)		(5.10, 25.22)		(-8.31, 14.02)	
P value‡	0.618		0.005		0.611	
Week 24, n | Mean (SD)	35	29.63 (52.81)	22	23.89 (15.35)	57	27.41 (42.30)
Change from Baseline, n†	33		21		54	
Mean (SD)	14.62 (42.09)		13.59 (15.02)		14.22 (33.99)	
95% CI	(-0.31, 29.54)		(6.75, 20.42)		(4.94, 23.49)	
P value‡	0.055		< 0.001		0.003	
No. of Overactive Detrusor Contractions (> 15 cm H_2O) Until End of Bladder-filling at Wks 4 and 24 (FAS)						
Baseline, n | Mean (SD)	42	3.07 (3.88)	24	2.04 (2.97)	66	2.70 (3.59)
Week 4, n | Mean (SD)	41	3.37 (7.70)	23	1.39 (2.15)	64	2.66 (6.34)
Change from Baseline, n†	41		22		63	
Mean (SD)	0.44 (5.82)		-0.64 (2.94)		0.06 (5.01)	
95% CI	(-1.40, 2.28)		(-1.94, 0.67)		(-1.20, 1.32)	

P value‡	0.632		0.321		0.920	
Week 24, n | Mean (SD)	37	1.08 (2.23)	23	1.48 (2.35)	60	1.23 (2.27)
Change *from Baseline,* n†	36		22		58	
Mean (SD)	-1.86 (4.16)		-0.77 (3.87)		-1.45 (4.05)	
95% CI	(-3.27, -0.45)		(-2.49, 0.94)		(-2.51, -0.38)	
P value‡	0.011		0.359		0.009	
Detrusor Pressure (cm H_2O) at End of Bladder Filling at Weeks 4 and 24 (FAS)						
Baseline, n | Mean (SD)	42	42.25 (26.27)	24	38.65 (17.97)	66	40.94 (23.51)
Week 4, n | Mean (SD)	41	30.17 (16.22)	23	33.00 (27.25)	64	31.19 (20.70)
Change from *Baseline,* n†	41		22		63	
Mean (SD)	-12.38 (19.56)		-6.48 (30.70)		-10.32 (23.96)	
95% CI	(-18.56, -6.21)		(-20.09, 7.13)		(-16.35, -4.28)	
P value‡	< 0.001		0.334		0.001	
Week 24, n | Mean (SD)	37	25.66 (21.24)	23	27.84 (18.92)	60	26.50 (20.24)
Change from Baseline, n†	36		22		58	
Mean (SD)	-18.11 (19.97)		-13.19 (19.91)		-16.24 (19.92)	
95% CI	(-24.87, -11.35)		(-22.02, -4.36)		(-21.48, -11.01)	
P value‡	< 0.001		0.005		< 0.001	
Bladder Volume until First Detrusor Contraction > 15 cm H_2O (FAS)						
Baseline, n | Mean (SD)	43	115.82 (86.97)	25	185.17 (121.25)	68	141.31 (105.56)
Week 4, n | Mean (SD)	41	118.98 (87.27)	23	184.73 (114.17)	64	142.61 (101.97)
Change from *Baseline,* n†	41		23		64	
Mean (SD)	56.09 (96.23)		73.80 (117.21)		62.45 (103.68)	
95% CI	(25.71, 86.46)		(23.11, 124.48)		(36.55, 88.35)	
P value‡	< 0.001		0.006		< 0.001	
Week 24, n | Mean (SD)	38	114.78 (82.90)	24	177.39 (117.30)	62	139.01 (101.50)
Change from Baseline, n†	38		24		62	
Mean (SD)	93.09 (88.14)		121.33 (159.84)		104.02 (120.57)	
95% CI	(64.12, 122.06)		(53.84, 188.82)		(73.40, 134.64)	
P value‡	< 0.001		0.001		< 0.001	

† The number of patients with a non-missing change from baseline to week 4 or 24.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: Compiled from 178-CL-206A CSR Tables 19-23, p. 73-75 and from Sponsor's Adhoc Table 12.3.6.3.

Reviewer's Comment: The final efficacy analysis results for bladder volume until first detrusor contraction >15 cm H_2O were submitted in response to an IR issued by our Biostatistics colleagues after they noted that the missing data imputation did not follow what was pre-specified in the SAP. The Sponsor made the appropriate corrections, such that if no detrusor contraction occurred, the imputation using MCC for the missing value was applied to the measurement for that specific visit, not to the change from baseline directly.

The table below provides a more succinct summary of changes from baseline in all the secondary endpoints based on urodynamic study parameters for each age group at 4 and 24 weeks.

Table 20 Change From Baseline in Secondary Efficacy Endpoints based on Urodynamic Studies for each Age Group at 4 and 24 Weeks (FAS); 178-CL-206A

SECONDARY EFFICACY ENDPOINT	Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
		4 weeks	24 weeks	4 weeks	24 weeks	4 weeks	24 weeks
Maximum Cystometric Capacity (mL)	Mean (SD) P value	41.4 (71.6) < 0.001	72.09 (87.09)* <0.001	80.78 (96.15) <0.001	113.21(82.99)* <0.001	55.5 (82.7) < 0.001	87.20 (87.30)* < 0.001
Bladder Compliance (mL/cm H_2O)	Mean (SD) P value	-4.09 (50.78) 0.618	14.6 (42.1) 0.055	15.16 (22.69) 0.005	13.6 (15.0) < 0.001	2.85 (43.59) 0.611	14.2 (34.0) 0.003
Number of Overactive Detrusor Contractions (> 15 cm H_2O) Until End of Bladder-filling	Mean (SD) P value	0.44 (5.82) 0.632	-1.9 (4.2) 0.011	-0.64 (2.94) 0.321	-0.8 (3.8) 0.359	0.06 (5.01) 0.920	-1.45 (4.05) 0.009
Detrusor Pressure at End of Bladder Filling (cm H_2O)	Mean (SD) P value	-12.38 (19.56) < 0.001	-18.1 (19.97) < 0.001	-6.48 (30.70) 0.334	-13.2 (19.9) 0.005	-10.32 (23.96) < 0.001	-16.2 (19.9) < 0.001
Bladder Volume Until First Detrusor Contraction > 15 H_2O (FAS)	Mean (SD) P value	56.09 (96.23) <0.001	93.09 (88.14) <0.001	73.80 (117.21) 0.006	121.33(159.84) 0.001	62.45(103.68) <0.001	104.02(120.6) <0.001

*Using LOCF – this is the primary efficacy endpoint (measured at week 24)
Source: 178-CL-206A CSR, Tables 12.3.3.2, 12.3.4.2, 12.3.5.2, 12.3.6.2, 12.3.2, 12.3.1.1.1.

Reviewer's Comment: Overall, urodynamic secondary endpoints supported the primary efficacy endpoint with clinically meaningful improvements that appear consistent with a treatment effect in all 5 measures in all patients and in each age group. Overall, the improvement in urodynamic endpoints was evident after 4 weeks of treatment in various age groups for each measure: MCC (in all groups), bladder compliance (in adolescents only), detrusor pressure (in children and all patients), and bladder volume until first detrusor contraction > 15 cm H_2O (in all groups).

Secondary endpoints based on bladder volume and leakage measures
All bladder volume and leakage measures were obtained from the electronic diary (e-diary). Endpoints were evaluated as change from baseline at weeks 2, 4, 8, 12, 24, 36, and 52. The Sponsor chose to highlight data from weeks 4, 24, and 52 in their summary tables but included graphs to illustrate the trajectory of change from baseline over the course of the 52-week treatment period.

- **Average catheterized volume per catheterization** compared to baseline increased in a clinically meaningful fashion at every time point measured for children, adolescents, and all patients (Table 12.3.7.2). At week 24, the mean change from baseline was 47.99 mL in all patients. For all groups, the change from baseline in volume per catheterization was highest at weeks 24 or 36, and trended lower from that point to week 52. The table below provides a summary of these results.

Table 21 Change From Baseline to Weeks 4, 24, and 52 in Average Catheterized Volume per Catheterization (mL) (FAS); Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	43	236.73 (70.52)	24	278.98 (91.96)	67	251.87 (80.80)
Week 4, n | Mean (SD)	42	264.24 (68.93)	25	334.59 (84.99)	67	290.49 (82.18)
Change from Baseline, n†	42		24		66	
Mean (SD)	30.08 (49.50)		51.96 (64.71)		38.04 (56.03)	
95% CI	(14.7, 45.5)		(24.6, 79.3)		(24.3, 51.8)	
P value‡	< 0.001		< 0.001		< 0.001	
Week 24, n | Mean (SD)	41	279.74 (71.86)	24	335.13 (97.89)	65	300.19 (86.01)
Change from Baseline, n†	41		23		64	
Mean (SD)	41.63 (58.03)		59.31 (82.22)		47.99 (67.62)	
95% CI	(23.3, 60.0)		(23.8, 94.9)		(31.1, 64.9)	
P value‡	< 0.001		0.002		< 0.001	
Week 52, n | Mean (SD)	40	282.03 (86.01)	24	316.84 (78.37)	64	295.08 (84.32)
Change from Baseline, n†	40		23		63	
Mean (SD)	42.84 (65.31)		42.40 (69.25)		42.68 (66.22)	
95% CI	(22.0, 63.7)		(12.5, 72.3)		(26.0, 59.4)	
P value‡	< 0.001		0.008		< 0.001	

† The number of patients with a non-missing change from baseline to analysis visit.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 24, p. 76.

- **Maximum catheterized volume per catheterization** showed an increased from baseline at week 2 in all age groups that was about 50% of the week 4 increase (Table 12.3.8.2), as shown in the table below. At week 24, the mean increase from baseline in all patients was 62.28 mL. In all age groups, the maximum increase from baseline occurred at week 24 or 36 and the improvement in mean maximum catheterized volume decreased slightly in all groups from that point to week 52. Table 22 below provides a summary of these results.

Table 22 Change From Baseline to Weeks 4, 24, and 52 in Maximum Catheterized Volume per Catheterization (mL) (FAS); Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	43	302.41 (107.29)	24	364.63 (111.27)	67	324.69 (112.00)
Week 4, n | Mean (SD)	42	346.13 (127.03)	25	448.02 (119.04)	67	384.15 (132.83)
Change from Baseline, n†	42		24		66	
Mean (SD)	46.69 (80.29)		73.25 (103.98)		56.35 (89.77)	
95% CI	(21.7, 71.7)		(29.3, 117.2)		(34.3, 78.4)	
P value‡	< 0.001		0.002		< 0.001	
Week 24, n | Mean (SD)	41	353.95 (104.47)	24	449.98 (146.62)	65	389.41 (129.34)

Change from Baseline, n†	41		23		64	
Mean (SD)	49.88 (103.70)		84.39 (121.98)		62.28 (110.91)	
95% CI	(17.1, 82.6)		(31.6, 137.1)		(34.6, 90.0)	
P value‡	0.004		0.003		< 0.001	
Week 52, n | Mean (SD)	40	359.82 (124.06)	24	413.76 (100.23)	64	380.05 (117.85)
Change from Baseline, n†	40		23		63	
Mean (SD)	53.51 (96.72)		54.30 (104.74)		53.80 (98.88)	
95% CI	(22.6, 84.4)		(9.0, 99.6)		(28.9, 78.7)	
P value‡	0.001		0.021		< 0.001	

For results at other weeks (2, 8, 12 and 36), the reader is referred to Table 12.3.8.2.
† The number of patients with a non-missing change from baseline to analysis visit.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 25, p. 78.

- **Maximum catheterized daytime volume** showed an increase from baseline as early as week 2 in all age groups (Table 12.3.9.2). For all three age groups, the maximum change from baseline was observed at 24 or 36 weeks and decreased slightly from that point to week 52. These results are summarized in Table 23.

Table 23 Change From Baseline to Weeks 4, 24, and 52 in Maximum Catheterized Daytime Volume (mL) (FAS); Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	43	300.16 (105.71)	24	367.52 (119.03)	67	324.29 (114.49)
Week 4, n | Mean (SD)	42	334.86 (127.04)	25	448.02 (119.04)	67	377.08 (134.98)
Change from Baseline, n†	42		24		66	
Mean (SD)	37.71 (83.33)		70.35 (113.98)		49.58 (96.06)	
95% CI	(11.7, 63.7)		(22.2, 118.5)		(26.0, 73.2)	
P value‡	0.005		0.006		< 0.001	
Week 24, n | Mean (SD)	41	345.91 (84.61)	24	449.98 (146.62)	65	384.34 (121.50)
Change from Baseline, n†	41		23		64	
Mean (SD)	44.20 (98.31)		81.37 (117.77)		57.56 (106.32)	
95% CI	(13.2, 75.2)		(30.4, 132.3)		(31.0, 84.1)	
P value‡	0.006		0.003		< 0.001	
Week 52, n | Mean (SD)	40	357.67 (123.30)	24	411.70 (103.32)	64	377.93 (118.34)
Change from Baseline, n†	40		23		63	
Mean (SD)	53.76 (100.24)		49.13 (117.23)		52.07 (105.84)	
95% CI	(21.7, 85.8)		(-1.6, 99.8)		(25.4, 78.7)	
P value‡	0.002		0.057		< 0.001	

For results at other weeks (2, 8, 12 and 36), the reader is referred to Table 12.3.9.2.
† The number of patients with a non-missing change from baseline to analysis visit.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 26, p.80.

- The **Average morning catheterized volume** (based on first catheterization after patient woke up) increased from baseline as early as week 2 only for all age groups [Table 12.3.10.2]. For all age groups, the highest mean increase from baseline occurred at weeks 24 or 36 and the mean increase decreased from that point to week 52. Table 24 provides a summary of change from baseline in average morning catheterized volume at 4, 24, and 52 weeks.

Table 24 Change From Baseline to Weeks 4, 24 and 52 in Average Morning Catheterized Volume (mL) (FAS); Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	42	272.23 (102.40)	23	305.00 (102.40)	65	283.82 (102.82)
Week 4, n | Mean (SD)	40	288.23 (76.20)	22	376.80 (112.90)	62	319.66 (99.63)
Change from Baseline, n†	40		20		60	
Mean (SD)	19.81 (89.04)		75.25 (105.72)		38.29 (97.64)	
95% CI	(-8.7, 48.3)		(25.8, 124.7)		(13.1, 63.5)	
P value‡	0.167		0.005		0.004	
Week 24, n | Mean (SD)	36	311.35 (82.33)	22	384.87 (135.46)	58	339.24 (110.53)
Change from Baseline, n†	36		20		56	
Mean (SD)	40.76 (116.41)		86.66 (96.55)		57.15 (111.07)	
95% CI	(1.4, 80.2)		(41.5, 131.8)		(27.4, 86.9)	
P value‡	0.043		< 0.001		< 0.001	
Week 52, n | Mean (SD)	40	307.32 (87.13)	23	328.08 (81.99)	63	314.90 (85.22)
Change from Baseline, n†	39		21		60	
Mean (SD)	31.83 (94.25)		38.14 (108.06)		34.04 (98.44)	
95% CI	(1.3, 62.4)		(-11.0, 87.3)		(8.6, 59.5)	
P value‡	0.042		0.121		0.010	

For results at other weeks (2, 8, 12 and 36), the reader is referred to Table 12.3.10.2.
† The number of patients with a non-missing change from baseline to analysis visit.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 27, p.82.

- **Mean number of leakage episodes per day (day and night time).** The initial analysis showed no pattern of statistically significant change from baseline across weeks for any individual group. Numerically, at week 52, per the prespecified analysis, the mean change from baseline in number of leakage episodes per day was -1.62 for all patients, -1.80 in the children's group and -1.36 in the adolescent group (Table 12.3.11.1).

  However, the Sponsor noted that one patient (in the children's group, Patient (b) (6)) had values that were approximately 10-fold higher than those of the other patients. This apparently reflected an error in self-reported data in which the weight of the leakages was mistakenly entered in the e-diary instead of the number of leakage episodes. These data were included in the pre-specified analysis.

In light of this error in self-reported data, the Sponsor performed two ad-hoc analyses. The first ad-hoc analysis imputed a "0" for each visit for which patients did not report any leakage episodes. This analysis showed similar results to the prespecified analysis. The second ad-hoc analysis employed the same data imputation method but also excluded the data from the child with extreme outlying values to assess the influence of this child's data on the analysis results. The second ad-hoc analysis showed that exclusion of the child with the erroneous data resulted in an improvement in the children group's change in baseline in mean number of leakage episodes per day, showing a decrease of 1.57 episodes at week 24 compared to an increase of 0.18 episodes in the first ad-hoc analysis. For adolescents, both ad-hoc analyses showed less improvement (-0.75 episodes) compared with the pre- specified analysis (-1.15 episodes) at week 24.

The two tables below provide a summary of the results for the two ad-hoc analyses.

Table 25 Change From Baseline to Weeks 4, 24 and 52 in Mean Number of Leakage Episodes per Day (Day and Night Time): Ad-hoc Analysis With Imputation (FAS); Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	39	4.54 (12.32)	20	1.93 (1.66)	59	3.65 (10.10)
Week 4, n | Mean (SD)	36	3.64 (14.47)	16	1.34 (1.06)	52	2.93 (12.05)
Change from Baseline, n†	36		15		51	
Mean (SD)	-1.14 (3.39)		-0.87 (1.68)		-1.06 (2.98)	
95% CI	(-2.3, 0.0)		(-1.8, 0.1)		(-1.9, -0.2)	
P value‡	0.052		0.066		0.014	
Week 24, n | Mean (SD)	31	5.00 (23.05)	15	1.63 (1.19)	46	3.90 (18.90)
Change from Baseline, n†	31		14		45	
Mean (SD)	0.18 (10.05)		-0.75 (1.28)		-0.11 (8.34)	
95% CI	(-3.5, 3.9)		(-1.5, 0.0)		(-2.6, 2.4)	
P value‡	0.922		0.047		0.929	
Week 52, n | Mean (SD)	32	3.56 (13.95)	13	1.23 (1.54)	45	2.89 (11.79)
Change from Baseline, n†	32		13		45	
Mean (SD)	-0.94 (2.96)		-1.12 (1.97)		-0.99 (2.69)	
95% CI	(-2.0, 0.1)		(-2.3, 0.1)		(-1.8, -0.2)	
P value‡	0.083		0.064		0.018	

Patients who did not report any leakage episode during the visit are imputed with a '0' for that visit.
For results at other weeks (2, 8, 12 and 36), the reader is referred to Table 12.3.11.4..
† The number of patients with a non-missing change from baseline to analysis visit.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 28, p.85.

Table 26 Change From Baseline to Weeks 4, 24 and 52 in Mean Number of Leakage Episodes per Day (Day and Night Time): Ad-hoc Analysis With Imputation and Excluding 1 Child's Data (FAS); Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	38	2.64 (3.51)	20	1.93 (1.66)	58	2.40 (3.00)
Week 4, n | Mean (SD)	35	1.24 (1.63)	16	1.34 (1.06)	51	1.27 (1.47)
Change from Baseline, n†	35		15		50	
Mean (SD)	-1.49 (2.72)		-0.87 (1.68)		-1.30 (2.45)	
95% CI	(-2.4, -0.6)		(-1.8, 0.1)		(-2.0, -0.6)	
P value‡	0.003		0.066		< 0.001	
Week 24, n | Mean (SD)	30	0.87 (1.35)	15	1.63 (1.19)	45	1.12 (1.34)
Change from Baseline, n†	30		14		44	
Mean (SD)	-1.57 (2.63)		-0.75 (1.28)		-1.31 (2.30)	
95% CI	(-2.5, -0.6)		(-1.5, 0.0)		(-2.0, -0.6)	
P value‡	0.003		0.047		< 0.001	
Week 52, n | Mean (SD)	31	1.11 (1.66)	13	1.23 (1.54)	44	1.15 (1.61)
Change from Baseline, n†	31		13		44	
Mean (SD)	-1.06 (2.92)		-1.12 (1.97)		-1.08 (2.65)	
95% CI	(-2.1, 0.0)		(-2.3, 0.1)		(-1.9, -0.3)	
P value‡	0.052		0.064		0.010	

Patients who did not report any leakage episode during the visit are imputed with a '0' for that visit. Data from Patient (b) (6) are excluded in this table due to the child's extreme values reported, which were later identified as an error in recording.
For results at other weeks (2, 8, 12 and 36), the reader is referred to Table 12.3.11.6.
† The number of patients with a non-missing change from baseline to analysis visit.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 29, p.86.

Reviewer's Comment: Our Biostatistics colleagues determined that it was not appropriate to simply impute a "0" for each visit for which patients did not report any leakage episodes. After responding to several FDA IRs and working with our Biostatistics colleagues, the Sponsor stated that the imputation rule they had applied did not adequately follow the outline of the questions in the e-diary. The Sponsor then completed an additional analysis (version 2) using a new algorithm that considered the outline of the e-diary question concerning whether the patient had any leakage episodes between catheterizations. In the new algorithm, if the patient answered No to the e-diary question regarding leakage episodes, the number of leakages was set to 0; if the patient answered Y and the number was present, the number would be used, if the patient answered Y and no number was present, then the number was set as "missing"). Ultimately, our Biostatisticians agreed with this new analysis (new algorithm, version 2), the results of which are summarized in the table below.

Table 27 Change From Baseline at Each Visit in Mean Number of Leakage Episodes per Day (Day and Night Time): Ad-hoc Analysis (new algorithm, version 2), excluding data from Subject (b) (6), Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	30	3.16 (3.71)	21	1.11 (1.22)	51	2.59 (3.10)
Week 4, n | Mean (SD)	28	3.17 (3.80)	21	1.79 (1.70)	49	2.57 (3.13)
Change from Baseline, n†	28		21		49	
Mean (SD)	-1.76 (2.81)		-0.95 (1.48)		-1.41 (2.35)	
95% CI	(-2.8, -0.7)		(-1.6, -0.3)		(-2.1, -0.7)	
P value‡	0.003		0.008		< 0.001	
Week 24, n | Mean (SD)	26	2.76 (3.72)	21	1.79 (1.70)	47	2.32 (3.00)
Change from Baseline, n†	26		21		47	
Mean (SD)	-1.97 (3.17)		-0.98 (1.08)		-1.53 (2.49)	
95% CI	(-3.2, -0.7)		(-1.5, -0.5)		(-2.3, -0.8)	
P value‡	0.004		<0.001		< 0.001	
Week 52, n | Mean (SD)	26	2.97 (3.71)	21	1.79 (1.70)	47	2.44 (3.02)
Change from Baseline, n†	26		21		47	
Mean (SD)	-2.19 (3.41)		-1.05 (1.61)		-1.68 (2.79)	
95% CI	(-3.6, -0.8)		(-1.8, -0.3)		(-2.5, -0.9)	
P value‡	0.003		0.007		<0.001	

Patients who answered No to the e-diary question regarding leakage episodes are imputed with a '0' for that visit; Patients who answered Yes and the number is present, the number would be used; Patients who answered Yes and no number was present, then the number was set as "missing."
Data from Patient (b) (6) are excluded in this table due to the child's extreme values reported, which were later identified as an error in recording.
For results at other weeks (2, 8, 12 and 36), the reader is referred to Table 12.3.11.16.
† The number of patients with a non-missing change from baseline to analysis visit.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 12.3.11.16 submitted on December 22, 2020.

Reviewer's Comment: This final ad-hoc analysis (version 2) of change from baseline in mean number of leakage episodes per day (Day and Night Time), excluding the data from the one subject with the error in data recording, showed clinically meaningful decreases at all time points for all age groups. The children's group appeared to have a greater improvement in leakage episodes than the adolescent group (change of baseline across visits ranged from -1.13 to -2.28 episodes for the children vs -0.71 to -1.05 episodes for the adolescents). For all patients, the improvement from baseline ranged from -0.95 to -1.68 episodes across weeks 2 to weeks 52. The changes from baseline appeared to peak at week 36 for the children, week 52 for adolescents, and at weeks 36 and 52 for all patients.

- **Mean number of dry (leakage-free) days/7 days (day and night time)** showed clinically meaningful improvement in all three groups at all time points. Furthermore, the trend for values showed that at week 52, the mean change from baseline was stable or

increasing. As shown below in Table 28, after 24 weeks of treatment, children, adolescents, and all patients experienced on average an increase of 1.34, 2.17, and 1.65, respectively, in number of dry (leakage free) days per 7 days. These results were maintained at week 52, which showed either stable or slightly improved results compared to week 36.

Table 28 Change From Baseline to Weeks 4, 24 and 52 in Number of Dry (Leakage-free) Days per 7 Days (Day and Night Time) (FAS), Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	43	0.83 (2.08)	24	1.56 (2.41)	67	1.09 (2.21)
Week 4, n | Mean (SD)	42	1.53 (2.39)	25	2.84 (2.91)	67	2.02 (2.65)
Change from Baseline, n†	42		24		66	
Mean (SD)	0.68 (1.69)		1.36 (1.91)		0.92 (1.79)	
95% CI	(0.1, 1.2)		(0.6, 2.2)		(0.5, 1.4)	
P value‡	0.013		0.002		< 0.001	
Week 24, n | Mean (SD)	41	2.22 (2.54)	25	3.58 (3.17)	66	2.73 (2.85)
Change from Baseline, n†	41		24		65	
Mean (SD)	1.34 (2.18)		2.17 (2.38)		1.65 (2.27)	
95% CI	(0.7, 2.0)		(1.2, 3.2)		(1.1, 2.2)	
P value‡	< 0.001		< 0.001		< 0.001	
Week 52, n | Mean (SD)	40	2.10 (2.56)	25	3.83 (3.30)	65	2.77 (2.97)
Change from Baseline, n†	40		24		64	
Mean (SD)	1.38 (2.65)		2.14 (2.51)		1.67 (2.60)	
95% CI	(0.5, 2.2)		(1.1, 3.2)		(1.0, 2.3)	
P value‡	0.002		< 0.001		< 0.001	

For results at other weeks (2, 8, 12 and 36), the reader is referred to the Table 12.3.12.2.
† The number of patients with a non-missing change from baseline to analysis visit.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 30, p.88.

Reviewer's Comment: Bladder volumes and leakage measures reflect a patient's functional experience of their condition. Of the 6 secondary efficacy endpoints based on bladder volume and leakage measures, all endpoints showed clinically meaningful improvement at 4 weeks, 24 weeks, and 52 weeks in all patients (including ad-hoc analysis version 2 and excluding 1 child's erroneous data for mean number of leakage episodes per day [day and night]). Improvement as early as week 2 was seen in all 6 measures for the children. The pattern of improvement for the first 4 endpoints showed maximum improvement from baseline at weeks 24 and 36, with values appearing stable or slightly less improved at week 52. Without further data points past week 52, conclusions regarding trends in improvement at week 52 are difficult to make. For the final two endpoints, improvement was stable from approximately week 12 through week 52. Measures for which confidence intervals include 0 are likely due to small sample size. Overall, these findings,

which provide patient measured evidence of improvement in NDO, support the primary efficacy endpoint.

Secondary endpoints based on PROs

Four exploratory PROs were used to collect and assess patient and clinician reported efficacy endpoints.

- **Total Pediatric Incontinence Questionnaire Score** (PIN-Q) measured quality of life using an e-diary. The results showed mild improvement in quality of life scores for adolescents and all patients. The effect on children was slight. None of the results showed statistically significant changes from baseline.
- **Patient Global Impression of Severity Scale** asks the question "How did you feel about your bladder condition DURING THE PAST 3 DAYS?" and is scored with values correlating to "Really Bad" (0), "Bad" (1), "Not Bad, Not Good" (2), "Good" (3) and "Really Good" (4). There was an increase in mean change from baseline to weeks 24 and 52, which reflected subjective improvement in the patient's condition in all age groups, as summarized in Table 29 below.

Table 29 Change From Baseline to Weeks 24 and 52 in Total Patient Global Impression of Severity Scale Score (FAS), Study 178-CL-206A

Statistic	Children (3 to < 12 Years) n = 43		Adolescents (12 to < 18 Years) n = 25		All Patients (3 to < 18 Years) n = 68	
Baseline, n | Mean (SD)	28	2.25 (0.84)	22	2.36 (0.90)	50	2.30 (0.86)
Week 24, n | Mean (SD)	40	2.68 (0.89)	25	3.00 (0.71)	65	2.80 (0.83)
Change from Baseline, n†	25		22		47	
Mean (SD)	0.36 (1.22)		0.64 (1.00)		0.49 (1.12)	
95% CI	(-0.14, 0.86)		(0.19, 1.08)		(0.16, 0.82)	
P value‡	0.153		0.007		0.004	
Week 52, n | Mean (SD)	39	2.67 (0.77)	22	3.14 (0.83)	61	2.84 (0.82)
Change from Baseline, n†	24		19		43	
Mean (SD)	0.42 (1.21)		0.95 (1.18)		0.65 (1.21)	
95% CI	(-0.10, 0.93)		(0.38, 1.51)		(0.28, 1.02)	
P value‡	0.106		0.003		0.001	

Patient Global Impression of Severity Scale: score ranges from 0 (really bad) to 4 (really good).
† The number of patients with a non-missing change from baseline to week 24/week 52.
‡ From a 2-sided paired t-test, testing the null hypothesis that change from baseline is equal to 0.
Source: 178-CL-206A, Table 32, p. 91.

- **Total Clinician Global Impression of Change** results at weeks 24 and 52 showed that most patients responded that their condition was very much improved or much improved. Table 30 below provides a summary of the results.

Table 30 Total Clinician Global Impression of Change at Weeks 24 and 52 (FAS), Study 178-CL-206A

Statistic, n (%)	Children (3 to < 12 Years) n = 43	Adolescents (12 to < 18 Years) n = 25	All Patients (3 to < 18 Years) n = 68
Week 24			
n	41	24	65
Very Much Improved	6 (14.6%)	10 (41.7%)	16 (24.6%)
Much Improved	24 (58.5%)	7 (29.2%)	31 (47.7%)
Minimally Improved	6 (14.6%)	5 (20.8%)	11 (16.9%)
No Change	4 (9.8%)	1 (4.2%)	5 (7.7%)
Minimally Worse	1 (2.4%)	1 (4.2%)	2 (3.1%)
Much Worse	0	0	0
Very Much Worse	0	0	0
Week 52			
n	38	23	61
Very Much Improved	8 (21.1%)	9 (39.1%)	17 (27.9%)
Much Improved	23 (60.5%)	12 (52.2%)	35 (57.4%)
Minimally Improved	5 (13.2%)	1 (4.3%)	6 (9.8%)
No Change	2 (5.3%)	0	2 (3.3%)
Minimally Worse	0	0	0
Much Worse	0	1 (4.3%)	1 (1.6%)
Very Much Worse	0	0	0

Source: 178-CL-206A, Table 33, p. 92.

- **Acceptability for Tablets and Oral Solution** was assessed by the acceptability questionnaire. At week 24, almost all (92.5%) patients indicated the taste acceptability of tablets was "really good," "good" or "not bad, not good", which increased to 100% at week 52. Approximately 60% of patients rated swallow acceptability as "really easy" at weeks 24 and 52 [Table 12.3.16.1]. For the oral solution, the majority of patients (approximately 85%) considered the taste as "really good," "good" or "not bad, not good" at weeks 24 and 52. The smell was described by most patients (approximately 90%) as "really good," "good" or "not bad, not good." The ability to take and to prepare the oral solution was described as "really easy," "easy" or "not difficult, not easy" by almost all patients (≥ 92% and ≥ 96%, respectively) [Table 12.3.16.2].

Reviewer's Comment: The Patient Global Impression of Severity Scale and the Total Clinician Global Impression of Change seemed to support that for adolescents, patients and clinicians recognized an improvement in the condition at weeks 24 and 52. Patients also appeared to find the tablets and oral solution acceptable in terms of taste, swallowability and preparation.

Subpopulations

Subgroup analyses of change from baseline to week 24 (LOCF) in MCC were performed for the FAS by sex (male, female), race (White, Asian), and formulation subgroup (tablet formulation

and suspension formulation).

For analyses by sex, a clinically meaningful increase in MCC from baseline to week 24 (LOCF) was seen in both sexes in all age groups for the FAS (using ANCOVA model including sex and age groups as fixed effects, sex by age group as interaction term and baseline value as a covariable). The magnitude of the increase in MCC from baseline at week 24 trended higher in males than females.

Table 31 Subgroup Analysis of Change from Baseline to Week 24 (LOCF) in Maximum Cystometric Capacity (mL): Effect of Sex (FAS), Study 178-CL-206A

Statistic	Male		Female	
Children (3 to < 12 Years)				
Baseline, n | Mean (SD)	17	173.24 (109.83)	26	149.10 (83.93)
Week 24 LOCF, n | Mean (SD)	17	267.05 (169.06)	26	206.98 (90.90)
Change from Baseline, n†	17		26	
LS mean (SE)‡	93.92 (20.90)		58.15 (17.13)	
95% CI	(52.6,135.3)		(24.3, 92.0)	
P value§	< 0.001		< 0.001	
Adolescents (12 to < 18 Years)				
Baseline, n | Mean (SD)	15	236.46 (104.49)	10	242.61 (95.92)
Week 24 LOCF, n | Mean (SD)	15	358.12 (132.61)	10	343.14 (119.64)
Change from Baseline, n†	15		10	
LS mean (SE)‡	121.32 (22.51)		100.15 (27.52)	
95% CI	(76.8, 165.9)		(45.7, 154.6)	
P value§	< 0.001		< 0.001	
All Patients (3 to < 18 Years)				
Baseline, n | Mean (SD)	32	202.87 (110.38)	36	175.08 (95.92)
Week 24 LOCF, n | Mean (SD)	32	309.74 (157.56)	36	244.80 (115.80)
Change from Baseline, n†	32		36	
LS mean (SE)‡	106.77 (15.25)		69.82 (14.37)	
95% CI	(76.6, 136.9)		(41.4, 98.3)	
P value§	< 0.001		< 0.001	

† The number of patients with a non-missing change from baseline to week 24 LOCF.
‡ From an ANCOVA model including sex and age group as fixed effects, sex by age group as interaction term and baseline value as a covariate.
§ From the ANCOVA model, testing the null hypothesis that LS mean change from baseline is equal to 0.
Source: 178-CL-206A CSR, Table 16, p. 70.

Reviewer's Comment: The data suggests a trend that the treatment may be slightly more effective in males than females (though confidence intervals are overlapping); however, the changes in MCC were improved to a meaningful degree in both sexes.

For analyses by race, the increase in MCC from baseline to week 24 was greater in White patients than in Asian patients.

Table 32 Subgroup Analysis of Maximum Cystometric Capacity (mL) at Week 24 (LOCF) by Race (FAS), Study 178-CL-206A

Statistic	White Race		Asian Race	
All Patients (3 to < 18 years)				
Baseline, n | Mean (SD)	49	189.89 (108.97)	19	183.68 (88.94)
Week 24 LOCF, n | Mean (SD)	49	294.68 (149.00)	19	225.53 (99.81)
Change from Baseline, n	49		19	
Mean (SD)	104.79 (89.81)		41.84 (61.98)	
Median (min. max)	89.00 (-53.0, 321.0)		43.00 (-83.0, 180.0)	

Source: 178-CL-206A CSR, Table 17, p. 71.

Reviewer's Comment: Although the data appears to suggest that White patients realized a larger mean increase in MCC than Asian patients, conclusions regarding race are difficult to draw given the small size of the Asian subgroup.

For analyses by formulation subgroup, both subgroups showed increases in the primary endpoint with the tablet formulation subgroup increasing more than the suspension formulation (increases of 121.61 mL and 50.71 mL, respectively).

Table 33 Subgroup Analysis of Change from Baseline to Week 24 (LOCF) in Maximum Cystometric Capacity (mL) by Formulation (FAS)

Statistic	Tablets		Suspension	
Baseline, n | Mean (SD)	35	230.49 (106.75)	33	143.26 (78.29)
Week 24 LOCF, n | Mean (SD)	35	348.44 (145.13)	33	197.85 (80.83)
Change from Baseline, n†	35		33	
LS mean (SE)‡	121.61 (14.60)		50.71 (15.08)	
95% CI	(92.4, 150.8)		(20.6, 80.8)	
P value§	< 0.001		0.001	
P value¶	< 0.001		< 0.001	

† The number of patients with a non-missing change from baseline to week 24 LOCF.
‡ From an ANCOVA model including age group as fixed effect and baseline MCC as a covariate.
§ From the ANCOVA model, testing the null hypothesis that LS mean change from baseline is equal to 0.
¶ From Wilcoxon signed-rank test, testing the null hypothesis that median change from baseline is equal to 0.
Source: 178-Cl-206A CSR, Table 18, p. 71.

Reviewer's Comment: We agree with the Sponsor that the formulation subgroup analyses may be confounded by age because adolescents generally took tablets while children generally took the suspension formulation, per protocol as formulation was determined primarily by patient weight. In the adolescent group (N=31), 3 patients weighed < 35 kg, and all 3 were treated with the suspension; 28 patients weighed ≥ 35 kg and all 28 were treated with the tablet. In the children's group (N=55), 35 patients weighed < 35 kg, and all 35 were treated with suspension; 20 patients weighed ≥ 35 kg, and 1 was treated with the suspension while 19 were treated with the tablet.

Additional analyses performed for the FAS, with and without LOCF, showed no meaningful impact on the overall effect size in MCC of the following covariates:

- NDO medication at screening prior to washout
- Insufficient efficacy leading to discontinuation of antimuscarinics intended to treat NDO prior to start of treatment
- The presence of a positive urine culture at baseline and/or week 4 and/or week 24

Dose/Dose Response

For a description of the Sponsor's approach to dose selection, the reader is referred to Section 6.4.1.

The Sponsor conducted a dosing regimen analysis of change from baseline to week 24 in MCC for patients who took only PED25 (N=4) and those who started at 25mg and titrated up to 50 mg by week 8 (N=65). The analysis showed that, using ANCOVA methods and Wilcoxon signed-rank test, the group that titrated up to 50 mg improved their MCC at 24 weeks by 89 mL ($P < 0.001$ for both tests). However, the Sponsor also noted that the patients who took only 25 mg did not demonstrate statistically significant changes from baseline ($P = 0.343$ and $P = 0.250$ for the ANCOVA model and Wilcoxon signed rank test, respectively [178-CL-206A CSR, Table 12.3.1.8.3, p. 471]).

Reviewer's Comment: This study was not powered for analysis of efficacy of final titration dose (25 mg or 50 mg). Only 4 patients remained at PED25 for the duration of the study. In light of this, no exposure-response analyses were performed for efficacy. Therefore, we are unable to draw conclusions regarding the efficacy of different dosing regimens.

An IR was sent to the Sponsor on January 8, 2021 requesting clarification of how many patients remained on PED25 for the duration of the study. In the CSR for study 178-CL-206A, Table 12.2.1.1 (p. 276) states that the "Mira 25only dose group includes subjects maintained at mirabegron 25 mg for the whole study." The Mira 25only group column has N=17 patients. However, the same table shows that only 4 patients (3 patients taking the tablets and 1 patient taking the suspension) maintained the 25mg equivalent dose throughout the study.

The Sponsor responded and clarified that 17 patients started at 25 mg (PED25) but 13 of these patients discontinued the study within the first 14 days, before the first opportunity be up-titrated. So while they remained on 25 mg for the course of their treatment (which was no more than 2 weeks), their inclusion in this group did not reflect treatment for the duration of the study at a final dose determined by efficacy (as determined by the investigator, based on urodynamic study results or e-diary data) and safety/tolerability considerations. Only 4 patients of the Mira25 group (or "25 only" group) remained in that group and completed the study at a dose of PED25.

Onset, duration, and Durability of Response

The earliest time point at which efficacy was examined was different for different endpoints.

For the primary endpoint, the change from baseline in MCC was evaluated at one timepoint: 24 weeks. One of the secondary endpoints was change from baseline in MCC at week 4, designed to examine the onset of treatment efficacy. The results showed that the effect of mirabegron treatment on MCC compared to baseline for all patients was evident after 4 weeks of treatment (increase of 55.53 mL) and was sustained though 24 weeks of treatment (increase of 87.20 mL).

For the secondary endpoints of change from baseline in other urodynamic measurements (excluding MCC at 4 weeks, mentioned above), data were collected and analyzed for timepoints at 4 and 24 weeks. The onset of the response to treatment with mirabegron for these endpoints in all patients was as early as 4 weeks for bladder compliance (adolescents only), detrusor pressure (children and all patients), bladder volume until first detrusor contraction > 15 cm H_2O (children and all patients). Efficacy was shown for all endpoints at 24 weeks (both age groups and all patients).

For secondary endpoints of change from baseline in the various bladder volume and leakage measures recorded by the patient in an e-diary, data were collected and analyzed at weeks 2, 4, 8, 12, 24, 36, and 52 weeks. Improvement as early as week 2 was seen in only 3 of the 6 measures for the children; however, for adolescents and all patients, all measures showed improvement by week 2 except for mean maximum catheterized daytime volume in the adolescents and mean average morning catheterized volume in all patients. By week 4, all endpoints showed statistically significant improvement, with continued significantly significant improvement at 24 weeks and 52 weeks in all patients (including ad-hoc analysis version 2 and excluding 1 child's data for mean number of leakage episodes per day [day and night]).

For secondary endpoints based on PRO questionnaires, data were collected and analyzed at weeks 24 and 52. As noted in the related sections above, for the Patient Global Impression of Severity Scale and the Total Clinician Global Impression of Change showed adolescents, all patients and clinicians recognized an improvement in the condition at week 24 that was maintained at week 52.

Reviewer's Comment: Overall, a majority of endpoints showed efficacy of response by week 4 and durability of response at week 52. For the subset of secondary endpoints for which data were collected before week 4 (bladder volume and leakage parameters), a response was generally evident as early as week 2 and remained strong through week 52.

7 Integrated Review of Effectiveness

7.4 Assessment of Efficacy Across Trials

Because there is only one study submitted for review in support of efficacy for this application, the reader is referred to the previous section, section 6, for a full review of efficacy for this study.

7.5 Additional Efficacy Considerations

7.5.1 Considerations on Benefit in the Postmarket Setting

Because the overall study population was small (n=91 enrolled, n=68 in the FAS) and included very small numbers of subjects from different racial subgroups, efficacy in various racial subgroups of pediatric patients with NDO is unknown.

7.5.2 Other Relevant Benefits

Mirabegron oral suspension is a once daily medication for NDO that has shown efficacy in clinical trials in pediatric patients as young as 3 years old. The first approved treatment for pediatric patients with neurogenic bladder, oxybutynin, is dosed 2-3 times a day and is approved for patients age 5 years and older. The second approved treatment, solifenacin oral suspension, was approved in May, 2020 for pediatric patients as young as 2. It has once daily dosing that is convenient for patients and caregivers and may lead to improved adherence and efficacy. The third and final approved treatment is onabotulinumtoxin A, is a more invasive option that is an intradetrusor injection intended for patients who have failed or who cannot tolerate anticholinergic therapy. Mirabegron tablets and suspension provides a third oral therapy option that shows efficacy in the youngest children (as young as 3), has once daily dosing, and has a different side effect profile than the anticholinergic medications.

In addition, while not an efficacy benefit, the safety findings described in subsequent sections of this review, shows no reports of neuropsychiatric AEs. In light of concerns that oxybutynin, and anticholinergics as a class, may be associated with adverse CNS effects, the results of this study could provide additional support for mirabegron oral suspension as an alternative treatment for pediatric patients with NDO.

7.6 Integrated Assessment of Effectiveness

Through the achievement of both the primary and secondary efficacy endpoints, substantial evidence of effectiveness has been demonstrated for mirabegron in the treatment of pediatric patients with NDO ages 3 to <18 years.

Study 178-CL-206A studied patients with NDO who had been practicing CIC technique. In these patients, an overall mean change in MCC of 87 mL was shown at 24 weeks of treatment with mirabegron oral suspension and tablets. The clinical meaningfulness of these results is supported by the secondary efficacy analyses, which showed improvements in urodynamic parameters (such as maximum cystometric capacity improvement at week 4 and bladder compliance, the number of overactive detrusor contractions until end of bladder filling, bladder, and detrusor pressure at end of bladder filling at weeks 4 and 24) and e-diary reported clinical measures (such as maximum catheterized volume per catheterization, average catheterized volume per catheterization, maximum catheterized daytime volume, average morning catheterized volume, mean number of leakage episodes per day (day and night time), and number of dry (leakage-free) days per 7 days (day and night time).

These findings appeared to be durable for over the fixed dose period out to 52 weeks of treatment. No clear gender or age differences in efficacy were noted. In regard to subgroup analysis, the change from baseline to 24 weeks in MCC appeared to be greater in White pediatric NDO patients than in Asian NDO patients, although this finding was observed in an exploratory subgroup analysis that pooled data from all ages, was conducted in a generally small overall population (n=91), included small number of subjects in each subgroup category (n=49 vs n=19), and included data which had wide variability as demonstrated by large standard deviations on the means. For these reasons, the clinical meaningfulness of this finding is unclear.

Finally, mirabegron oral suspension and tablets has an effect on important clinical endpoints that may exceed the demonstrated effects of the two current approved first-line oral therapies, oxybutynin and solifenacin. Oxybutynin syrup and solifenacin oral suspension are approved for patients with NDO ages 5 and older and 3 and older, respectively. While many of the secondary efficacy endpoints in the oxybutynin studies were slightly different from the secondary efficacy endpoints in the Phase 3 studies for solifenacin oral suspension and mirabegron oral suspension and tablets in pediatric NDO patients, the increase from baseline to 24 weeks in MCC was used as a measure of efficacy for all three drug therapies. For oxybutynin syrup, the mean change from baseline (230 mL) to 24 weeks (279 mL) was 49 mL, and for solifenacin oral suspension, the mean change from baseline (224 mL) to 24 weeks (279 mL) was 55 mL. For mirabegron oral suspension and tablets, the mean increase in MCC from baseline (188 mL) to 24 weeks (275 mL) was larger: 87 mL, although caution is advised when comparing efficacy results across studies.

8 Review of Safety

8.4 Safety Review Approach

The Sponsor's pediatric clinical development program includes: 2 pharmacokinetic Phase 1 studies (178-CL-202 and 178-CL-203) in patients with NDO and OAB symptoms and 1 Phase 3 study in patients with NDO (178-CL-206A). Data for pediatric patients with OAB symptoms are considered supportive for the understanding of safety for the proposed U.S. indication of pediatric patients with NDO. Bioavailability studies (178-CL-201 and 178-CL-208) were also performed in healthy adult volunteers. The clinical development program was conducted globally in 20 countries.

The safety analysis was performed for each study separately, without pooling of safety data across studies. The safety analysis set (SAF) of each study included patients who received at least 1 dose of mirabegron tablets or oral suspension.

8.5 Review of the Safety Database

8.5.1 Overall Exposure

For the entire mirabegron pediatric development program, of the 129 total patients (with NDO or OAB symptoms) who received mirabegron, 43 received a single dose and 86 received multiple doses of mirabegron oral suspension or tablets. Of those 129 patients, 103 had NDO. Table 34 below provides an overview of the SAF according to age group, condition, and dose regimen.

Table 34 Pediatric Studies Safety Population in the Mirabegron Pediatric NDO Development Program

Patient Indication Age Group Study	Number of Patients Dosed With Mirabegron		
	Single dose	Multiple Dose	Any Dose
Pediatric patients with NDO or OAB symptoms	**43**	**86**	**129**
Pediatric patients with NDO	**17**	**86**	**103**
Children (3 to < 12 years)	12	55	67
Phase 3 Study 178-CL-206A	-	55	55
Supportive Phase 1 Study 178-CL-202	6	-	6
Supportive Phase 1 Study 178-CL-203	6	-	6
Adolescents (12 to < 18 years)	5	31	36
Phase 3 Study 178-CL-206A	-	31	31
Supportive Phase 1 Study 178-CL-202	5	-	5
Supportive Phase 1 Study 178-CL-203	0	-	0
Pediatric patients with OAB symptoms	**26**	-	**26**
Children (3 to < 12 years)	16	-	16
Supportive Phase 1 Study 178-CL-202	13	-	13
Supportive Phase 1 Study 178-CL-203	3	-	3
Adolescents (12 to < 18 years)	10	-	10
Supportive Phase 1 Study 178-CL-202	10	-	10
Supportive Phase 1 Study 178-CL-203	0	-	0

Source: Summary of Clinical Safety, Table 1, p 7.

For the Phase 3 study 178-CL-206A, the median duration of treatment was 302.6 days with a range of 293.7 (children) to 318.6 (adolescents) days. A majority of patients who received multiple doses continued treatment for ≥ 364 days, and >75% of patients continued treatment for ≥ 252 days. All but 4 patients in study 178-CL-206A were up-titrated to a PED50 by week 8 of the 12-week titration period. The reader is referred back to Table 12 in section 6.4.2 for a summary of study drug exposure and treatment compliance, as well as Table 11 for a summary of drug dosing exposure.

Overall for the Phase 1 pediatric studies, a total of 43 patients received a single dose of study drug: 34 patients (11 with NDO and 23 with OAB symptoms) in study 178-CL-202 and 9 patients (6 with NDO and 3 with OAB symptoms) in study 178-CL-203.

For the Phase 1 bioavailability studies, a total of 49 healthy adults received a single dose of the study drug: 25 in 178-CL 201 and 24 in 178-CL-208.

8.5.2 Relevant characteristics of the safety population

The demographic characteristics in the SAF of study 178-CL-206A are described as predominantly female (54.7%); White (72.1%) and Asian (23.3%) with some Hispanic or Latino (3.5%); the age (mean±SD) of the population was 10.1±3.7 years; the mean weight (SD) was 29.83 (13.41) kg in children 3 to < 12 and 50.96 (13.78) kg in adolescents 12 to <18 years. A majority of patients (55 [64%]) were children aged 3 to <12 while 31(46%) patients were adolescents aged 12 to <18.

The demographic characteristics of the supportive Phase 1 studies were described in the CSRs for the individual studies. For 178-CL-202, the SAF was predominantly female (67.6%) and all were White. The median age was 10 years (range 7 to 17 years) and the mean weight (SD) was 29.73 (5.37) kg in children 3 to <12 and 53.31 (11.27) kg in adolescents aged 12 to <18. (14.50) kg. A majority of patients (19[56%]) were children and 15(44%) were adolescents. Eleven (32%) of the patients had NDO, 23 (68%) had OAB symptoms. For 178-CL-203, the study population consisted of a total of nine (9) children and no adolescents: 5 (56%) were female, all were White. The median age was 8 years (range 4 to 10) and the mean weight (SD) was 25.92 (8.80) kg. Six patients (67%) aged 3 to <12 years had NDO, and 3 patients (33%) aged 5 to <12 years had OAB.

Reviewer's Comment: With the exception of those patients in the Phase 1 studies who had OAB symptoms and not NDO, baseline characteristics were similar across the three studies included in the SAF.

8.5.3 Adequacy of the safety database

The extent of the safety database was determined by the relative infrequency of this condition in the population, especially in the United States. As mentioned in relevant earlier sections of this review, there is no reason to expect region-based differences in the underlying etiologies contributing to NDO or the clinical management of NDO, nor race-based differences in drug exposure or pharmacology for mirabegron oral suspension or tablets in the pediatric NDO or population with OAB symptoms. Therefore, the data in this this program, which did not include US patients or a racially diverse population, can be generalized to pediatric patients of diverse races with NDO in the US, and does not raise concerns regarding the adequacy of the safety database.

8.6 Adequacy of Applicant's Clinical Safety Assessments

8.6.1 Issues Regarding Data Integrity and Submission Quality

The overall quality of the submission was good. The information was well organized and readily located. The Sponsor implemented and maintained quality assurance and quality control

systems, performed audits, and conducted periodic monitoring site visits. No evidence of compromised data was found.

8.6.2 Categorization of Adverse Events

The Sponsor's process for recording, coding and categorizing AEs, as well as their approach to safety analyses, were reasonable and appropriate.

8.6.3 Routine Clinical Tests

Details of the routine clinical testing, including various clinical laboratory tests, are reviewed in the related sections of this review, and this testing was adequate.

8.7 Safety Results

The Sponsor analyzed the incidence of TEAEs in the two age groups (children and adolescents) and in all patients combined. Table 35 below provides an overview of the TEAEs from study 178-CL-206A. Overall, TEAEs were reported with a similar frequency in the children and adolescents (60.0% vs 58.1%) and in all patients (59.3%). TEAEs assessed by the investigator to be possibly or probably related were reported in 14.5% of the children, 19.4% of the adolescents, and 16.3% of all patients.

There were no deaths reported.

Overall, for all patients, serious TEAEs were reported in 16.3% with similar frequency in children (16.4%) and adolescents (16.1%). According to assessments by the investigator, none of these serious TEAEs were drug-related. Similarly, TEAEs in general were considered by the investigator to be possibly or probably related to the study drug in only 13 (15.1%) and 1 (1.2%) of patients, respectively. A small number (3) of children experienced TEAEs leading to permanent discontinuation; 2 of those 3 children had TEAEs assessed by the investigator to be drug-related.

Table 35 Overview of Treatment-emergent Adverse Events (SAF); Study 178-CL-206A

Incidence of TEAE/Number of TEAE	Children (3 to < 12 Years) n = 55		Adolescents (12 to < 18 Years) n = 31		All Patients (3 to < 18 Years) n = 86	
	n (%)	Events	n (%)	Events	n (%)	Events
TEAE	33 (60.0%)	78	18 (58.1%)	61	51 (59.3%)	139
Drug-related† TEAE	8 (14.5%)	12	6 (19.4%)	8	14 (16.3%)	20
Serious TEAE‡	9 (16.4%)	10	5 (16.1%)	9	14 (16.3%)	19
Drug-related† Serious TEAE‡	0	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0	0
Drug-related† TEAE Leading to Death	0	0	0	0	0	0

TEAE Leading to Permanent Discontinuation	3 (5.5%)	3	0	0	3 (3.5%)	3
Drug-related† TEAE Leading to Permanent Discontinuation	2 (3.6%)	2	0	0	2 (2.3%)	2
Death§	0	0	0	0	0	0

All patients who received ≥ 1 dose of study drug (SAF).
A treatment-emergent adverse event was defined as an adverse event with date of onset occurring on or after the first dose of study medication and up to the end of study.
SAF: safety analysis set; TEAE: treatment-emergent adverse event.
† Possible or probable, as assessed by the investigator, or records where relationship is missing.
‡ Includes serious TEAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.
§ All reported deaths after the first study drug administration.
Source: 178-CL-206A, Table 34, p. 96.

The table below provides an overview of the TEAEs in the Phase 1 studies 178-CL-202 and 178-CL-203. In these Phase 1 studies, there were no deaths, no serious TEAEs, and no TEAEs leading to discontinuation. Overall, in study 178-CL-202, TEAEs were reported with a similar frequency in children and adolescents (2 [10.5%] vs 2 [13.3%]) and in all patients (4[11.8%]). In study 178-CL-203, which included only children, TEAEs occurred in 1(11.1%) patient. TEAEs that were assessed by the investigator to be possibly or probably related were reported in only one adolescent in study 178-CL-202. There were no drug-related TEAEs (per the investigator) in study 178-CL-203.

Table 36 Overview of TEAEs and Death (SAF); Studies 178-CL-202 and 178-CL-203

	Study 178-CL-202†						Study 178-CL-203‡
Incidence of TEAE	Cohort 1 Adolescents (12 to < 18 Years) Low Dose Fed (n = 7) n (%)	Cohort 2 Children (5 to < 12 Years) Low Dose Fed (n = 7) n (%)	Cohort 3 Adolescents (12 to < 18 Years) High Dose Fed (n = 8) n (%)	Cohort 4 Children (5 to < 12 Years) High Dose Fed (n = 6) n (%)	Cohort 5 Children (5 to < 12 Years) High Dose Fasted (n = 6) n (%)	Total (5 to < 18 Years) (n = 34) n (%)	Total/ Children (3 to < 12 Years) Fed (n = 9) n (%)
TEAE	1 (14.3)	1 (14.3)	1 (12.5)	0	1 (16.7)	4 (11.8)	1 (11.1)
Drug-related§ TEAE	0	0	1 (12.5)	0	0	1 (2.9)	0
Death	0	0	0	0	0	0	0
SAE¶	0	0	0	0	0	0	0
Drug-related§ SAE¶	0	0	0	0	0	0	0

All subjects who took the dose of study medication (SAF).
SAE: serious adverse event.
† In Study 178-CL-202, patients received mirabegron extended-release tablets. Low dose was 25 mg (body weight between 20.0 to < 55.0 kg) or 50 mg (body weight ≥ 55.0 kg). High dose was 50 mg (body weight 20.0 to < 40.0 kg) or 75 mg (body weight ≥ 40.0 kg).
‡ In Study 178-CL-203, patients received mirabegron oral suspension formulation B (granules were

reconstituted with water to prepare a suspension with a concentration of 2 mg/mL). Dose was 40 mL suspension (body weight 15 to 19 kg), 50 mL suspension (body weight 20 to 29 kg), 55 mL suspension (body weight 30 to 39 kg) or 65 mL suspension (body weight > 40 kg).
§ Possible or probable, as assessed by the investigator, or records where relationship is missing.
¶ Includes SAEs upgraded by the Sponsor based on review of the Sponsor's list of always serious terms, if any upgrade was done.
Source: Summary of Clinical Safety, Table 8, p. 18.

8.7.1Serious Adverse Events

A total of 19 SAEs were reported in 14 (16.3%) of patients: 9 (16.4%) children and 5 (16.1%) of adolescents. The only SAE reported in more than one patient was device malfunction (dysfunction of ventriculo-peritoneal shunt), which was reported in 2 children. Another occurrence of device malfunction, shunt malfunction, was reported by 1 adolescent. These three device malfunction PTs are categorized in two SOCs, General Disorder of Administration Site Conditions (device malfunction) and Injury, Poisoning and Procedural Complications (shunt malfunction). Table 37 provides a summary of the SAEs in the Phase 3 study 178-CL-206A, and shows the diverse nature of the reported SAEs, as well as their incidence in the different age groups.

Table 37 Serious TEAEs (SAF); Study 178-CL-206A

MedDRA v16.0 System Organ Class Preferred Term	Children (3 to < 12 Years) n = 55		Adolescents (12 to < 18 Years) n = 31		All Patients (3 to < 18 Years) n = 86
	n (%)	Patient ID/Link to Narrative	n (%)	Patient ID/Link to Narrative	n (%)
Overall	**9 (16.4)**		**5 (16.1)**		**14 (16.3)**
Congenital, Familial and Genetic Disorders					
Talipes	1 (1.8)	(b) (6)	0	--	1 (1.2)
Gastrointestinal Disorders					
Colitis	0	--	1 (3.2)	(b) (6)	1 (1.2)
General Disorders and Administration Site Conditions					
Device malfunction	2 (3.6)	(b) (6)	0	--	2 (2.3)
Pyrexia	0	--	1 (3.2)	(b) (6)	1 (1.2)
Infections and Infestations					
Appendicitis	0	--	1 (3.2)	(b) (6)	1 (1.2)
Bronchitis	1 (1.8)	(b) (6)	0	--	1 (1.2)
Escherichia urinary tract infection	0		1 (3.2)	(b) (6)	1 (1.2)
Pneumonia bacterial	1 (1.8)		0	--	1 (1.2)
Pyelonephritis acute	1 (1.8)		0	--	1 (1.2)
Viral infection	1 (1.8)		0	--	1 (1.2)
Injury, Poisoning and Procedural Complications					
Shunt malfunction	0	--	1 (3.2)	(b) (6)	1 (1.2)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)					

Benign neoplasm of skin	1 (1.8)	(b) (6)	0	--	1 (1.2)
Nervous System Disorders					
Convulsion	0	--	1 (3.2)	(b) (6)	1 (1.2)
Hydrocephalus	0	--	1 (3.2)		1 (1.2)
Renal and Urinary Disorders					
Urethral perforation	1 (1.8)	(b) (6)	0	--	1 (1.2)
Reproductive System and Breast Disorders					
Epididymitis	0	--	1 (3.2)	(b) (6)	1 (1.2)
Skin and Subcutaneous Tissue Disorders					
Rash generalised	0	--	1 (3.2)	(b) (6)	1 (1.2)
Surgical and Medical Procedures					
Talipes correction	1 (1.8)	(b) (6)	0	--	1 (1.2)

--: not applicable; ID: identification.
Source: Summary of Clinical Safety, Table 6, p. 15.

Reviewer's Comment: The limited number and diverse nature of the SAEs make it difficult to appreciate differences in SAE incidence across age groups.

Table 38 shows the SAEs reported for the patients in 178-CL-206A. All the SAEs were determined by the investigator to be not related to the study drug. Ten (10) SAEs occurred in 9 children, and 9 SAEs occurred in 5 adolescents.

Table 38 Serious Treatment-emergent Adverse Events (SAF)

Patient Number	Age/ Sex†	MedDRA (v16.0) Preferred Term (investigator's verbatim term)	Last Dose Day	Onset/ Stop Day	Outcome	Relationship to Study Drug*
Children (3 to < 12 years)						
(b) (6)	6/F	Bronchitis (worsening of acute obstructive bronchitis)	80	62/66	Recovered/Resolved	Not related
		Pneumonia bacterial (acute bacterial pneumonia)	80	81/90	Recovered/Resolved	Not related
	7/F	Device malfunction (ventriculoperitoneal shunt dysfunction)	379	359/370	Recovered/Resolved	Not related
	10/F	Pyelonephritis acute (acute pyelonephritis)	364	72/83	Recovered/Resolved	Not related
	11/M	Urethral perforation (false route in urethra worsening)	362	111/122	Recovered/Resolved	Not related
	9/M	Talipes (worsening of walking difficulties [due to Pes Calcaneovalgus)]	356	326/329	Recovered/Resolved	Not related
	5/M	Device malfunction (dysfunction of ventriculo-peritoneal shunt)	365	28/30	Recovered/Resolved	Not related
	10/F	Talipes correction (clubfoot correction left)	374	182/275	Recovered/Resolved	Not related
	6/M	Viral infection (systemic viral infection)	371	301/308	Recovered/Resolved	Not related

(b) (6)	6/F	Benign neoplasm of skin (benign scalp tumor)	365	103/106	Recovered/Resolved	Not related
Adolescents (12 to < 18 years)						
(b) (6)	17/M	Colitis (segmental colitis)	364	202/218	Recovered/Resolved	Not related
	15/M	Shunt malfunction (shunt failure)	376	307/NR	Not recovered/ Not resolved	Not related
		Hydrocephalus (hydrocephalus with shunt failure)	376	307/NR	Not recovered/ Not resolved	Not related
		Convulsion (seizure)	376	320/NR	Recovering/Resolving	Not related
	16/M	Pyrexia (fever)	364	86/104	Recovered/Resolved	Not related
		Escherichia urinary tract infection (*E. coli* urinary tract infection)	364	108/136	Recovered/Resolved	Not related
		Epididymitis (acute bilateral epididymitis)	364	181/252	Recovered/Resolved	Not related
	13/F	Appendicitis (appendicitis)	364	141/144	Recovered/Resolved	Not related
	12/M	Rash generalised (full body rash NOS)	364	31/33	Recovered/Resolved	Not related

NOS: not otherwise specified; NR: not reported.
† Age (years) at screening
*as assessed by the investigator.
Source: 178-CL-206A, Table 36, p. 98.

Below are narratives for patients who were treated with mirabegron and experienced SAEs. For each narrative the SAE is presented in bold type. For those cases that also include AEs of Special Interest or AEs that resulted in discontinuation, text to describe those AEs is included.

Four (4) of the SAEs are of particular interest: urologic infection (pyelonephritis, *E.Coli* UTI), structural damage to the urinary tract (urethral perforation), or hypersensitivity (generalized rash). The complete narratives for these 4 patients are presented below.

Case (b) (6) is a 10-year old white female from Croatia with a history of NDO of unknown cause, vesicouretheral reflux, acute kidney injury, chronic pyelonephritis, and chronic kidney disease, who was taking mirabegron 50 mg when she experienced the SAE **acute pyelonephritis** on study day 72. Prior to developing the SAE, her medications included cefixime as prophylaxis for UTI (until day 35), cefixime for UTI treatment (until day 44), nitrofurantoin for another UTI (day 51-61), and UTI prophylaxis with nitrofurantoin until day 73.
Lab tests performed on day 71 included a CBC (presented without normal ranges), a urinalysis with 3+ bacteria, and a urine culture that was positive for *Klebsiella pneumonia*. The next day, the patient became febrile, the urine appeared "blurred" during CIC, the patient was hospitalized, and the serious adverse event (SAE) of acute pyelonephritis was reported. The patient was treated with IV cefepime for 10 days, and ferrous fumarate (previously started for mild microcytic anemia). On day 80, lab results included a normal UA and a sterile urine culture. Treatment with mirabegron was not interrupted and the dose was not changed in response to the event. The SAE of acute pyelonephritis resolved on day 83, and the patient was discharged from the hospital that day.

Reviewer's Comment: This is a patient with a history of chronic pyelonephritis maintained on frequent UTI prophylaxis. The patient's underlying condition puts her at high risk for recurrent acute urinary tract infection, including UTI and pyelonephritis. For these reasons, we assess pyelonephritis as not likely related to the study drug.

Case (b) (6) is a 16-year old Asian male from Malaysia with a history of premature birth at 30 weeks, thoracic ½ diastomyotomelia, paraplegia, NDO, UTIs, chronic lung disease, history of gastric perforation with repair, pyloric stenosis, patent ductus arteriosus, neonatal fits/convulsions, bilateral congenital hydroceles treated with bilateral herniotomies, thoracic scoliosis, GERD, constipation, allergy to Augmentin, bilateral hip subluxation, and left gluteal chronic bedsores. On day 86, the patient developed the SAE of **pyrexia/fever** of 38.5, had chills and rigors with a BP of 128/85 mm Hg and HR of 113 bpm and was hospitalized. Physical exam and review of symptoms was reported otherwise to be normal, with "no abdominal pain or diarrhea, no urinary symptoms, cough, running nose or rashes, lungs were clear, cardiovascular system showed dual rhythm no murmur and p/a was soft." WBC was elevated at 12800/mm^3 (normal range not provided), and blood culture and urine culture and sensitivity were negative. Initially, the patient was treated with IV cefuroxime and oral paracetamol. The fever persisted, and antibiotics were changed to IV meropenem 1 g every 8 hours (day 92 to day 101). On day 92, ESR was 105 mm/hour and urine and blood cultures remained negative. Ultrasound showed bilateral lobulated and calcified lesions in the psoas major muscles with no hydronephrosis. The patient became afebrile. On day 93, CT showed bilateral multilobulated psoas collections with a gibbus deformity of the L1 vertebra; lobulated lesions in the bladder; and bilateral hydronephrosis and hydroureters. On day 94, a cystoscopy showed a trabeculated bladder with cystitis at the dome of the posterior wall and dome of the bladder. On day 96, a magnetic resonance imaging of the whole spine showed a gibbus deformity of the L1 vertebra with spondylitis; L1 and L2 discitis with bilateral psoas collection, paravertebral and right posterior paraspinal muscle inflammation and spinal cord stenosis.
The patient was discharged from the hospital on an unspecified date that month (prior to day 99). Treatment with mirabegron was not interrupted, and the dose was not changed in response to the event. The SAE of pyrexia/fever resolved on day 104. The final diagnosis was determined to be pyrexia of unknown origin.

Two days later, on day 106, the patient was admitted with chills and rigors, and on day 107, the patient complained of chills, but no fever or other symptoms were reported; WBCs 10480/mm^3 (normal range not provided). The next day, urine culture grew *E.coli,* the patient experienced a fever, and the SAE of ***E.coli* urinary tract infection** was diagnosed. On day 112, the patient started treatment with oral sulfamethoxazole trimethoprim 960 mg every 8 hours and was discharged from the hospital. Treatment was continued until day 136, when the *E.coli* UTI was determined to be resolved. On day 113, a Bactec blood culture found that no mycobacterium tuberculosis was isolated.

Also on day 112, the patient also experienced the nonserious adverse event of fungal infection in both groins. Treatment was started with topical miconazole weeks later (on day 144) and continued until the fungal infection in both groins was resolved, on day 151. The study drug was not interrupted, and the dose was not changed in response to the events. The fungal infection was mild in intensity and considered to be not related to treatment by the investigator.

On day 181, the patient developed the SAE of **acute bilateral epididymitis** and was hospitalized. The patient complained of fever (temperature not specified), experienced swelling and redness of the left scrotum, and an ultrasound confirmed bilateral epididymitis (worse on the left side). The next day (day 182), the patient (alert and conscious) was admitted to the hospital for treatment of an edematous left scrotum. Another ultrasound of the scrotum confirmed bilateral epididymitis, worse on the left side, with reactive hydrocele. Urine culture and sensitivity were performed, but the results were not reported. The final diagnosis was left epididymo-orchitis with underlying neurogenic bladder. The patient was treated with IV ceftriaxone for two days and then oral ciprofloxacin. The fever resolved, and the patient was discharged from the hospital on day 185. Oral ciprofloxacin was continued through day 206. The SAE of acute bilateral epididymitis was reported to be resolved on day 252. On an unknown date it was reported the patient was asymptomatic, had no scrotal pain, but a bilateral hydrocele was present. Mirabegron was not interrupted during the course of this SAE, and the dose was not changed in response to the event.

On day 241, the patient developed **dermatitis** at neck, an Event of Interest. Treatment was started with topical vitamin E, grape, and hyaluronate sodium (Atopiclair). Mirabegron was not interrupted and the dose was not changed in response to the event. On an unspecified date, the dermatitis was reported as not resolved.

The list of concomitant medications for treatment was extensive and included in the narrative. As needed and ongoing medications included: lactulose for constipation (ongoing); glycerine enema (intermittently) for constipation; and prednisolone for prophylaxis against contrast allergy.

Reviewer's Comment: This is an extensive narrative of a patient who experienced a number of AEs, including three separate SAEs of particular interest (E.coli UTI, acute bilateral epididymitis [left epididymo-orchitis], and pyrexia) and one AE of special interest, dermatitis. The patient continued treatment with mirabegron throughout treatment for all these AEs. Regarding the pyrexia of unknown origin: and extensive workup was performed. White cell count appeared to be mildly elevated (but no normal range was provided) and ESR was elevated. Although cultures were negative, the patient was treated with antibiotics. Cystoscopy showed chronic bladder changes (trabeculated bladder) and cystitis. While CT imaging showed chronic boney changes in the spine and findings in the urinary tract consistent with cystitis and bilateral hydronephrosis and hydroureter, it also showed "bilateral multilobulated psoas collections." It is unclear what was meant by this finding, but a retroperitoneal fluid collection could certainly be the source of the fever. Overall, based on the evidence presented, and the resolution of the fever with meropenem, we assess the fever to be related to an infectious cause, and we consider the SAE pyrexia to be not related to treatment with mirabegron.

Regarding the E.coli UTI and acute bilateral epididymitis: the patient's history of NDO predisposed him to these two SAEs. Our assessment is that mirabegron and these SAEs are not likely causally related.

Regarding the AE of special interest, dermatitis: very little information is available for this AE, and there is no report of resolution (date of that assessment was not recorded) with the continuation of mirabegron. Based on what little information is provided, we consider this case unassessable.

Case (b) (6) is an 11-year old White male from Denmark with a history of spinal dysraphism, closure of spina bifida, and NDO, who developed difficulties with CIC starting on day -2. On an unspecified day 1.5 to 2.5 months into the study, an intravesical catheter was inserted to create a fausse (false) route. Difficulties with CIC increased, and Mitrofanoff Channel (cystoenterocutaneostomy) insertion procedure was planned. However, on day 111, sometime before the planned procedure, the patient developed the SAE of **false route in urethra worsening/urethral perforation** and was hospitalized. On day 112, the intravesical catheter was removed, and a Mitrofanoff Channel was inserted successful; CIC was subsequently performed through the Mitrofanoff Channel. The SAE of false route in urethra worsening resolved on day 122, and the patient was discharged from the hospital that day.

Concomitant medications included: ongoing nitrofurantoin for UTI prophylaxis and piperacillin/tazobactam (IV) for pseudomonas colonization (day 111 to 122).

Reviewer's Comment: This case lacks detail regarding the days leading up to hospitalization, during which the patient was having worsening of his baseline difficulties with CIC. Although the patient was taking mirabegron without interruption throughout the study and a temporal relationship exists between study drug exposure and this AE, it is more likely that the urethral perforation was caused by urethral trauma sustained by the patient in the course of attempting CIC, as difficulties with CIC had been increasing. Based on the course of events and the stated challenges of CIC prior to hospitalization, we consider this SAE not related to the study drug.

Case (b) (6) is a 12-year old male from Israel with a history of spinal dysraphism, lipomyelomeningocele, tethered cord "ayndron" (syndrome) treated twice with surgery to untether the spinal cord, NDO, intermittent fecal incontinence, and walking problems with mild inversion of feet. On day 31, the patient developed the SAE of **rash generalized**/full body rash NOS, fever (38ºC), peripheral edema, and erythematous skin lesions. He was hospitalized. He was treated with dimetindene drops, and the study drug was interrupted. The fever, edema, and rash resolved on day 33. That same day, dimetindene drops were discontinued, and the patient was discharged from the hospital. The investigator consulted with an allergy specialist, and it was decided to rechallenge the patient to study drug at a reduced dose (25 mg). On day 42, the patient was given mirabegron while in the clinic and was supervised for several hours. That day, the mean vital sign results were BP 102.7/63.7 mm Hg and pulse rate 63.7 beats per minute. The dose of study drug was uptitrated to 50 mg per day at the next planned visit (day 50). Of note, the narrative states that the patient's siblings were also sick, had presented with fever, and then some of them later developed a rash.

Later in the study, on day 168, the patient was reported to have **bradycardia** (AE of special interest, mild) and **diastolic hypotension** (nonserious, mild AE). Vital sign measurements during the study were as follows:

Baseline mean values: 112/66 mm Hg, HR 58 bpm.
Day 42 mean values: 102.7/63.7 mm Hg, HR 63.7 bpm.
Day 168 mean values: BP 107.3/50.3 mm Hg, HR 55.3 bpm.
Day 364 (week 52) mean values: 99/55.7 mm Hg and 61.7 bpm.

No treatment was required for any of the vital sign abnormalities, and mirabegron treatment was not interrupted after day 42.

Concomitant medications included only dimetindene for rash.

Reviewer's Comment: The narrative for this case had two parts – the first to describe the SAE rash generalized, and the second was drafted in response to an FDA IR regarding the bradycardia and diastolic hypotension AEs. Regarding the rash generalized AE: while a temporal relationship between treatment and the development of the rash is acknowledged, and a positive dechallenge is reported, the patient was also treated with dimetindene drops for the rash and rechallenge was negative. Furthermore, that similar symptoms were experienced by the patient's siblings suggests the alternative explanation that the cause was infectious or environmental. For these reasons, we conclude that mirabegron and the rash in this case are not likely causally related.

The treatment-emergent AEs of bradycardia and diastolic hypotension are not supported as having occurred by the narratives or vital sign data provided in the appendices. Compared to the baseline HR (58 bpm, which itself qualifies as modest bradycardia), at the time of the AE (day 168), the decrease from baseline was minimal at -2.7 bpm. For DBP, the change from baseline was more notable at -15.7 mm Hg. However, because mirabegron had been interrupted on day 32 for an intercurrent viral event, then restarted on day 42 and uptitrated to 50 mg on day 50, it is reasonable to consider day 42 to be a more appropriate timepoint to use for baseline measurements for purpose of evaluating drug causality for this AE. We would also expect that changes in diastolic BP and HR would continue with ongoing mirabegron treatment. Heart rate decreased from day 42 to 168, but by day 364 it increased again and was similar to the day 42 measurement. Diastolic BP did decrease from day 42 to day 168, but it subsequently increased again on day 364. It is also possible that autonomic dysreflexia could have played a part in the patient's heartrate response, although the typical increase in BP with autonomic dysreflexia is not apparent in this case. In summary, we consider the patient's bradycardia on Day 168 (55 bpm) to be borderline and not a clinically significant change from baseline, and given the return to normal during continued exposure to mirabegron, to be unlikely to be causally related to the study drug. For the nonserious AE of diastolic hypotension, the temporal relationship supports a possible causal relationship to mirabegron. However, given the limited evidence presented and the upward trending DBP at the end of the study, we cannot assess this as causally related to the study drug, mirabegron.

Case (b) (6) is a 15-year old White male from Norway with spinal dysraphism, nut allergy, latex allergy, Arnold Chiaris type 2, closure of spina bifida, draining of hydrocephalus, spherocytic anemia, NDO, colostomy/appendicostomy, asthma, and repeated urinary tract infections. Prior to the reported SAEs, the patient had been treated with many medications, all before day 244: pain medications (IV Fentanyl, IV Thiopental, inhaled Sevoflurane, and

Septanest, and Paracetamol (rectal)] for a mislocated tooth, with oral paracetamol and Ethylmorphine Hydrochloride for a cold, and with rectal sheriproct for hemorrhoids. On study day 307, the patient experienced the SAEs of **hydrochephalus with shunt failure/hydrocephalus** and **shunt failure/shunt malfunction** and was hospitalized. The patient was treated with codeine / paracetamol suppository and oral diclofenac and then started paracetamol suppository as needed. The patient was discharged from the hospital the following day.

On day 320, the patient developed moderate hydrocephalus with shunt failure and the SAE of **convulsion/seizure**. He was hospitalized again. An MRI was performed, but the findings were not provided. On day 322, the shunt valve was reprogrammed "due to an increase of fluid/cerebrospinal fluid in the ventricles," and the patient was discharged from the hospital. The study drug was not interrupted, and the dose was not changed in response to the event. Seizure was listed as unresolved and ongoing (no end date recorded); however, the study ended on day 376 and the narrative stated that the outcomes of hydrocephalus with shunt failure and seizure were reported as recovered/resolved 10 days after the last study drug dose was given. Of note, shortly before the end of the study, the patient developed an *E.Coli* UTI and was treated with oral Pivmecillinam hydroklorid.

The patient also developed an elevated **total bilirubin > 2xULN**, which met PCS values. Of note, bilirubin levels of 20 umol/L (1.42 xULN) and 24 umol/L (1.68 xULN), at screening and baseline, respectively, were elevated prior to treatment with mirabegron. Mirabegron 25 mg was started and was uptitrated per protocol by 8 weeks into the study. On day 82, the patient's bilirubin had risen to 37 umol/L (2.60 xULN) and then on day 376, it was 31 umol/L (2.17 xULN). No other liver function tests were elevated in association with the day 82 total bilirubin peak measurement. The only other selected biochemistry abnormalities were ALT (33 U/L [1.38 xULN] and 28 U/L [1.17 xULN]) and GGT (labs not provided) were also above normal during screening and baseline assessments but were normal during the treatment period.

Reviewer's Comment: The patient experienced a malfunction of his shunt, which is not plausibly related to the study drug. However, shunt failure can cause hydrocephalus which in turn can cause seizure. Additionally, the information regarding the outcome of the seizure is confusing because the seizure is stated as unresolved (date not recorded) but also as resolved 10 days after the discontinuation of the study medication/end of study. Given the alternate plausible explanation of seizure resulting from hydrocephalus related to the shunt malfunction, we consider the three shunt-related SAEs in this case as not causally related to the study drug.

Regarding the total bilirubin measurement that met PCS values for being > 2xULN, the patient had an elevated total bilirubin at screening and baseline, and the past medical history included spherocytic anemia – a plausible alternative cause of hyperbilirubinemia. Furthermore, while ALT was slightly elevated prior to mirabegron treatment (1.38 and 1.17 xULN at screening and baseline), no other liver function tests were elevated during the course of treatment with mirabegron. Additionally, the total bilirubin improved with continued mirabegron administration. Given a temporal relationship of the peak elevated total bilirubin and

mirabegron treatment, we consider a causal association possible, but confounded by the pre-existing condition of spherocytic anemia.

Narratives for the two SAEs for talipes are presented below:

Case (b) (6) is a 9-year old white male from Norway with spinal dysraphism, Arnold Chiari 2 malformation, NDO, neurogenic muscular hypotonia, closure of spina bifida, draining of hydrocephalus, constipation, and appendicostomy. On day 166, he developed prolonged single QTc Bazzett's interval of 461 ms which resolved the same day. No treatment was required. The study drug was not interrupted. On day 326, the patient developed the serious adverse event (SAE) of **talipes/worsening of walking difficulties (due to Pes Calcaneovalgus)**. On an unknown date, the patient was hospitalized. It was reported that the patient had pronounced pes calcaneovalgus with pressure ulcer. On day 328, the patient underwent surgery for subtalar arthrodesis and prolongation of the ligamentum achilles, and the SAE was reported to be resolved the next day. Concomitant medications included movicol for constipation, remifentanil, dexalgen, paracetamol, propofol, fentanyl, sensorcain with epinephrine bitartrate and bupicakainhydroklorid and adrenalinbitartrat, paracetamol, cefalotin, morphine, ketorolac, and ibuprofen. After the surgery, the patient took ibuprofen and paracetamol. The study drug was not interrupted.

Reviewer's Comment: Pes Calcaneovalgus is a congenital deformity of the foot. The deformity itself, or the noted pressure ulcer, could be responsible for worsening of walking difficulties. The SAE resolved as a result of surgical treatment, and the study drug was continued until the end of the study. We consider this SAE to be not related to the study drug.

Case (b) (6) concerns a 10-year old Asian female from the Philippines with lipomyelomeningocele, clubfoot (talipes equinovarus), repair of myelomeningocele, release of tethered cord, ventriculoperitoneal shunting, and NDO. On day 182, the patient was hospitalized and underwent a preplanned orthopedic surgery (posteromedial release, calcaneal osteotomy firming and casting of the left foot) of the talipes equinovarus (clubfoot). The SAE reported was **talipes correction/clubfoot correction left**. On day 187, the patient was discharged from the hospital on three days of cefuroxime for infection prophylaxis and tablet ibuprofen for pain. The event of clubfoot correction left was reported to have resolved on day 275. The study drug was not interrupted, and the dose was not changed in response to the event.

Concomitant medications included disudrin for acute rhinitis, ascorbic acid, nitrofurantoin for prevention of UTI,

On day 240, the patient developed **allergic rhinitis** that was an Event of Interest. Further information was not specified regarding this event. Two weeks later, the patient was treated with two weeks of montelukast and cetirizine, and the event resolved that day. The study drug was not interrupted, and the dose was not changed in response to the event.

Reviewer's Comment: The reported SAE of talipes correction/correction of the left clubfoot was a preplanned procedure to treat a congenital foot deformity, which was a pre-existing condition

and unrelated to the study drug. Very little information is provided regarding the nonserious adverse event of interest, allergic rhinitis. Based on the information provided, the event was treated and resolved on the same day. There was no dechallenge, and the study drug was continued with no recurrent events. We consider the study drug to be not related to the event of allergic rhinitis.

The narratives for the benign skin tumor and appendicitis are below:

Case (b) (6) is a 6 year old female from South Korea with a history of Arnold-Chiari malformation, meningomyelocele, meningomyelocele repair, external ventricular drainage x 2, ventriculo-peritoneal shunt, scoliosis, neuromuscular, neuromuscular hip dislocation,(right), congenital vertical talus.(right), suboccipital decompression, and NDO, who developed the SAE of **benign neoplasm of the skin/benign scalp tumor**. The narrative noted that an MRI around day -343 showed a Chiari malformation with syringomyelia findings and that about 1.5 months later, the patient underwent suboccipital decompression.

On day 93, the narrative indicated that an ultrasound showed a small amount of complicated fluid with mild cellulitis at the left occipital scalp. It was not reported if this was treated. On day 103, an ultrasound was performed and showed continued small amount of complicated fluid with mild cellulitis at the left occipital scalp, apparently unchanged from "MRI results of day 93." An MRI was performed on day 104 and then the next day, the patient underwent surgical excision of a benign scalp mass. It was apparently confirmed that the benign scalp tumor was not present when the patient entered the study (no details were provided). Pathology revealed a fibrinoid clot, myxoid degeneration and granulation tissue formation. The tumor was resolved on day 106, and the patient was discharged from the hospital.

Prior to diagnosis and treatment of the benign scalp mass, the patient received oxybutynin and trospium for NDO (pre-study) and then received the study medication. For the MRI on day 104, the patient received a sedatives midazolam and choloral hydrate, motilitone for constipation; post-operatively, the patient received oral paracetamol, ofloxacin ointment, and IV MG TNA peri, acetylcysteine, metoclopramide, ketorolac, famotidine, and cefazolin.

Reviewer's Comment: This report is confusing and lacks important clinical information. The narrative refers to MRI results from day 93 when the only study recorded for that day in the narrative was an ultrasound. Additionally, it is not clear if the fluid collection and cellulitis were located at the site of the suboccipital decompression. Furthermore, it is not clear if the benign scalp mass is itself related to the findings from the previous ultrasound because the pathology suggests a solid mass which would not appear as fluid on ultrasound. Finally, no details are provided to confirm that the mass was not present at the start of the study. Based on these inconsistencies and lack of detail and the short duration of treatment with mirabegron (3 months) prior to the tumor development, we find this SAE to be not related to mirabegron treatment.

Case (b) (6) is a 13-year old female from Jordan with a history of spina bifida (L5, S1, S2) and surgery, lipoma of the cord with excision (x 2), tethered cord, syringomyelia, cerebrospinal

fluid leakage repair (dura mater reconstruction with wound closure using myofascial flap and Duraplasty), chord adhesolysis x 2, subarachnoid tube drainage of CSF, and NDO. On day 141, after two days of lower abdominal pain, nausea, and vomiting, the patient was hospitalized for the SAE of **appendicitis**. A CT of the abdomen and pelvis confirmed appendicitis with a small calcific focus noted in the appendix wall and signs of possible concealed perforation. The patient was treated with IV cefuroxime, metronidazole, morphine, and metoclopramide. An appendectomy was performed. The next day, labs showed normal WBC (8.30 x 10^3/mm^3), and elevated neutrophil count 91.30%. The event was reported as resolved on day 144, and the patient was discharged on cefuroxime, metronidazole, and paracetamol.

The patient continued the study drug uninterrupted for the duration of the study. Additional ongoing medication taken by the patient throughout the study were lactulose syrup (constipation prophylaxis), co-trimoxazole (UTI prophylaxis) and lidocaine gel (pain prophylaxis).

Reviewer's Comment: Appendicitis commonly occurs in this age group and can be related to the constipation resulting from the patient's underlying condition. We assess this SAE as not related to the study drug.

The narratives for the device malfunction SAEs are below:

Case (b) (6) is a 7-year old White female from Lithuania with spinal dysraphism, myelomeningocele, meningomyelocele repair (plastic of myelomeningocele), ventriculoperitoeostomia, NDO, reposition and fixation of fibula, change of ventriculoperitoneal shunt x 3, change of ventriculoperitoneal shunt and implanted ventriculostomic reservoir, change of ventriculorstomic reservoir, and UTI. On day 357, the patient started experiencing headaches and nausea. On day 359, after becoming sluggish, the patient was hospitalized in the ICU for the SAE of **device malfunction/ventriculoperitoneal shunt dysfunction**. Labs were normal. A CT of the brain showed the lateral ventricles were enlarged, the left one was lower, and the end of the shunt was within its body, unchanged from a CT from two years earlier. Mirabegron was interrupted, and the patient was treated with IV mannitol, vancomycin, and gentamycin, anesthesia was administered, and shunt revision was performed. The study drug was restarted on day 363, the patient's conditions improved slightly, she was transferred to another hospital for ongoing treatment, and she was ultimately discharged on day 367. Three days later, the SAE was reported to be resolved (day 370). The last dose of mirabegron was given on the final study day, day 379.

Reviewer's Comment: The patient experienced a device malfunction. We agree with the investigator that this event is not related to the study drug.

Case (b) (6) concerns a 5-year old White male from Poland with a history of spinal dysraphism, ixatio coxis sinister, neurogenic malformation of vertebral column, closure of spina bifida, luxation coxis dexter, small neurogenic feet malformation (plano-valga), drainage of hydrocephalus, NDO, and revision of ventriculo-peritoneal shunt. On study day 28, the patient developed the serious adverse event (SAE) of **device malfunction/dysfunction of ventriculo-peritoneal shunt**. He was hospitalized with unspecified periodic symptoms of increased

intracranial pressure. On the day of admission, the patient developed a headache. CT showed findings consistent with dysfunction of ventriculo-peritoneal shunt, including distortion of the the lateral ventricles with left-right asymmetry, narrow anterior horns, the left end of the shunt drain that was placed in the right parietal region passed into the cerebral tissue adjacent to the left lateral ventricle, and the ventricle IV was clamped. On study day 30, implantation of a Pudenz medium-pressure ventriculoperitoneal shunt valve system on the left side was performed, and the event resolved. The patient was discharged from the hospital the next day. The postoperative course was uncomplicated, and the surgical wounds healed by primary intention. The study drug was not interrupted, the dose was not changed in response to the event.

Concomitant medications included: Akritoin for UTI prophylaxis and EMLA for local anesthesia for blood sampling.

Reviewer's Comment: Shunt malfunction is a common complication of shunts and is considered not related to the study drug,

The narrative for worsening acute obstructive bronchitis and acute polysegmental bacterial pneumonia and the narrative for viral infection are below.

Case (b) (6): A 6-year old White female from Lithuania with a history of NDO, ventricular septal defect, hand dysplasia, arcuate kidney, pulmonary artery valve insufficiency grade I, bilateral upper urinary tract dilatation, left pelviureteric junction obstruction, bilateral vesicoureteral reflux grade I, chronic kidney disease grade I, and increased blood pressure. On day 61, the patient experienced shortness of breath and cough and was treated with dexamethasone and inhalation salbutamol. The next day the patient was hospitalized for **bronchitis/worsening acute obstructive bronchitis** (SAE) and the study drug was interrupted. The patient was afebrile (36.8°C) with an elevated CRP of 56.13 mg/L. CXR showed obstructive bronchitis. The patient was treated with continuous inhalation oxygen as needed, inhalation salbutamol, IV methylprednisolone x 1 dose, and 250 mL IV isotonic saline. Three days later, she was given oral dexamethasone and intranasal dimetindene maleate, neomycin sulfate, and phenylephrine drops. On day 66, the SAE of worsening of acute obstructive bronchitis had resolved, and the patient was discharged from the hospital with SpO_2 - 96%, isolated dry crackles on auscultation, moderate obstruction, and on treatment wirh clarithromycin (oral suspension) 125 mcg, bid for one week. Mirabegron was restarted on day 74.

Six days later, on day 80, the patient started coughing again. CXR showed polysegmental infiltration in the left lung: decreased aeration in the central and bottom fields of the left lung (in the background of the heart shadow); hila were infiltrated; and diaphragm arches and sinuses were unremarkable. The study drug was interrupted that day. The next day, the patient was hospitalized with a worsening cough, shortness of breath, and a body temperature of 37.9ºC, and the SAE of **acute bacterial pneumonia** was diagnosed. Labs were notable for a WBCs 12.58 (units not provided), neutrophils 82.7%, PCO_2 34.7 mm Hg, PO_2 54.9 mm Hg, and C-reactive protein 21.08 mg/L. The patient was treated with one dose of dexamethasone oral solution; ibuprofen, inhalation salbutamol and oral amoxicillin. On day 86, chest CT showed no lung infiltrates, only slightly decreased aeration in the left lower lung, and enlarged lymph nodes in

the neck. However, that same day, the patient developed stomatitis and a skin rash that was considered **allergic dermatitis**. No information was provided regarding the location of the mild allergic dermatitis, how diffuse or localized it was, or its appearance. Treatment for itching with Clemastine was prescribed. On day 90, the rash had diminished, and the lung exam improved. Antibiotics and inhaled salbutamol were stopped and the patient was discharged on Clemastine. On day 101, the allergic dermatitis was reported to be resolved.

Reviewer's Comment: This is a complicated case of a single patients with two SAEs and an AE of Special Interest (allergic dermatitis). The patient's events began with shortness of breath and cough, often related to a viral infection. However, the patient's condition progressed to bronchitis (which is typically viral, and the patient had normal WBC count) which appeared to respond to steroids and antibiotics. Mirabegron was restarted and 6 days later, the patient was treated for bacterial pneumonia with amoxicillin. While mirabegron was discontinued each time and the patient improved, the lung infections were also treated with antibiotics each time. This patient also had several cardiac comorbidities that could possibly put her at increased risk for pulmonary infections. While we cannot exclude a possible causal relationship between mirabegron and these SAEs, we note that an assessment of causality is confounded by this patient's comorbidities.

The allergic dermatitis occurred 6 days after mirabegron was discontinued. Details regarding the location and appearance were lacking. Furthermore, there were many confounding concomitant drugs including oral ibuprofen, inhalation salbutamol, and oral amoxicillin. Given the lack of information provided for the rash, we find causality to be unassessable and highly confounded.

Case (b) (6) a 6-year old male from the Philippines with a history of spina bifida, repair of lipomyelomeningocele, constipation, and NDO, who developed the SAE of **viral infection** on day 301 of the study. The patient had a moderate to high grade intermittent fever, WBCs and platelets were low, and urinalysis showed pyuria. The patient was initially thought to have Dengue fever and was treated with oral paracetamol. On day 305, the patient was hospitalized for fluid management and monitoring. Initial lab results showed the following ranges: WBC 2.3 to 2.7 and a differential with neutrophils 52 to 69 and lymphocytes 31 to 45. Initial urinalysis was positive for leukocytes and blood, with RBCs 4.5/hpf, WBCs 10 to 15/hpf, and few squamous epithelial cells. A repeat CBC showed a low WBC and low platelets, while the urinalysis was normal. Immunoglobulin G was positive, immunoglobulin M was negative, and Dengue fever was ruled out.

The patient was then treated with 4 days of IV ampicillin. Labs over the next few days showed stable hemoglobin/hematocrit at 12.3/36, and WBCs normalized to 4.9 and 6.8. The viral infection resolved on day 308, and the next day, the patient was discharged from the hospital on Beta Glucan with Chlorella Growth Factor and Lysine, zinc plus vitamin C and iron and vitamin B complex. The study drug was not interrupted, and the dose was not changed in response to the event.

Reviewer's Comment: This is a relatively complete report of a child evaluated for a fever and determined to have a viral infection. Viral infections are common, and hospitalization in this case was related to fluid management in the setting of high intermittent fevers. Clinical results supported the diagnosis, despite use of antibiotics. Mirabegron was continued throughout the clinical course. We consider mirabegron to be not related to this SAE.

The narrative for one remaining SAE, segmental colitis, is below.

Case (b) (6) concerns a 17-year old male with tetraplegia, spinal cord injury, fixation of fractured C3-C4, asymptomatic bacteriuria, decubital wound, obstipation, and NDO. On study day 202, the patient had chills, fever, diarrhea, and extreme weakness and fatigue. He was admitted to the hospital with the SAE of **segmental colitis**.

On admission, the patient was conscious and communicative, but drowsy, adynamic, immobile, afebrile and extremely dehydrated and hypotensive (blood pressure 70/50 mm Hg), bradycardic (heart rate 52 beats per minute), eupneic, and with satisfactory O_2 saturation (by pulse oximeter, value not specified). Physical exam was notable for a shallow decubitus lesion on the skin of the perineum, a soft and painless abdomen with slow peristalsis, and quadriplegia. Laboratory results supported a diagnosis of sepsis: WBC 17.34 (normal 4 to 10), neutrophils 84.8 (normal 50 to 70), CRP 166 (normal 0 to 5). The narrative indicated that urine test (not specified) showed "slightly turbid, protein+, nitrite+, copious WBCs, some bacteria, WBC 18, bacteria 28, some mucus, fungi, WBC 2, no bacteria, a little mucus, fungi, a little bacteria, and WBC 35." No stool studies were reported. The patient was treated with 9 days of triple parenteral antibiotic therapy (meropenem, metronidazole, and vancomycin hydrochloride). On day 8 of antibiotics, a CT of the abdomen and lesser pelvis revealed distended convolution of the colon without formed gas-liquid levels, thickening of the wall of the rectum, intraperitoneal lymphadenopathy, and a small quantity of free fluid in the lesser pelvis. The patient's vital sign normalized, watery stools stopped, and labs improved with WBC 4.5, neutrophils 50.5, and CRP 2.6.

After "bloody mucosal content" was observed on digital rectal examination, a colonoscopy (day 212) and showed segmental ischemic colitis. By day 218, the colitis had resolved, lab tests were normal, and the patient was afebrile and "in good general condition." The patient was discharged on metronidazole (prophylaxis for colitis), fluconazole (for urinary candidiasis), probiotic capsules, enemas. The patient continued to take mirabegron during the course of his illness.

Reviewer's Comment: This quadriplegic patient presented with sepsis. The urine results are confusing but may be consistent with a fungal, and possibly bacterial, urinary tract infection. Colonoscopy confirmed segmental ischemic colitis. It is known that quadriplegic patients have an increased risk for ischemic colitis. Mirabegron was never discontinued throughout this patient's treatment. We assess segmental colitis as not related to mirabegron treatment.

Reviewer's Comment: The Clinical review team evaluated all 19 SAEs. Overall, we agree with the Sponsor that none of the SAEs had a causal relationship to the study drug. Although all the

SAEs had a temporal relationship to the study drug, they were mostly confounded by complications of the patients underlying medical conditions.

8.7.2Dropouts and/or Discontinuations Due to Adverse Effects

In 178-CL-206A, only 3 TEAEs led to discontinuation, and all were reported in female children. The table below summaries the TEAEs leading to permanent discontinuation. Of the 3 TEAEs leading to permanent discontinuation, 2 were assessed by the investigator to be possibly (AST increased) or probably (urinary incontinence) related to the study drug and 1 (dermatitis allergic) was assessed to be not related to the study drug.

Table 39 Treatment-emergent Adverse Events Leading to Permanent Discontinuation (SAF)

Patient Number	Age/ Sex†	MedDRA (v16.0) Preferred Term (investigator's verbatim term)	Last Dose Day	Onset/ Stop Day	Outcome	Relationship to Study Drug*
Children (3 to < 12 years)						
(b) (6)	3/F	Aspartate aminotransferase increased (elevated AST level)	87	84/166	Recovered/Resolved	Possible
	6/F	Dermatitis allergic (allergic dermatitis)	80	86/101	Recovered/ Resolved	Not Related
	3/F	Urinary incontinence (worsening of urinary incontinence)	228	125 E/ NR	Not recovered/ Not resolved	Probable
Adolescents (12 to < 18 years)						
Not reported						

All patients who received ≥ 1 dose of study drug (SAF).
E: estimated value; NR: not reported; SAF: safety analysis set.
† Age (years) at screening.
*as assessed by the investigator.
Source: 178-CL-206A, Table 37, p. 98.

Below are mini-narratives for two of the patients who had the following AEs leading to discontinuation: elevated AST level and urinary incontinence. The reader is referred to Section 8.7.1 for the narrative describing the patient who had the AE of dermatitis allergic.

Case (b) (6) concerns a 3-year old female patient from Belgium with a history of spinal dysraphism, NDO, tethered cord release, fecal incontinence, intermittent constipation, behavioral disorder due to dridase (oxybutynin), and behavioral disorder due to propiverine. Prior to the AEs of elevated AST level and CPK level, the patient had experienced AEs of constipation, *E.coli* UTI, gastroenteritis, pyrexia, and a second *E.coli* UTI. On day 84, the patient developed an elevated AST level of 52 U/L (21-44) (1.18 x upper limit of normal [ULN]) and CK of 440 U/L (26-192) (2.29 x ULN) that led to discontinuation of study drug on day 87. Treatment was not required.

On day 112, 25 days after the study had been discontinued (day 87), the patient's creatine kinase level dropped to 267 U/L (1.39 x ULN), AST decreased to 1.07 x ULN. On day 123, creatine kinase and AST again increased to 2.7 x ULN and 1.50 x ULN, respectively. On day 158,

creatine kinase decreased to 2.16 x ULN and AST decreased to 1.25 x ULN. Finally, on day 166, the AST level had normalized (AST 37 U/L) and the creatine kinase level was trending to normalization (creatine kinase 200 U/L, 1.04 x ULN), and both events were reported as resolved.

Reviewer's Comment: After the initial elevations of AST and CK, mirabegron was discontinued. Both AST and CK decreased slightly at 25 days after discontinuation, then increased again 45 days later. Both values declined 71 days after discontinuation. The timing of the increase and decrease and AST and CK does not correlate well with the discontinuation of the study drug. We consider this a negative dechallenge and assess the causality of these lab test changes as not likely related to the study drug.

This case was also of interest for the AE of moderate constipation. The narrative includes minimal information on this AE. The patient's pre-existing diagnosis of intermittent constipation confounds an assessment of causality.

Case (b) (6) is a 3-year old white female from South Korea with spinal dysraphism, subtotal laminectomy, L3, TL, L4 and dysraphism repair, detethering of lipomeningomyelocele, lipomeningomyelocele operation site swelling and flunctuation, NDO, and bilateral pes calcaneus, who experienced mild worsening of urinary incontinence on day 125. The treatment that was given was not specified. The study drug was ultimately discontinued on day 228, and the worsening of urinary incontinence was reported as not resolved on an unspecified date. The only concomitant medication was Lactobacillus Rhamnosus/Ramnos granule for constipation prophylaxis.

Reviewer's Comment: The information on this AE is lacking. Furthermore, incontinence is a characteristic of NDO and worsening of incontinence simply may be related to this patient's underlying condition. The child's worsening of incontinence was not relieved by discontinuation of study medication. We assess this AE as unassessable and highly confounded.

Reviewer's Comment: In our opinion, none of the three AEs leading to discontinuation of the study drug is related to treatment with the study drug.

8.7.3 Adverse Events

The following per-protocol definitions were used to grade the severity of AEs, including abnormal clinical laboratory values:

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

The term "severe" was used to describe the severity of the AE, not its seriousness.

Table 40 below shows that a majority of TEAEs were mild to moderate in severity. The adolescent group appeared to have a higher percentage of severe TEAEs compared to the children, and the children appeared to have a higher percentage of mild TEAEs.

Table 40 Treatment-Emergent Adverse Events by Severity (SAF)

MedDRA (v16.0) SOC, PT, n (%)	Children (3 to < 12 Years) n = 43	Adolescents (12 to < 18 Years) n = 25	All Patients (3 to < 18 Years) n = 68
Mild	23 (41.8%)	8 (25.8%)	6 (36.0%)
Moderate	9 (16.4%)	7 (22.6%)	16 (18.6%)
Severe	1 (1.8%)	3 (9.7%)	4 (4.7%)
Total	33 (60.0%)	18 (58.1%)	51(59.3%)

Source: Compiled from 178-CL-206A CSR Table 12.6.1.1.6, p. 937.

Reviewer's Comment: Given the low number of severe TEAEs, and considering that all but 4 patients in the entire study population were titrated to the 50 mg dose, we are unable to compare the incidence of TEAEs according to treatment dose in the two age groups.

8.7.4Treatment Emergent Adverse Events and Adverse Reactions

8.7.4.1 Commonly Reported TEAEs

The most commonly reported TEAEs were defined by the Sponsor as TEAEs occurring in ≥ 2% in the all patient group. Those were *E.coli* urinary tract infection (UTI) (8 [9.3%] patients), followed by nasopharyngitis, pyrexia and UTI bacterial (5 [5.8%] patients each). In children, the most commonly reported TEAEs were respiratory tract infection viral, UTI, and UTI bacterial (4 [7.3%] patients each). In adolescents, the most commonly reported TEAEs were *E.coli* UTI (5 [16.1%] patients), pyrexia, and upper respiratory tract infection (3 [9.7%] patients each).

For all groups, the SOCs in which TEAEs were most commonly reported were Infection and Infestations (28 patients [32.6%] in all patients), General disorders and administration site conditions (7 patients [8.1%] in all patients), and Gastrointestinal disorders (6 patients [7.0%]). Table 41 below shows the incidence of the most common TEAEs. PTs of *E.coli* urinary tract infection (8 [9.3%] patients), nasopharyngitis (5 [5.8%] patients), and UTI bacterial (5 [5.8%] patients) had the highest incidence. These next most frequent TEAEs were reported in 4 (4.7%) patients each: respiratory tract infection viral, upper respiratory tract infection, urinary tract infection, and constipation. For a closer look at UTI-related TEAEs, the reader is referred to section 8.4.4.2.

Table 41 TEAEs in at Least 2% of All Patients (SAF); Study 178-CL-206A

MedDRA v16.0 System Organ Class Preferred Term, n (%)	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Overall	**33 (60.0)**	**18 (58.1)**	**51 (59.3)**
Gastrointestinal Disorders			
Constipation	3 (5.5)	1 (3.2)	4 (4.7)
Nausea	2 (3.6)	0	2 (2.3)
General Disorders and Administration Site Conditions			

Pyrexia	2 (3.6)	3 (9.7)	5 (5.8)
Device malfunction	2 (3.6)	0	2 (2.3)
Infections and Infestations			
Escherichia urinary tract infection	3 (5.5)	5 (16.1)	8 (9.3)
Nasopharyngitis	3 (5.5)	2 (6.5)	5 (5.8)
Urinary tract infection bacterial	4 (7.3)	1 (3.2)	5 (5.8)
Respiratory tract infection viral	4 (7.3)	0	4 (4.7)
Upper respiratory tract infection	1 (1.8)	3 (9.7)	4 (4.7)
Urinary tract infection	4 (7.3)	0	4 (4.7)
Gastroenteritis	1 (1.8)	1 (3.2)	2 (2.3)
Rhinitis	1 (1.8)	1 (3.2)	2 (2.3)
Urinary tract infection pseudomonal	1 (1.8)	1 (3.2)	2 (2.3)
Viral infection	1 (1.8)	1 (3.2)	2 (2.3)
Nervous System Disorders			
Headache	2 (3.6)	1 (3.2)	3 (3.5)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	2 (3.6)	0	2 (2.3)

Sorting order: ascending order by system organ class code and descending by the number of patients in the all patients group by preferred term. In case of ties, alphabetical order by preferred term was applied.
Source: Summary of Clinical Safety, Table 5, p. 14.

Reviewer's Comment: The most common TEAEs in 178-CL-206A (NDO patients) were E.coli UTI, nasopharyngitis, UTI bacterial, and pyrexia.

Reviewer's Comment: The Sponsor originally included a table in the label summarizing the most common adverse reactions according to drug formulation, based on Table 12.6.1.1.27 (page 1359 of the CSR). However, as noted previously, analyses of data by drug formulation is confounded by patient age, as the patients taking oral suspension were all the children and only 3 adolescents (weighing <35 kg) and the patients taking the tablet were all adolescents. Therefore, analyzing AE incidence by drug formulation is not informative.

Instead, we proposed the Sponsor include a table summarizing the most common adverse reactions for all patients. In an effort to convey more meaningfully adverse reaction information, we requested the Sponsor combine all UTI terms into a single line listing "Urinary Tract Infection" which should include E.Coli UTI, Psuedomonas UTI, UTI bacterial, and UTI. We then deleted events not considered adverse reactions such as device malfunction, URI, pyrexia, and viral infection.

The resulting table is provided below. The most common adverse reactions in 178-CL-206A were UTI, nasopharyngitis, constipation, and headache. The most common adverse reactions reported in the clinical trials for mirabegron in adults with OAB were hypertension, UTI, nasopharyngitis, and headache. The differences may be due to many factors related to the different populations studied, including age, target condition, and cultural differences.

Table 42 Percentages of Patients with Adverse Reactions Reported in ≥ 2% of Patients in Study 178-CL-206A (SAF)

Adverse Reaction	Percentage (%) of Patients Reporting Adverse Reactions N=86
Number of Patients	**51 (59.3)**
Urinary tract infection	24.4
Nasopharyngitis	5.8
Constipation	4.7
Headache	3.5
Nausea	2.3
Gastroenteritis	2.3
Rhinitis	2.3
Cough	2.3

Drug-related AEs (as determined by the investigator) over 52 weeks of treatment, shown in the table below, were reported in 14 (16.3%) patients in study 178-CL-206A. In children, the most common drug-related TEAEs were nausea and urinary tract infection bacterial (each with 2 [3.6%] patients). In adolescents, each of the 7 TEAEs considered drug-related by the investigator occurred only once.

Table 43 Drug-related* TEAEs in Study 178-CL-206A (SAF)

MedDRA v16.0 System Organ Class Preferred Term, n (%)	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Overall	8 (14.5)	**6 (19.4)**	**14 (16.3)**
Gastrointestinal Disorders			
Constipation	1 (1.8)	1 (3.2)	2 (2.3)
Nausea	2 (3.6)		2 (2.3)
Dry mouth		1 (3.2)	1 (1.2)
Infections and Infestations			
Escherichia urinary tract infection		1 (3.2)	1 (1.2)
Bacteriuria	1 (1.8)		1(1.2)
Urinary tract infection bacterial	2 (3.6)	1 (3.2)	3(3.5)
Investigations			
Aspartate aminotransferase increased	1 (1.8)		1 (1.2)
Blood creatine phosphokinase	1 (1.8)		1 (1.2)
Electrocardiogram QT prolonged	1 (1.8)		1 (1.2)
Renal and urinary disorders			
Urinary incontinence	1 (1.8)		1 (1.2)
Skin and subcutaneous tissue disorders			
Alopecia	1 (1.8)		1 (1.2)
Dermatitis diaper		1 (3.2)	1 (1.2)
Cardiac disorders			
Bradycardia		1 (3.2)	1 (1.2)
Vascular disorders			
Diastolic hypotension		1 (3.2)	1 (1.2)

Number of PTs does not add up to overall number of patients as some patients reported more than one PT.
*as assessed by the investigator.
Source: Compiled from 178-CL-206A CSR, Table 12.6.1.1.4, p. 895.

Reviewer's Comment: In all patients, the most common drug-related adverse events, as assessed by the investigator, were constipation, nausea, and UTI bacterial. Constipation and UTI are both listed as most common adverse reactions for mirabegron tablets in adults with OAB. Nausea is not. Due to the limited number of AEs for the Phase 1 studies which included pediatric patients with OAB symptoms, it is difficult to compare the incidence of specific drug-related AEs in pediatric patients with NDO vs pediatric patients with OAB symptoms.

Table **44** table below shows TEAEs from the supportive Phase 1 studies 178-CL-202 (tablets) and 178-CL-203 (oral suspension) in patients with NDO and OAB symptoms. Only 1 TEAE was assessed as drug-related by the investigator (ECG QT prolonged, 178-CL-202). All TEAEs in both Phase 1 studies were mild in severity.

Table 44 TEAEs in at Least 2% of All Patients (SAF); Study 178-CL-202 and 128-CL-203

	Study 178-CL-202†						Study 178-CL-203‡
Incidence of TEAE	Cohort 1 Adolescents (12 to < 18 Years) Low Dose Fed (n = 7) n (%)	Cohort 2 Children (5 to < 12 Years) Low Dose Fed (n = 7) n (%)	Cohort 3 Adolescents (12 to < 18 Years) High Dose Fed (n = 8) n (%)	Cohort 4 Children (5 to < 12 Years) High Dose Fed (n = 6) n (%)	Cohort 5 Children (5 to < 12 Years) High Dose Fasted (n = 6) n (%)	Total (5 to < 18 Years) (n = 34) n (%)	Total/ Children (3 to < 12 Years) Fed (n = 9) n (%)
Overall	1 (14.3)	1 (14.3)	1 (12.5)	0	1 (16.7)	4 (11.8)	1 (11.1)
Gastrointestinal disorders							
Vomiting	1 (14.3)	0	0	0	1 (16.7)	2 (5.9)	0
Investigations							
ECG QT prolonged	0	1 (14.3)	1 (12.5)	0	0	2 (5.9)	0
General disorders and administration site conditions							
Pyrexia	1 (14.3)	0	0	0	0	1 (2.9)	1 (11.1)

† In Study 178-CL-202, patients received mirabegron extended-release tablets. Low dose was 25 mg (body weight between 20.0 to < 55.0 kg) or 50 mg (body weight ≥ 55.0 kg). High dose was 50 mg (body weight 20.0 to < 40.0 kg) or 75 mg (body weight ≥ 40.0 kg).
‡ In Study 178-CL-203, patients received mirabegron oral suspension formulation B (granules were reconstituted with water to prepare a suspension with a concentration of 2 mg/mL). Dose was 40 mL suspension (body weight 15 to 19 kg), 50 mL suspension (body weight 20 to 29 kg), 55 mL suspension (body weight 30 to 39 kg) or 65 mL suspension (body weight > 40 kg).
Source: Compiled from 178-CL-202 CSR, Table 12.6.1.3.1, p. 109 and 178-CL-203 CSR, Table 12.6.1.2, p. 93.

Reviewer's Comment: Given the low number of TEAEs reported in the Phase 1 studies and only one assessed as drug-related, the safety profile of the pediatric development program is largely

described by the assessment of safety data from Phase 3 study 178-CL-206A. Of note, for the case of ECG QTc prolonged, we obtained consultation from the Interdisciplinary Review Team for QT Studies (IRT-QT) in the Division of Cardiology and Nephrology (DCN). The consultant determined that the case was not related study medication. The consultant's findings are described in later sections of this review.

8.7.4.2 TEAEs of Special Interest

Study 178-CL-206A

Table 45 summarizes the incidence of pre-determined TEAEs of special interest in study 178-CL-206A, which included cardiovascular TEAEs (increased blood pressure; increased heart rate, tachycardia, atrial fibrillation, or palpitations; and QT prolongation), neoplasm, hypersensitivity reactions, urinary tract infection, urinary retention, seizures, syncope, fetal disorders after exposure during pregnancy, and concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated.

Table 45 Overview of Incidence of TEAEs of Special Interest (SAF); Study 178-CL-206A

MedDRA v16.0 TEAE of Special Interest, n (%)	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Cardiovascular	1 (1.8)	1 (3.2)	2 (2.3)
Increased blood pressure	0	0	0
Increased heart rate, tachycardia, atrial fibrillation, or palpitations	0	1 (3.2)	1 (1.2)
QT prolongation	1 (1.8)	0	1 (1.2)
Neoplasm	1 (1.8)	0	1 (1.2)
Hypersensitivity reactions	2 (3.6)	3 (9.7)	5 (5.8)
Urinary tract infection	13 (23.6)	8 (25.8)	21 (24.4)
Urinary retention	0	0	0
Seizures	0	1 (3.2)	1 (1.2)
Syncope	0	0	0
Fetal disorders after exposure during pregnancy	1 (1.8)	0	1 (1.2)
Concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated	0	0	0

CYP2D6: cytochrome P450 2D6.
Source: Summary of Clinical Safety, Table 9, p. 19.

Reviewer's Comment: No TEAEs of increased blood pressure were reported.

Cardiovascular Events
Two (2) patients reported a cardiovascular TEAE of special interest: QT prolongation (n=1, children's group) and bradycardia (n=1, adolescent group). Both of these TEAEs were considered by the investigator as possibly drug-related. The table below provides a summary of the cardiovascular TEAEs of special interest in study 178-CL-206A.

Table 46 Cardiovascular TEAEs of Special Interest (SAF); Study 178-CL-206A

Patient ID	Age/ Sex†	MedDRA (v16.0) Preferred Term	Last Dose Day	Onset/ Stop Day	Outcome	Relationship to Study Drug*
Children (3 to < 12 years)						
(b) (6)	9/M	Electrocardiogram QT prolonged	356	166/166	Recovered/Resolved	Possible
Adolescents (12 to < 18 years)						
(b) (6)	12/M	Bradycardia	364	168/NR	Not recovered/	Possible

ID: identification.
*as assessed by the investigator.
Source: Summary of Clinical Safety, Table 10, p. 20.

The narratives for the following TEAEs were presented in section 8.7.1:

- QT prolongation
- Bradycardia (and diastolic hypotension)

Reviewer's Comment: We do not agree with the investigator's determination regarding the relationship of the study drug for these two AEs. The single measurement of prolonged QTc was corrected using Bazett's formula, which has been shown to be associated with false positive increases in QTc if heart rate is elevated. Mirabegron was shown to increase mean heart rate in the thorough QT study submitted as part of the original NDA. Therefore, it is inappropriate to use Bazett's formula for correction of QT interval measurement and the finding of prolonged QTcB does not reflect true QT prolongation. Regarding the TEAE of bradycardia, we have concluded that the TEAE of bradycardia was reported in error for reasons noted in the reviewer's comment in section 8.4.1.

Neoplasm Events
One (1) patient (case (b) (6)) reported a neoplasm TEAE: benign neoplasm of the skin (n=1, children's group). A narrative and reviewer's comment for this patient is presented in Serious Adverse Events 8.7.1.

Reviewer's Comment: This event was considered not related to the study drug.

Hypersensitivity Reactions
Five (5) patients reported hypersensitivity TEAEs of special interest: dermatitis allergic (n=1, children's group), rhinitis allergic (n=1, children's group), urticaria (n=1, adolescent group), dermatitis (n=1, adolescent group), and rash generalized (n=1, adolescent group). None of these TEAEs was considered by the investigator to be drug-related.

Table 47 TEAEs of Special Interest: Hypersensitivity Reactions (SAF); Study 178-CL-206A

Patient ID	Age/ Sex†	MedDRA (v16.0) Preferred Term	Last Dose Day	Onset/ Stop Day	Outcome	Relationship to Study Drug*
Children (3 to < 12 years)						
(b) (6)	6/F	Dermatitis allergic	80	86/101	Recovered/Resolved	Not related
	10/F	Rhinitis allergic	374	240/254	Recovered/Resolved	Not related
Adolescents (12 to < 18 years)						
(b) (6)	14/F	Urticaria	356	32/37	Recovered/Resolved	Not related
	16/M	Dermatitis	364	241/NR	Not recovered/ Not resolved	Not related
	12/M	Rash generalized	364	31/33	Recovered/Resolved	Not related

*as assessed by the investigator
Source: Summary of Clinical Safety, Table 11, p. 20.

Narratives describing each of the following hypersensitivity AEs except for urticaria are presented in Serious Adverse Events Section 8.7.1. A mini-narrative for the urticaria case is provided below.

- Dermatitis allergic
- Rhinitis allergic
- Urticaria – This 14-year old female from Croatia developed urticaria on day 32 of the study. She was treated with levocetirizine for 5 days, after which the urticaria resolved. The patient had no history of allergies and did not report any exposures that could provide an alternative cause. She continued treatment with mirabegron (there was no dechallenge) and the urticaria did not recur.
- Dermatitis
- Rash generalized

Reviewer's Comment: For narratives and a discussion of causality determinations, the reader is referred to section 8.7.1. In summary, we consider the AEs of Dermatitis allergic and Dermatitis to be unassessable and the AEs of allergic rhinitis and rash generalized to be not related to the study drug. Additionally, we assess the AE of urticaria to be not related to the study drug given that further exposure to mirabegron did not cause further episodes of urticaria.

UTI Events

Twenty-one (21) patients reported UTI TEAEs of special interest. Table 48 below provides a summary of these TEAEs.

Table 48 TEAEs of Special Interest: Urinary Tract Infection (SAF); Study 178-CL-206A

	Children (3 to < 12 Years) n = 55		Adolescents (12 to < 18 Years) n = 31		All Patients (3 to < 18 Years) n = 86
MedDRA v16.0	n (%)	Patient ID	n (%)	Patient ID	n (%)
Overall	13 (23.6)		8 (25.8)		21 (24.4)

E.coli urinary tract infection	3 (5.5)	--	5 (16.1)	(b) (6) --	8 (9.3)
Urinary tract infection bacterial	4 (7.3)	--	1 (3.2)	--	5 (5.8)
Urinary tract infection	4 (7.3)	--	0	--	4 (4.7)
Urinary tract infection pseudomonal	1 (1.8)	--	1 (3.2)	--	2 (2.3)
Bacteriuria	1 (1.8)	--	0	--	1 (1.2)
Cystitis	0	--	1 (3.2)	--	1 (1.2)
Cystitis bacterial	0	--	1 (3.2)	--	1 (1.2)
Pyelonephritis acute	1 (1.8)	(b) (6)	0	--	1 (1.2)
Urinary tract infection enterococcal	0	--	1 (3.2)	--	1 (1.2)

Source: Summary of Clinical Safety, Table 12, p. 21.

Narratives for the two patients with serious UTI events, pyelonephritis acute in 1 (1.8%) child and *E.coli* UTI in 1 (3.2%) adolescent, can be found in Serious Adverse Events Section 8.7.1 of this review. Four (4) UTI events of special interest were reported in 2 or more patients: *E.coli* UTI (3 [5.5%] children and 5 [16.1%] adolescents), UTI bacterial (4 [7.3%] children and 1 [3.2%] adolescents), UTI (4 [7.3%] children and no adolescents) and UTI pseudomonal (1 [1.8%] child and 1 [3.2%] adolescent). All other UTI events of special interest were each reported by 1 (1.2%) patient.

Reviewer's Comment: The relatively high incidence of UTI is thought to reflect the high background incidence of UTI in the patient population. We assessed the two SAEs, pyelonephritis acute and E.coli UTI, as not likely causally related to mirabegron.

Seizure Events
One (1) patient reported a seizure event. The narrative for this adolescent is presented in Serious Adverse Events 8.7.1. The seizure (TEAE had preferred term convulsion/seizure) was considered not related to the study drug.

Fetal Disorders After Exposure During Pregnancy Events
The TEAE coded as "Fetal disorders after exposure during pregnancy" was defined in the search strategy; however, there was no pregnancy. The TEAE was worsening of talipes, a congenital condition, in a 9-year old boy. The narrative for this patient is included in Serious Adverse Events 8.7.1, because talipes was considered an SAE. We concluded that the SAE worsening of talipes was not causally related to mirabegron treatment.

No TEAEs were reported for the remaining TEAEs of special interest: Urinary retention, Syncope, and Concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated.

Supportive Phase 1 Studies in Pediatric Patients with NDO or OAB Symptoms, 178-CL-202 and 178-CL 203

QT prolongation (n=2, one child and one adolescent) was the only TEAE of special interest in the single dose studies and both cases were reported in study 178-CL-202.

- Subject (b) (6) was a 15-year old female with OAB symptoms in the high-dose cohort 3 receiving a single dose of 75 mg mirabegron. The ECG showed a mean increase of QT interval corrected by Bazett's formula (QTcB) > 30 ms compared to baseline at 4 h postdose (448.33 vs 407.83 ms, respectively) which, per investigator assessment, was considered to be clinically significant and reported as a TEAE of ECG QT prolonged. The mean QT interval corrected by Fridericia's formula (QTcF) increased 29.4 ms compared to baseline at 4 h postdose (432.7 vs 403.3 ms, respectively).

- Subject (b) (6) was 9-year old female with OAB symptoms in the low-dose cohort 2 receiving a single dose of 25 mg mirabegron. The mean QTc Bazett's value (452.5 ms at 4 h postdose after 2 measurements, increased from 428 ms at baseline). The change from baseline for QTcF was >30ms for a single measurement at 4h but the average change from baseline in QTcF was normal at 19.75 ms.

Reviewer's Comment: *Neither of these reported two QT prolongation TEAEs elevate the risk of QT prolongation by mirabegron because both are corrected for heart rate insufficiently by Bazett's correction. See later sections of this review for a summary of the IRT-QT/DCN consultant's reports.*

Finally, because constipation and dry mouth are typical side effects of the two already approved first line oral therapies (both anticholinergics), we reviewed the narratives for the 4 reports of constipation and 1 report of dry mouth in study 178-CL-206A. The following are mini-narratives and Clinical review team assessments of each case:

- Case (b) (6) is a 3-year old female patient with a history of intermittent constipation who developed moderate constipation/"slow colon transit" on the same day she started Trimethoprim for treatment of an *E.Coli* UTI. Her constipation was treated with colon irrigation. Subsequently, after completing the 5-day treatment course of trimethoprim, she had gastroenteritis x 2 days and then took an 8-day course of nitrofurantoin. Ultimately, the study drug was discontinued on day 87 due to elevated AST and CPK (the reader is referred to the narrative in section 8.7.2. for more details). We assess the adverse events in this case as not related to the study drug for the following reasons: the constipation was not worsened with dose escalation, the dechallenge at end of treatment (day 87) was negative, her pre-existing condition of intermittent constipation is a confounder, and the intercurrent illnesses (UTIs and gastroenteritis) may have contributed to her slow colon transit symptoms.
- Case (b) (6) is a 5-year old male patient with a history of constipation prior to taking the study drug, who experienced mild constipation while simultaneously taking ibuprofen (for which constipation is a labeled AR). The episode was not related to start of study drug or dose escalation. This case is confounded and considered not likely related to the study drug.
- Case (b) (6) is a 15-year old female patient who experienced moderate constipation (x 7 days, starting on day 36) which resolved after treatment with Ricinus

communis/castor oil and disacodyl/Dulcolax for 3 days. The patient was maintained on daily sodium picosulfate/dulcolax SP. There were no confounders, mirabegron dose was not uptitrated, and prophylaxis was ongoing, limiting the information available for causality assessment. We know only that the onset of the constipation did not coincide with mirabegron initiation. We assess this is possibly related, but important clinical information is lacking.

- Case (b) (6) is a 9-year old male patient who developed mild constipation on day 128 that lasted 6 days then resolved without treatment. The study drug was continued. There were no concomitant meds or other adverse events. The dose of mirabegron had been increased on day 15. We consider this case of transient constipation unlikely to be causally related to mirabegron treatment because the constipation did not recur with ongoing treatment.
- Case (b) (6) is a 12-year old male patient who developed mild dry mouth starting two days after finishing a 7-day course of loratadine (taken to treat allergic rhinitis) and on same day mirabegron was uptitrated to 50 mg. No treatment was administered, the study drug was continued, and dry mouth resolved 2 days later. Of note, dry mouth was not reported by the patient upon initiation of mirabegron 25 mg. In this case, dry mouth is possibly related to mirabegron given the temporal relationship, but causality is confounded by recent loratadine use.

Reviewer's Comment: None of the 4 AEs of constipation and 1 AE of dry mouth is assessed as drug-related. The cases mostly are confounded, lacked adequate information, or additional evidence did not support a causal relationship with the study drug.

8.7.4.3 Relation of AEs to Study Drug Exposure or Other Factors

Consequences of increased exposure to mirabegron granules in the fasting state
In healthy adult subjects, a high-fat meal decreased the AUC_{0-inf}, AUC_{0-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-inf}, AUC_{0-t} and C_{max} of mirabegron ER tablets by 57%, 60% and 60%, respectively.

Based on these results, in the Phase 3 pediatric NDO study 178-CL-206A, mirabegron tablets or oral suspension were taken within 1 hour of eating food (breakfast). Accordingly, mirabegron tablets and oral suspension are proposed to be administered with food in pediatric NDO patients.

Reviewer's Comment: The consequences of increased exposure in pediatric patients, such as would result from taking mirabegron fasting, are not clear from the data in this submission. The Phase 3 study was not designed to collect dose-response AE data. However, after identifying increased BP in children (especially in children less than 8 years old), Clinical Pharmacology and the Division of Pediatric and Maternal Health (DPMH) worked closely to determine whether increased BP in pediatric patients was associated with increased exposure to mirabegron. The Clinical Pharmacology and DPMH teams determined that the noted increase in BP in pediatric patients was not exposure-related. We have no additional information on exposure-response for other AEs in the pediatric population, however, we note that no clear dose

relatedness was demonstrated for the AEs that were reported in clinical studies of adults with OAB.

Onset of TEAEs related to duration of study drug treatment

A summary of the Sponsor's analysis of the pattern of the onset, prevalence, and first onset of TEAEs by time intervals is presented in the table below.

Table 49 TEAEs by Time Intervals in Study 178-CL-206A (SAF)

Time Intervals (weeks)	Onset of TEAEs	First Onset of TEAEs	Prevalence of TEAEs
	n = 86, n (%)		
< 2	4 (4.7%)	2 (2.3%)	4 (4.7%)
≥ 2 to < 4	9 (10.5%)	8 (9.3%)	13 (15.1%)
≥ 4 to < 8	23 (26.7%)	20 (23.3%)	25 (29.1%)
≥ 8 to < 12	11 (12.8%)	10 (11.6%)	14 (16.3%)
≥ 12 to < 24	23 (26.7%)	20 (23.3%)	28 (32.6%)
≥ 24 to < 36	19 (22.1%)	17 (19.8%)	22 (25.6%)
≥ 36 to < 52	10 (11.6%)	10 (11.6%)	18 (20.9%)
>52	4 (4.7%)	3 (3.5%)	9 (10.5%)

Source: Compiled from 178-CL-206A CSR, Tables 12.6.1.1.17, and 12.6.1.1.21, and 12.6.1.1.19.

Overall, the onset of TEAEs and the first onset of TEAEs was highest at weeks 4 to <36. Only 12.8% of TEAEs and 11.6% of first onset TEAEs were reported from weeks 8 to <12, but approximately 20% or more were reported at each of the other 4-week intervals for both categories. The data for prevalence reflected a similar pattern.

Reviewer's Comment: The relation of AEs to study drug exposure is unclear. A majority of patients (51.2%) were uptitrated to PED50 by week 2, and by week 4, all but 2 (77.9%) of those who would uptitrate had done so. From week 8 onward, exposure was mostly stable (with the exception of patients whose treatment was interrupted according to protocol-specified criteria) but the data for onset, first onset, and prevalence of TEAEs shows a notable decrease in TEAE's for weeks ≥ 8 to < 12 and ≥ 36 to < 52.

Intrinsic and Extrinsic Factors

The incidence of TEAEs was analyzed according to sex, race, drug formulation, dosing regimen, and use of NDO medication at screening/prior to start of washout. Table 50 provides an overview of the incidence of TEAEs in each age group according to these factors.

Table 50 TEAEs by Sex, Race, Drug Formulation, and NDO Medication Use at Baseline in Study 178-CL-206A (SAF)

MedDRA v16.0 System Organ Class Preferred Term, n (%)	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Overall	**33 (60.0)**	**18 (58.1)**	**51 (59.3)**
Sex			

Male	54.5	70.6	61.5
Female	63.6	42.9	57.4
Race			
Asian	69.2	85.7	75
White	60	50	56.5
Drug Formulation			
Tablets	57.9	60.7	59.6
Suspension	61.1	33.3*	59.0
Use of NDO Medications at Screening			
Yes	63.2	47.4	57.9
No	52.9	75.0	62.1

*In the adolescent group, only 3 patients total took the oral suspension.
Source: 178-CL-206A CSR, Tables 12.6.1.1.37, 12.6.1.1.23, 12.6.1.1.27, 12.6.1.1.31.

Analyses were also performed by stop of antimuscarinics medications (no TEAEs were reported for those who stopped an antimuscarinic medication specifically intended for NDO treatment for lack of efficacy) [Table 12.6.1.1.33, p. 1433]. The incidence of TEAEs in the study population when patients with positive urine cultures at baseline, week 4, or week 24 were excluded showed that TEAEs occurred in 38.2% of children, 25.8% of adolescents, and 33.7% overall, suggesting that having a positive urine culture at any of these times increased the risk of TEAEs [Table 12.6.1.1.35, p. 1465].

Drug-related TEAEs (as determined by the investigator) were infrequently reported. Regarding sex, for patients of all ages, male patients reported drug-related TEAEs at higher rates than female patients (20.5% vs 12.8% respectively). Children of both sexes reported drug-related TEAEs at similar rates (13.6% vs 15.2% respectively), whereas adolescent males reported them at higher rates than females (29.4% vs 7.1%, respectively). Regarding race, White patients reported drug-related TEAEs more frequently than Asian patients (19.5% vs 10%, respectively). Regarding drug formulation, patients taking tablets reported drug-related TEAEs more frequently than patients taking oral suspension (23.4% vs 7.7%, respectively). Regarding patients who took NDO medication at screening/prior to start of washout, drug-related TEAEs were reported more frequently by those who did not use NDO medications (27.6%) vs those who did use NDO medications (10.5%).

Reviewer's Comment: Overall, the analysis of TEAEs by subgroup (sex, race, drug formulation, and use of NDO medications at screening) revealed no differences in TEAE incidence across children, adolescents and all patients. The drug formulation results, as noted previously in this review, were confounded by patient age (only 3 [7.7%] adolescents took the oral suspension). The higher incidence of TEAEs in Asian patients compared to White patients is difficult to interpret because there were so few patients in the Asian subgroup. Similarly, the subgroup analyses of TEAEs were not meaningful for the subgroups of ethnicity (only 3.5% of patients were Hispanic or Latino) and dose regimen (only 23.5% of patients had not uptitrated their dose to 50 mg by week 2, and all but 4 patients had uptitrated their mirabegron dose by week 8).

8.7.5 Laboratory Findings

Analysis of routine clinical laboratory parameters provided no evidence of influence of therapy with mirabegron on hematology laboratory test results or clinical chemistry test results in the Phase 3 study 178-CL-206A in patients with NDO and in the supportive Phase 1 studies in patients with NDO and OAB symptoms.

No "Hy's Law" cases were reported. Only one patient had liver function tests results that met PCS values: an adolescent had a total bilirubin > 2xULN (1/30 [3.3%]). The total bilirubin elevation was not reported as an AE. For the narrative for this patient (b) (6) the reader is referred to Section 8.7.1.

No trends in change from baseline in urinalysis were observed for patients in the Phase 3 study 178-CL-206A and supportive Phase 1 studies.

Reviewer's Comment: AST increased and blood creatine phosphokinase increased were the only two TEAEs reported that were related to clinical laboratory testing. These two TEAEs occurred in the same patient, whose narrative is provided in Section 8.7.2.

Renal function did not appear affected by mirabegron therapy. In the Phase 3 study 178-CL-206A, there was no change from baseline in creatinine through the end of study drug treatment, and shift tables showed similar percentages of patients increased in category as decreased (17.2% vs 15.6%). For eGFR calculated using Cystatin C (according to the Larsson formula), eGFR remained unchanged in category from baseline to week 52 in 98% (50/51) of patients. Creatinine clearance using the Schwartz equation showed 81.3% (25/32) categorized as no change from baseline to 52 weeks, with no patients with available data increasing or decreasing in category. One patient had a low GFR at baseline and week 52 as calculated using the Schwartz equation. Data from the Phase 1 studies 178-CL-202 and 178-CL-203 for renal function was also unremarkable.

Reviewer's Comments: Overall, there is no evidence to suggest that mirabegron treatment increases risk for laboratory abnormalities, including measures of renal function.

8.7.6Vital Signs

Reviewer's Comment: We consulted the Division of Pediatric and Maternal Health (DPMH) on several occasions during the course of the pediatric IND drug development program, in particular, to assist in the approach to vital sign assessments in the pediatric clinical studies. For example, DPMH evaluated the vital sign data from Phase 1 study 178-CL-203 to determine whether the Applicant could safety proceed with the planned Phase 3 study 178-CL-206. For the current NDA 213801 and NDA 202611/S-17, the DPMH team was consulted again, this time to provide an assessment of the overall adequacy of the Sponsor's collection and analyses of the vital signs (heart rate and blood pressure) data in the submitted pediatric studies. In this section, we will present a summary of the Sponsor's analysis and findings, followed by an overview of DPMH's assessment, findings, and recommendations.

In the phase 3 study 178-CL-206A, two methods were used for measurement of blood pressure:

the oscillometric method (used in 46/55 children and 29/31 adolescents) and the auscultatory method (used in 9 children and 2 adolescents). Because 8 of the 86 patients discontinued the study drug prior to the first postbaseline assessment, the total number of patients included in the vital sign analysis was 78 (50 children and 28 adolescents).

The Sponsor analyzed blood pressure measurements for each age group by assessing the central tendency of vital sign (SBP, DBP and HR at weeks 2, 4, 8, 12, 24, 36, and 52), potentially clinically relevant (PCR) values, and shifts in BP category for measurements taken in the clinic and at home. The Sponsor used different sources for norms in their assessment of vital signs, PCR values, and shift categories for measurements taken in the clinic and home.

For vital signs measured in a clinic setting, the Sponsor completed analyses using the following standards:

- BP norms were based on NHLBI Fourth Report (2005) and AAP Clinical Practice Guidelines (2017); HR norms based on Fleming (2011)
- PCR categories were based on NHLBI Fourth Report (2005) and AAP Clinical Practice Guidelines (2017); HR norms were based on Fleming (2011)
- Shift tables used categories based on NHLBI Fourth Report (2005) and AAP Clinical Practice Guidelines (2017).

For vital signs measured in the home setting:

- BP norms were based on Stergiou (2007) and AAP Clinical Practice Guidelines (2017); HR norms were based on Fleming (2011)
- PCR categories were based on AAP Clinical Practice Guidelines (2017); HR -- norms based on Fleming (2011)
- Shift tables used categories based on Stergiou (2007) and AAP Clinical Practice Guidelines (2017)

Clinic Measurements

The Sponsor's presented their analysis of BP using the categories and stages of SBP and DBP based on AAP Clinical Practice Guidelines.

In their analysis of SBP, the Sponsor found that the mean *percentile* SBP change from baseline for children was +1.52%, +9.70%, +7.00% and +11.07% at weeks 4, 12, 24, and 52, respectively. In adolescents, the Sponsor found the mean *percentile* SBP change from baseline was +0.25%, +0.50%, +1.51% and -1.10% at weeks 4, 12, 24 and 52, respectively. In their analysis of DBP, the Sponsor found that the mean *percentile* DBP change from baseline for children was +3.29%, +6.40%, +3.00% and +1.96% at weeks 4, 12, 24 and 52, respectively. In adolescents, the Sponsor found the mean *percentile* DBP change from baseline was +4.73%, +4.25%, +3.01% and -2.38% at weeks 4, 12, 24 and 52, respectively.
Table 51 below summarizes the Sponsor's analysis results.

Shift in categories for SBP from baseline (normal or elevated SBP or Stage 1 HTN) to postbaseline (Stage 1 HTN or Stage 2 HTN) occurred in 10 (20%) children. In adolescents, 6

(21.4%) patients reported a similar shift in categories (normal or elevated SBP or Stage 1 HTN to Stage 1 HTN or Stage 2 HTN, respectively). For DBP, similar shift in categories occurred in 11 (22.0%) children and 6 (21.4%) adolescents. The Sponsor chose to present their blood pressure shift analyses using norm values based on the AAP Clinical Practice Guidelines (2017).

PCR values for SBP were reported in no children and in 1 adolescent. No PCR values for DBP were reported in children or adolescents.

Reviewer's Comment: The Sponsor presented their mean changes from baseline in percentages, instead of mm Hg, which is less informative at first glance and required manipulation for comparison with DPMH's analysis of mean changes. See later parts of this section for information on mean changes in blood pressure.

In their analysis of pulse rate, the Sponsor found that the *mean* change from baseline for children was +1.94, +0.72, -0.47 and +2.32 bpm at weeks 4, 12, 24 and 52, respectively. In adolescents, the Sponsor found that the mean change from baseline in pulse rate was +2.79, -1.13, +1.77 and +0.89 bpm at weeks 4, 12, 24 and 52, respectively. These findings are included in the Table 51.

The Sponsor found that *PCR values* above the reference range for pulse rate were reported 3 (6%) children, and 3 children reported readings above the reference range at weeks 4, 24, and 52; no children reported pulse rate readings below the reference range. Two (7.1%) adolescents reported a PCR values for pulse rate. No pulse rate readings were below the reference range, but 4 readings were above the reference range, at baseline and at weeks 4, 24 and 52.

Table 52 below summarizes the incidence of PCR values for SBP and DBP (using both Clinical Practice Guidelines and the NHLBI Fourth Report as norms) and HR and includes shift information in each age group for the Sponsor's analysis.

Reviewer's Comment: The increases in SBP and DBP in children identified by the Sponsor was a review issue and prompted our consultation to DPMH to assist in the assessment of the vital sign data.

The Sponsor considered potential confounding variables for vital sign measurements. They noted that in study 178-CL-206A, vital signs were intended to have been collected preceding venipuncture for PK assessments. If, instead, the PK sample was drawn in the one hour before vital signs were collected, the Sponsor including an asterisk in the vital sign plot for that patient. Additionally, the study sites (at the investigator's discretion) could have employed clinical activities to decrease the stress caused to patients by the hospital setting and the study assessments, including blood draws. Those clinical activities or the patients' demeanor during the vital sign measurements were not captured in the study database. The only information included in the database reflecting potentially confounding factors was the timing of blood draws relative to the timing of vital sign measurements.

Reviewer's Comment: Ten (10) children and 5 adolescents had at least 1 blood draw within one hour before the vital sign measurement, based on review of the individual plots marked with

asterisks. However, in 7 of the 10 children identified with an asterisk, the blood pressure measurements associated with the blood draw were normal; in 2 children, blood pressures were in the pre-hypertensive range, and 1 child had a BP in the stage 1 hypertension category. Based on the low number of elevated pressures associated with blood draws performed <1 hour before vital sign measurement, stress related to venipuncture appears not to be a significant confounding factor for vital sign assessments.

Table 51 Vital Signs: Changes From Baseline in Blood Pressure (Percentiles) and Pulse Rate - Clinic Measurement (Clinical Practice Guidelines, 2017) (SAF)

Parameter	Children (3 to < 12 Years) n = 55					Adolescents (12 to < 18 Years) n = 31					All Patients (3 to < 18 Years) n = 86				
Study Visit	n	Mean (SD)	Min	Med	Max	n	Mean (SD)	Min	Med	Max	n	Mean (SD)	Min	Med	Max
Percentile SBP: Change From Baseline															
Week 4	50	1.52 (20.86)	-49.4	1.75	61.3	28	0.25 (18.88)	-36.6	-0.55	33.8	78	1.06 (20.05)	-49.4	0.55	61.3
Week 12	46	9.70 (20.23)	-29.2	9.50	46.2	27	0.50 (25.88)	-64.3	-1.30	70.5	73	6.30 (22.75)	-64.3	3.80	70.5
Week 24	45	7.00 (19.41)	-51.5	7.50	45.9	27	1.51 (25.82)	-60.1	0.00	57.7	72	4.94 (22.02)	-60.1	1.45	57.7
Week 52	41	11.07 (21.37)	-26.5	9.20	56.6	26	-1.10 (17.48)	-48.7	-2.45	32.5	67	6.35 (20.69)	-48.7	2.50	56.6
Percentile DBP: Change From Baseline															
Week 4	50	3.29 (17.69)	-44.7	5.45	39.3	28	4.73 (14.44)	-32.3	7.85	28.8	78	3.81 (16.52)	-44.7	5.85	39.3
Week 12	46	6.40 (17.71)	-38.0	7.95	39.1	27	4.25 (23.44)	-50.7	4.70	46.2	73	5.61 (19.89)	-50.7	7.20	46.2
Week 24	45	3.00 (17.92)	-30.8	1.60	45.3	27	3.01 (24.21)	-50.4	0.40	50.7	72	3.00 (20.34)	-50.4	1.35	50.7
Week 52	41	1.96 (18.41)	-34.7	4.20	36.2	26	-2.38 (22.74)	-72.3	0.50	29.1	67	0.27 (20.14)	-72.3	1.00	36.2
Pulse Rate: Change From Baseline															
Week 4	50	1.94 (10.96)	-23.4	2.50	25.0	28	2.79 (8.06)	-12.4	2.85	26.0	78	2.24 (9.97)	-23.4	2.70	26.0
Week 12	46	0.72 (10.77)	-19.6	-0.35	35.0	27	-1.13 (7.77)	-18.4	-1.60	14.0	73	0.04 (9.75)	-19.6	-1.00	35.0
Week 24	45	-0.47 (11.00)	-20.0	-0.70	31.0	27	1.77 (11.55)	-15.6	-2.40	33.4	72	0.37 (11.18)	-20.0	-1.00	33.4
Week 52	41	2.32 (13.40)	-29.7	2.00	33.7	26	0.89 (11.33)	-24.0	0.80	23.0	67	1.77 (12.57)	-29.7	1.60	33.7

Source: Adapted from 178-CL-206A CSR, Table 40, p.105.

Table 52 Potentially Clinically Relevant Values in Vital Signs – Clinic Measurements (SAF)

Vital Sign: Criteria†	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Clinical Practice Guidelines, 2017			
Systolic Blood Pressure (mmHg):			
• 3 to < 13 years: Any SBP above the 95th percentile + 12 mmHg or ≥ 140 mmHg (whichever is lower) at a postbaseline visit • ≥ 13 years: SBP ≥ 140 mmHg at a postbaseline visit	0/50	1/28 (3.6%)	1/78 (1.3%)
• Change in category from baseline (normal or elevated BP or Stage 1 HTN) to postbaseline (Stage 1 HTN or Stage 2 HTN)	10/50 (20.0%)	6/28 (21.4%)	16/78 (20.5%)
Diastolic Blood Pressure (mmHg):			
• 3 to < 13 years: Any DBP above the 95th percentile + 12 mmHg or ≥ 90 mmHg (whichever is lower) at a postbaseline visit • ≥ 13 years: DBP ≥ 90 mmHg at a postbaseline visit	0/50	0/28	0/78
• Change in category from baseline (normal or elevated BP or Stage 1 HTN) to postbaseline (Stage 1 HTN or Stage 2 HTN)	11/50 (22.0%)	6/28 (21.4%)	17/78 (21.8%)
Fourth Report (NIH), 2005			
Systolic Blood Pressure (mmHg):			
• Any SBP above the 99th percentile + 5 mmHg at a postbaseline visit	0/50	1/28 (3.6%)	1/78 (1.3%)
• Change in category from baseline (normal or prehypertension or Stage 1) to postbaseline (Stage 1 or Stage 2)	10/50 (20.0%)	5/28 (17.9%)	15/78 (19.2%)
Diastolic Blood Pressure (mmHg):			
• Any DBP above the 99th percentile + 5 mmHg at a postbaseline visit	0/50	0/28	0/78
• Change in category from baseline (normal or prehypertension or Stage 1) to postbaseline (Stage 1 or Stage 2)	9/50 (18.0%)	4/28 (14.3%)	13/78 (16.7%)
Fleming et al, 2011			
Pulse Rate (bpm):			
• Above the 99th percentile compared to age-related norms pulse rate and ≥ 15 bpm change from baseline	3/50 (6.0%)	2/28 (7.1%)	5/78 (6.4%)

Note: 8/86 patients discontinued before first postbaseline assessment of vital signs, hence the denominator equals 78.
† For each patient, the worst case among all postbaseline measurements was used.
Source: 178-CL-206A CSR, Table 41, p. 106.

Home Measurements

The Sponsor reported that results for home measurement of vital signs were similar to clinic measurements. However, they did note that the overall numbers of patients meeting the home measurement criteria for potentially clinically relevant SBP, DBP, and pulse rate were *lower* when compared with clinic measurements.

Finally, The Sponsor analyzed clinic and home vital signs by the following subpopulations: race, ethnicity, formulation, dosing regimen, NDO medication treatment at screening/prior to start of washout.

Reviewer's Comments: There was no evidence of vital sign differences based on subpopulations categories. The analysis based on formulation was confounded by age, as have similar analyses by subpopulation throughout this review.

In collaboration with the Office of Clinical Pharmacology (OCP), including the Division of Pharmacometrics (DM), DPMH conducted a comprehensive review of the vital signs data. To describe their process in overview, they made the three following choices concerning their data assessment:

- DPMH chose to focus on BP changes with mirabegron therapy based on in-clinic measurements, obtained by trained personnel using standardized measurement methods, instead of home measurements collected by parents and caregivers because the former would be more reliable.
- DPMH chose to use BP categories according to the NHLBI Fourth Report to evaluate shifts in BP categories to be consistent with the Sponsor's analysis, which determined BP percentiles based on the NHLBI Fourth Report. They noted that the Sponsor had calculated BP percentiles using the NHLBI Fourth report reference standard but expressed concern that the Sponsor used the criteria from the AAP CPG for BP PCR change categories. Use of the CPG was considered inappropriate because these guidelines exclude obese children and adolescents from the reference population, resulting in lower BPs for each percentile.
- DPMH chose to assess HR elevations based on criteria according to Fleming et al. and assessed changes in HR above the 90^{th} and 99^{th} percentile to explore the range of HR increases leading to changes above these two percentile points. They noted that the Sponsor had more stringent criteria -- exceeding the higher cutoff (99^{th}%) and also required a > 15 bpm change -- to determine PCR values, and that these criteria were not endorsed by the Fleming publication.

Reviewer's Comment: DPMH's focus on clinic measurements appears reasonable. Their use of the NHLBI Fourth report for BP PCR change categories and the chosen criteria of changes in HR also appears reasonable.

Regarding the central tendency for blood pressure in children, DPMH found that SBP and DBP and their percentiles increased over the course of the study visits. The pattern of increase for DBP, however, seemed to match SBP increases through week 12, but then increased less notably

than SBP after week 12. DPMH also noted that after week 4, children appeared to have had higher exposures (expressed as AUC) and larger increases from baseline in BP than did adolescents. Adolescents had a less pronounced and sustained increase in BPs overall. The table below provides a summary of mean BP changes and drug exposure from clinic visits over the course of the study.

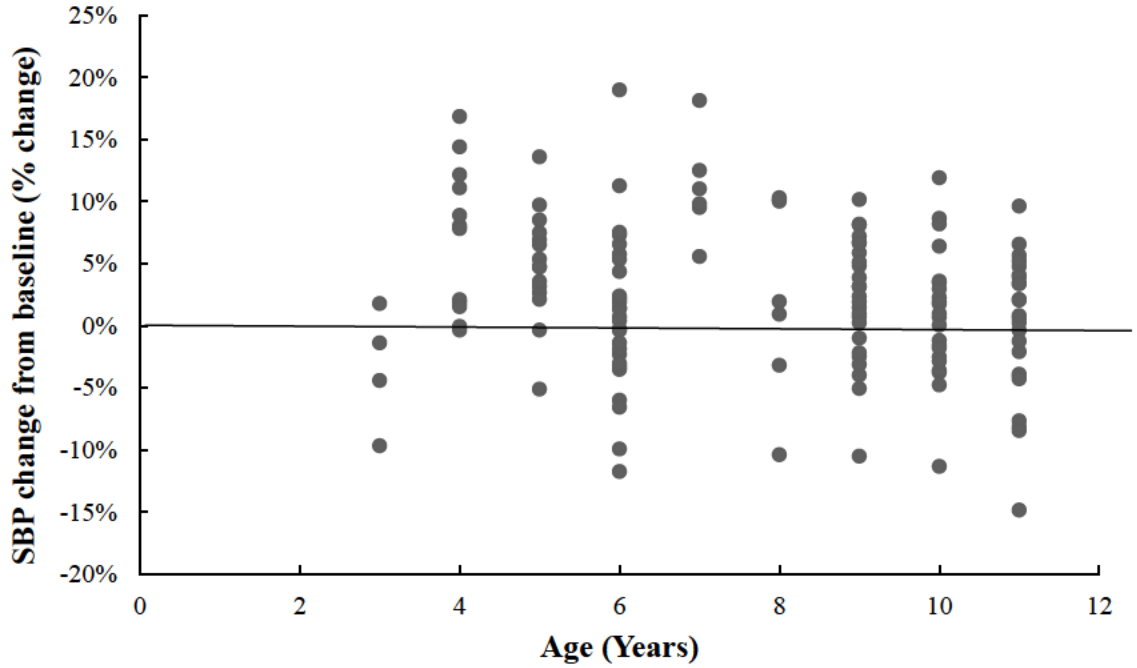
Table 53 Changes in Blood Pressure Relative to Mirabegron Exposure from Clinic Visits in Study 178-CL-206A

Study Visit	Children (3 to < 12 Years)				Adolescents (12 to < 18 Years)			
	n	AUC	SBP (Percentile)	% Normal	n	AUC	SBP (Percentile)	% Normal
Baseline	55	-	102.1 (60.9)	81.8%	31	-	112.8 (61.2)	61.3%
Week 4	50	259.8	+ 1.1 (+ 2.1)	82.0%	28	256.8	+ 0.2 (- 1.5)	67.9%
Week 12	46	306.9	+ 3.9 (+ 9.8)	67.4%	27	270.0	- 0.4 (- 1.5)	70.4%
Week 24	45	298.4	+ 2.9 (+ 6.4)	73.3%	27	247.1	+ 0.9 (- 0.5)	70.4%
Week 52	41	267.4	+ 6.4 (+10.5)	63.4%	26	203.3	+ 0.3 (- 3.0)	65.4%
	n	AUC	DBP (Percentile)	% Normal	n	AUC	DBP (Percentile)	% Normal
Baseline	55	-	65.4 (69.9)	81.8%	31	-	69.8 (65.8)	71%
Week 4	50	259.8	+ 0.8 (+ 3.1)	80%	28	256.8	+ 0.9 (+ 1.9)	71.4%
Week 12	46	306.9	+ 2.2 (+ 5.6)	73.9%	27	270.0	+ 1.0 (+ 0.9)	74.1%
Week 24	45	298.4	+ 1.3 (+ 1.5)	73.3%	27	247.1	+ 1.2 (- 0.4)	66.7%
Week 52	41	267.4	+ 1.5 (- 0.6)	75.6%	26	203.3	- 0.2 (- 4.7)	76.9%

SBP and DBP in mm Hg and expressed as the mean for the baseline study clinic visit and mean change from baseline for subsequent study clinic visits (Mean percentile change from baseline in parentheses)
Source: DPMH consultation, Table 3, p. 13. The original source: per the consult, this Table was abstracted, in part, from Table 15 in the Summary of Clinical Safety (Module 2.7.4, eCTD #1).

Additionally, DPMH generated a plot of the changes in mean SBP by age and found that for children, a majority of the blood pressure elevations occurred in those aged 4 to 7 years old. This finding is illustrated in the figure below.

Figure 1 Changes in Systolic Blood Pressure by Age in Children Study 178-CL-206A



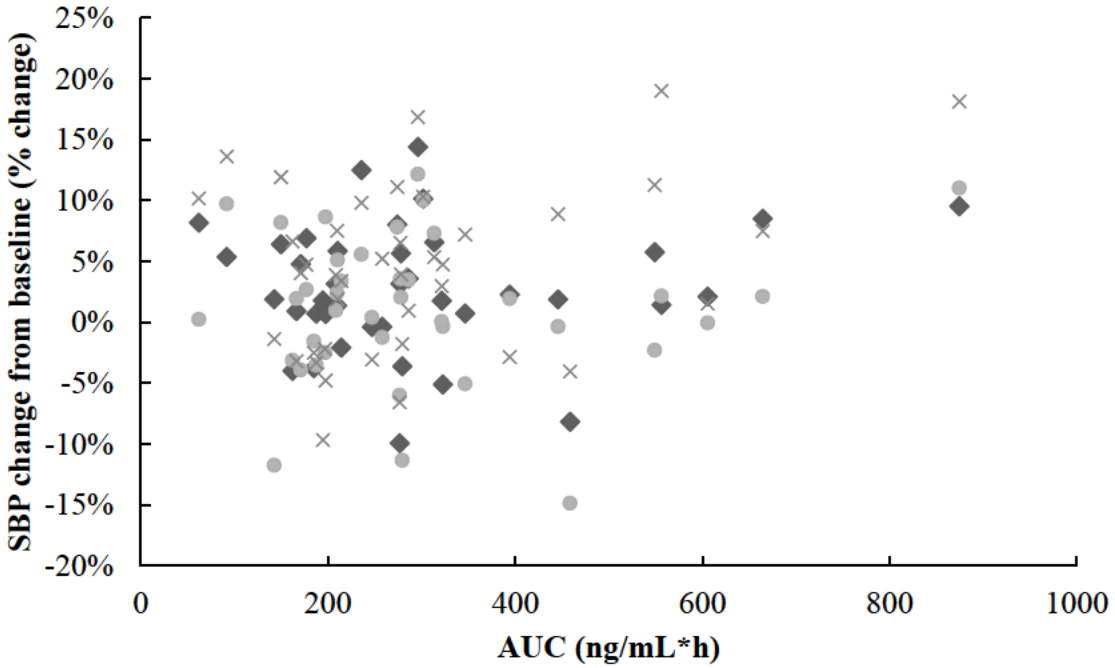
Source: DPMH consultation, Figure 1, p. 14. The original source: per the consult, this figure was generated from vital sign datasets submitted under Study 178-CL-206A (Module 5.3.5.1, eCTD #1).

As a result of their analysis, the DPMH team determined that, in children, the SBP increased by 4.3 mm Hg and the DBP by 1.7 mm Hg from baseline after the week 4 in-clinic visit. Within this group, the SBP increased by 5.9 mm Hg and the DBP increased by 2.3 mm Hg from baseline after the week 4 in-clinic visit in patients less than 8 years of age. The corresponding increase from baseline for adolescents after the week 4 in-clinic visit was 0.3 mm Hg for SBP and 0.7 mm Hg for DBP.

Reviewer's Comment: Change from baseline was calculated for patients starting at the 12 week visit because by that visit, all patients who had uptitrated to the PED50 mirabegron dose had done so. The weighted mean was calculated using the 12 week, 24 week, and 52 week in-clinic BP measurements.

To explore whether the observed increase in BP for children was correlated with increased drug exposure, DPMH performed an analysis of mean AUC at each clinic visit that showed that after the 4-week visit, children had a 14 to 32% higher exposure compared with adolescents at the same visit. The reviewer remarked that 5 children with AUCs exceeding 500 ng/mL*hr appeared to be responsible for this increase. Of note, no adolescents had similarly elevated AUCs. However, after collaboration with the Clinical Pharmacology team, DPMH concluded the following: *"Despite a higher overall mirabegron exposure, there was not a clear exposure-response relationship in children with larger blood pressure elevations."* DPMH provided the figure below to illustrate their conclusion.

Figure 2 Exposure-Response for SBP Change in Children in Study 178-CL-206A



Source: DPMH consultation, Figure 2, p. 15. The original source: per the consult, this figure was generated from PK (ADPC) and vital sign (ADVS) datasets submitted under Study 178-CL-206A (Module 5.3.5.1, eCTD #1).

Overall, for patients who had at least one post-baseline BP, a greater number of children had a normal baseline BP than adolescents (41 [82%] and 18 [64%], respectively), while a greater number of adolescents had a pre-hypertensive baseline BP than children (6 [22%] and 2 [4%], respectively). However, more children than adolescents with normotensive BP at baseline had at least one SBP above the 95th percentile based on the NHLBI Fourth Report during one of the in-clinic study visits (10 [24%] and 1 [6%], respectively). Of those children who had at least one SBP above the 95th percentile for normal, 6 (60%) shifted to Stage I HTN by SBP (compared to no adolescents). Only one adolescent (compared to no children) who was prehypertensive at baseline shifted to Stage I HTN by SBP. Regarding patients who were normotensive at baseline, the percentages of patients who had at least 1 DBP above the 95th percentile for normal at a follow up visit was similar between the two age groups (15% for children and 10% for adolescents). It is notable that all 6 of the children who were normotensive at baseline but had at least 1 DBP above the 95th percentile of normal were included in the 10 children who met that criteria for SBP. Overall, a small and similar number of patients shifted to Stage I HTN by DBP criteria: one baseline normotensive and one baseline prehypertensive from each age group. A single adolescent who had Stage I HTN at baseline did develop Stage II HTN (by SBP) but then switched back to Stage I HTN without alterations to his study drug treatment.

Table 54 below provides a summary of these results.

Reviewer's Comment: To better understand the conclusions from BP category shift analyses, it is important to clarify the way subjects were categorized.

First, in order to be categorized as having experienced a shift in BP category, the post-baseline shift had to be confirmed by a follow-up that was "separate in time". However, such confirmation was not required for the baseline BP categorization. The Sponsor's categorization of patients at baseline as normotensive, prehypertensive, Stage I HTN or Stage II HTN is based on BPs collected at the baseline visit only (using criteria from the NHLBI Fourth Report). It is unknown whether results of the shift analysis would have been different if repeated baseline measurements, separated in time, would have been required to define the baseline BP category. For example, if patients categorized as non-normotensive by the Sponsor were required to have had a subsequent abnormal BP to confirm their categorization as non-normotensive at baseline, would more patients have been categorized as normotensive at baseline, leading to a larger number and percentage of patients with BP shifts?

Also, in conducting their analysis, the DPMH team differentiated between those patients with at least 1 SBP or DBP above the 95th percentile during a follow-up visit and those patients with 2 or more such elevated BPs, separated by time. Patients with repeated elevated BPs above the 95th percentile who were normotensive at baseline were categorized as having shifted to Stage I HTN.

Table 54 Summary of BP at Baseline and Shifts to Stage I and Stage II Hypertension†, 178-CL-206A

Category#	Baseline BP Categorization‡					
	Children (3 to < 12 Years)			Adolescents (12 to < 18 Years)		
	Normotensive	PreHTN	Stage I HTN	Normotensive	PreHTN	Stage I HTN
Baseline SBP **Baseline DBP**	41 (82%) 41 (82%)	2 (4%) 3 (6%)	7 (14%) 6 (12%)	18 (64%) 21 (76%)	6 (22%) 4 (14%)	4 (14%) 3 (10%)
At least 1 SBP > the 95th percentile at a later visit	10 (24%)	0	6 (86%)	1 (6%)	3 (50%)	3 (75%)
Shift to Stage I HTN by SBP	6 (60%) of the 10 above	0	N/A	0	1 (33%) of the 3 above	N/A
At least 1 DBP > the 95th percentile at a later visit	6 (15%)	3 (100%)	5 (83%)	2 (10%)	2 (50%)	2 (67%)
Shift to Stage I HTN by DBP	1 (17%) of the 6 above	1 (33%) of the 3 above	N/A	1 (50%) of the 2 above	1 (50%) of the 2 above	N/A
Shift to Stage II HTN	0	0	0	0	0	1*

†All patients with at least one follow-up BP measurement.
‡ Criteria for baseline categories per Sponsor are defined by the NHLBI Fourth Report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents.
# Determination regarding shift to Stage I HTN is based on the NHLBI Fourth Report which recommends multiple BP measurements over time, recorded at above the 95th percentile, before diagnosing HTN. Counts of patients who had as few as one post baseline measurement above the 95th percentile, according to the NHLBI Fourth Report criteria, are also presented.
* This patient returned to Stage I HTN at subsequent visits without change to mirabegron treatment.

Source: Compiled from text of DPMH consultation and in collaboration with DMPH reviewer.

Reviewer's Comment: According to our discussions with DPMH, their method of evaluating shifts to Stage I HTN is considered the most clinically meaningful, as single elevations can reflect BP variability and are more likely to be confounded by other factors.

DPMH team made three additional observations about the BP data:

- Analysis according to study completion: Whether a patient completed the follow-up through the full 52 weeks or not complete the full 52 weeks did not affect the proportion of patients, for SBP or DBP, in each post-baseline hypertension category. However, for those patients who did complete the full 52-week study follow up, children were more likely than adolescents to change from normotensive to Stage I HTN (24% and 8%, respectively).
- Trends in BP category changes: For those patients who completed the full 52 weeks of follow up, DPMH analysis showed that while the percentage of children with normal SBPs declined over the course of the study, the greatest decline occurred at the week 12 visit. For adolescents, the percentage with normal SBP or DBP declined as well, but the decrease for each group was modest and not sustained.
- PCR changes were not related to method of BP measurement (oscillometric method vs auscultation)
- No AEs reflecting symptoms of acute hypertension were reported in associated with any BP elevations.

The assessment of HR changes from baseline and the associated AUC at each visit are shown in the table below. Small increases in HR (mean increase in HR was 1.1 bpm for children and adolescents) were observed in both children and adolescents, and those increases did not appear to be correlated with AUC.

Table 55 Changes in Heart Rate from Study Clinic Visits in Children and Adolescents in Study 178-CL-206A

Study Visit	Children (3 to < 12 Years)			Adolescents (12 to < 18 Years)		
	n	AUC	HR*	n	AUC	HR*
Baseline	55	-	93.4	31	-	85.4
Week 4	50	259.8	+ 1.9 (+2%)	28	256.8	+ 2.8 (+3.3%)
Week 12	46	306.9	+ 0.7 (+0.8%)	27	270.0	- 1.1 (-1.3%)
Week 24	45	298.4	- 0.5 (-0.5%)	27	247.1	+ 1.8 (+2.1%)
Week 52	41	267.4	+ 2.3 (+2.5%)	26	203.3	+ 0.9 (+1.1%)

*HR in beats per minute and expressed as the mean for the baseline study clinic visit and mean change from baseline for subsequent study clinic visits (Percent change from baseline in parenthesis).
Source: modified from DPMH consultation Table 4, p. 17. Original source: Table abstracted from Table 15 in the Summary of Clinical Safety (Module 2.7.4, eCTD #1)

PCR HR values occurred in similar percentages of children and adolescents during visits in clinic (6% and 7.1%, respectively). When PCR HR value incidence was analyzed by method of

measurement, no PCR HR value was associated with auscultation, while 7% of patients measured with oscillometric methods had PCR HR values.

The percentage of patients with a baseline HR > 90th percentile was higher in adolescents than children (22.6% vs 9.1%). No patients had a baseline HR > 99th percentile. Over the course of the study visits, the percentage of patients with HR > 90th percentile narrowly fluctuated but no trend over time was apparent. Increased AUC appeared not to be related to increased incidence of HR exceeding the 90th or the 99th percentile thresholds. The table below provides a summary of DPMH's HR findings.

Table 56 Heart Rate Parameters from Study Clinic Visits in Children and Adolescents in Study 178-CL-206A

Study Visit	Children (3 to < 12 Years)				Adolescents (12 to < 18 Years)			
	n	AUC	Proportion > 90%ile*	Proportion > 99%ile*	n	AUC	Proportion > 90%ile*	Proportion > 99%ile*
Baseline	55	-	9.1%	0%	31	-	22.6%	0%
Week 4	50	259.8	14%	2%	28	256.8	35.7%	7.1%
Week 12	46	306.9	8.7%	0%	27	270.0	14.8%	0%
Week 24	45	298.4	6.7%	0%	27	247.1	33.3%	3.7%
Week 52	41	267.4	12.2%	2.4%	26	203.3	15.4%	3.8%

*HR Percentiles abstracted from Figure 4: Centiles of heart rate for normal children from birth to 18 years of age from Fleming et al.

Source: modified from DPMH consultation Table 5, p.18. Original source:Table generated from vital sign (ADVS) datasets submitted under Study 178-CL-206A (Module 5.3.5.1, eCTD #1).

Analysis of percentages of patients with HR values > 90th and 99th percentiles by complete follow up at all study visits compared to the full safety analysis set showed no differences between groups.

Finally, in the consultation, DPMH compared the home and clinic BP and HR measurements for children between 4 and 7 years old. They determined that home measurements were generally higher than clinic measurements and that the direction and magnitude of BP changes per visit in the two settings was correlated. HR measurements were relatively stable and small increases at home were less pronounced than in the clinic measurements. Based on these determinations, DPMH concluded that anxiety did not play an important role in the BP elevation measured in clinic for the 4 to 7-year old patients.

Reviewer's Comment: In summary, the DPMH team provided the following conclusions on their assessment of the BP and HR findings in pediatric NDO patients:

"Mirabegron appears to have increased BP disproportionately in children compared with adolescents participating in Study 178-CL-206A. The reasons for this occurrence are unclear based on review of the vital sign data. Approximately 24% of the children who were

normotensive at baseline developed at least one measured BP at or above the 95th percentile (of normal) in Study 178-CL-206A, and HTN was sustained in approximately 60% of these children. The magnitude of the observed SBP and DBP increases seen in adolescents from Study 178-CL-206A were similar to those already reported in the approved adult population. None of the observed BPs in children led to Stage II HTN, and one adolescent developed Stage II HTN which was not sustained. No patients required discontinuation from the trial because of changes in BP or HR."

They added, "Mirabegron appeared to impact SBP more than DBP after the 12 week study visit in enrolled children, but the precise reason for mirabegron's discrepant effect on BP in the pediatric study population is unclear."

Finally, they concluded that "The increases in BP, which caused sustained shifts in BP categories in more than half of the children, do not represent a barrier to approvability of mirabegron but should be described in mirabegron labeling. Symptoms, such as headaches, which may be attributable to BP increases were uncommon in Study 178-CL-206A and did not lead to discontinuation of mirabegron. Furthermore, monitoring for an adverse reaction of HTN is readily possible with mirabegron use and approved anti-hypertensive drug products can be used to lower BP in children where chronic use is needed."

They recommended that "labeling should reflect changes in BP associated with use at the approved dosages, particularly in younger children (e.g. 3 to 7 years of age)."

Regarding HR, "Mirabegron did not cause clinically meaningful changes from baseline in HR in children and adolescent patients in Study 178-CL-206A."

Reviewer's Comment: We agree with the DPMH consult recommendations. Revisions to labeling will include language in WARNINGS AND PRECAUTIONS regarding the risk of increased blood pressure in children, especially in those less than 8 years old.

8.7.7 Electrocardiograms (ECGs)

In response to information requested in our 74-day letter, the Sponsor submitted narratives for all cases reported as QT interval prolongation, whether by Bazett's or Fridericia's correction.

As described in the consultation reports DUOG received from IRT-QT in DCN, the use of Bazett's correction for QT has been shown to be inferior for adults and has been shown to be associated with false positive increases in QTc if heart rate is elevated (a known effect of mirabegron). For this reason, our review focused on cases reported as QTcF prolongation. Our review also touches briefly on the rest of the cases that were reported as TEAEs of QT prolongation (some of these have been reviewed in earlier sections of this review).

In phase 3 study 178-CL-206A, the only reported cases of QTcF prolongation were for QTcF prolongation ≥ 30 ms from baseline, which was reported in 2 patients at week 24 (one child, one adolescent) and one patient at week 52 (child). These prolongations were not reported as TEAEs

and were not considered by the investigator to be clinically significant. The following are mini-narratives for these three patients:

- Case (b) (6) is a 14-year old White female from Poland with no QTcF measurements > 450 ms. A single CFB (average) of 34.2 ms was recorded at week 24. Mirabegron was continued and QTc prolongation resolved.
- Case (b) (6) is a 10-year old White female from Croatia with no QTcF measurements > 450 ms. A single CFB (average) of 33 ms was recorded at week 24. Mirabegron was continued and QTc prolongation resolved.
- Case (b) (6) is a 60-year old Asian male from South Korea with no QTcF measurements > 450 ms. A single CFB (average) of 41 ms was recorded at week 52 for QTcF's all < 420ms.

Reviewer's Comment: In none of these three cases was even a single measurement of QTcF prolonged. We agree with our colleagues from the IRT-QT and the Sponsor that these cases were not cases of QT prolongation, were not clinically significant, and show no evidence of increased risk of prolonged QT interval in patients taking mirabegron.

The single case in study 178-CL-206A reported as a TEAE of QT prolonged was reported for a patient with a prolonged QTcBazett's. As noted previously, use of Bazett's correction is not recommended in circumstances where heart rate is affected by a drug. The QTcF measurement at the same time for this patient was normal at 417 ms (<30 ms change from baseline). A narrative for this patient can be found in section 8.7.1.

In the Phase 1 study 178-CL-203, one patient was reported to have a single measurement with CFB QTcF > 30 ms. In this patient, average QTcF and average CFB were normal, and no QTcF intervals > 450 ms were observed. No TEAEs of prolonged QT intervals were reported.

In the Phase 1 study 178-CL-202, seven (7) patients were reported to have at least one prolonged QTcF interval or CFB in QTcF >30.

- 3 patients had ECGs with a single, isolated measurement of QTcF > 450, without elevated average measurements at any time point for QTcF or CFB
- 1 patient had an ECG with a single, isolated measurement of QTcF > 450 at the pre-dose time point only.
- 1 patient had ECGs showing elevated QTcF average at the pre-dose timepoint and at 2h, 4h, 6h, and end of study timepoints.
- 1 patient had ECGs with no evidence of elevated QTcF, but one elevated average QTcF CFB
- 1 patient had ECGs with no evidence of elevated QTcF, but one single measurement of elevated QTcF CFB.

Reviewer's Comment: We consulted IRT-QT in DCN to review individual cases reported as QT prolonged in this application. IRT-QT commented that none of the cases that they reviewed raised a concern about QT prolongation related to mirabegron. For the cases described above, none of the cases report prolongation of an average QTcF. All cases reported either isolated

single measurements of QTcF >450msec, QTcF >450 msec at pre-dose and throughout the study, an isolated QTcF CFB with no evidence of prolonged QTcF intervals or a single mildly elevated average QTcF CFB. We agree with our colleagues in IRT-QT that such findings do not raise concerns about QT prolongation related to mirabegron. Fluctuations in QTcF, seen in isolated measurements of prolonged QTcF, are due to normal variability in the QTcF. We agree with the IRT-QT and the Sponsor that these findings are not clinically significant.

ECG QT prolonged TEAEs were reported in two individual patients in the phase 1 supportive study 178-CL-202. Narratives for these two cases are presented and reviewed in section 8.7.4.2.

We consulted the IRT-QT to help DUOG evaluate the reports of QT prolongation in these studies. In their consult, dated January 27, 2021, the IRT-QT confirmed that Fridericia's correction is the preferred QTc formula unless there is a mean HR increase of >10 bpm, and in that situation, individualized correction methods are used; and that use of Bazett's correction is not recommended in the current situation. The IRT-QT consult further noted that in the thorough QT study for mirabegron, the observed mean heart rate increase at 50 mg was less than 10 bpm; therefore use of Fridericia's correction method was appropriate. The consultant also reviewed 9 individual cases reported either as a TEAE of QT prolongation (n=3) or as an ECG abnormality (n=6). Each of these cases was also reviewed by the Clinical review team in DUOG and each has been summarized in this review. In none of these cases was the QTcF prolonged. Based on the cases reviewed, the consultant concluded that there was no evidence of increased risk of QT prolongation related to mirabegron.

Reviewer's Comment: We agree with IRT-QT that the ECG data and the reports of QT prolongation that we reviewed do not provide evidence to support new safety concerns for mirabegron.

8.7.8QT

No additional QT trials were needed to support the supplement. See the section that immediately precedes this one for additional information on QT.

8.7.9Immunogenicity

No studies on immunogenicity were conducted in support of this supplement.

8.7.10 Urinary Tract Ultrasound and PVR

In study 178-CL-206A, ultrasound examinations of the upper urinary tract were performed as safety monitoring for the upper urinary tract. PVR urine assessments were not conducted because all patients used CIC. In studies 178-CL-202 and 178-CL-203, that included pediatric patients not using CIC, PVR was assessed using ultrasound or bladder scan.

Upper urinary tract ultrasound results were interpreted and classified as normal, not clinically significant abnormal, and clinically significant abnormal. Of the 84 patients examined with upper tract urinary ultrasound at baseline, 68 (81%) had normal study results, 15 (17.9%) had not clinically significant abnormal results, and 1 (1.2%) had clinically significant abnormal results. At week 52, of the 65 patients examined, those numbers were 54 (83.1%), 11 (16.9%) and 0 patients. Table 57 provides a summary of the interpretation of the ultrasound results for study 178-CL-206A.

Table 57 Interpretation of Upper Urinary Tract Results (SAF); Study 178-CL-206A

Study Visit Upper Urinary Tract Result, n (%)	Children (3 to < 12 Years) n = 55	Adolescents (12 to < 18 Years) n = 31	All Patients (3 to < 18 Years) n = 86
Baseline, n	54	30	84
Normal	46 (85.2)	22 (73.3)	68 (81.0)
Abnormal-not clinically significant	7 (13.0)	8 (26.7)	15 (17.9)
Abnormal-clinically significant	1 (1.9)	0	1 (1.2)
Week 52, n	40	25	65
Normal	34 (85.0)	20 (80.0)	54 (83.1)
Abnormal-not clinically significant	6 (15.0)	5 (20.0)	11 (16.9)
Abnormal-clinically significant	0	0	0

Source: Summary of Clinical Safety, Table 18, p. 38.

The one patient with clinically significant abnormal results at baseline was withdrawn from the study on day 16 after central review of his baseline urodynamic assessment. In this patient, mirabegron oral suspension was discontinued on day 3. The Sponsor notes that an additional upper urinary tract ultrasound on day 16 was interpreted as abnormal but not clinically significant.

In our 74-day letter, we requested from the Sponsor additional information regarding the 16.9% (n=19) of patients with not clinically significant abnormal results. The Sponsor provided narratives for all 19 of these patients. While the narratives did not optimally document the ultrasound findings and contained limited information, we evaluated them for possible safety signals.

Of the 19 narratives for patients who had abnormal upper urinary tract ultrasounds, all of which were considered not clinically significant by the Sponsor, we determined that:

- 5 showed abnormal findings likely due to pre-existing NDO
- 8 showed findings of NDO with possibly improvement from baseline
- 1 showed no changes from baseline
- 1 showed findings of a non-NDO pre-existing condition (impacted ureteral stone) in a patient who received only 3 days of mirabegron
- 1 showed a new, unrelated condition (ovarian cyst)
- 2 were unassessable because either baseline or follow-up ultrasound was not performed
- 1 was potentially concerning

A single case that raised a potential concern is described below:

Case (b) (6) is a 9-year old Asian female from the Philippines with a history of myelomeningocele, transverse colostomy, closure of colostomy, trans anorectal malformation, endorectal pull through, posterior sagittal anorectovagino-urethroplasty, and NDO, who had taken solifenacin and oxybutynin in the past for NDO. During the study, she was treated with amoxicillin-clavulanic acid for a UTI, the supplement clusivol, and mupirocin for xeroderma. On day -1, the patient's baseline ultrasound showed grade 1 hydronephrosis in the left kidney and a normal right kidney. On day 376, the patient's ultrasound showed bilateral grade 2 hydronephrosis. This progression of hydronephrosis over one year in bother kidneys was classified by the investigator as not clinically significant and it was considered more plausible that this progression was part of the pre-existing condition of NDO. The Sponsor concluded that an effect of the study drug could not be excluded. The only TEAE reported for this patient was a single measurement of prolonged QTcB at week 4.

Reviewer's Comment: To further evaluate this case, we analyzed the urodynamic and eDiary findings in this patient and determined that mirabegron was associated with the expected increase in her bladder capacity and her intermittent catheterizations volumes, at the same detrusor pressure as baseline, indicating improved bladder compliance. In this situation, it appears implausible that mirabegron was the source of the change in the patient's ultrasound finding at week 52.

Reviewer's Comment: All 19 narratives were reviewed. Based on the information provided, we agree with the Sponsor that most of the abnormal findings are not clinically significant. The single case of worsening hydronephrosis after mirabegron treatment cannot be explained by the information provided. There is no evidence of inadequately performed CIC. Based on diary data urodynamic parameters, this patient appeared to improve (detrusor pressure and number of catheterizations per day remained unchanged, while volume per catheterization increased). Further information was not provided for this single case with progression of hydronephrosis described above, and further examination is not possible. We assess this case as possibly related, but lacking clinical information.

In study 178-CL-202, no patient had a PVR exceeding the 20 ml threshold (per the International Children's Continence Society definition). In study 178-CL-203, the three patients not on CIC were all patients with OAB symptoms. In those 3 patients, bladder scans detected no PVR at 5 hours postdose.

8.8 Analysis of Submission-Specific Safety Issues

8.8.1 Submission-Specific Safety Issues

The Submission-Specific Safety issues (SSSI) are those issues that are selected because they are pre-identified important risks or potential risks of mirabegron, as derived from clinical studies of adults with OAB. These issues were identified by the Sponsor and included in their TEAEs of special interest. The reader is referred to section 8.7.4.2 for a full review of the TEAEs of

special interest. These include: cardiovascular TEAEs (increased blood pressure; increased heart rate, tachycardia, atrial fibrillation, or palpitations; and QT prolongation), neoplasms, hypersensitivity reactions, urinary tract infection, urinary retention, seizures, syncope, fetal disorders after exposure during pregnancy, and concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated. Additional analyses of vital signs (section 8.7.6) and ECGs/QT intervals (section 8.7.7) further address the potential cardiovascular risks. The eDiary catheterization volumes and our determinations concerning the results of upper urinary tract ultrasounds (section 8.7.10) are relevant to the potential risk of urinary retention.

In regard to potential cardiovascular risks of mirabegron, based on the analysis conducted by the DPMH Team in collaboration with OCP, it was determined that overall, in the children's group, mirabegron use resulted in a mean increase from baseline of 4.3 mm Hg for SBP and 1.7 mm Hg for DBP. In children 8 years old and younger, the mean increase from baseline was larger at 5.9 mm Hg for SBP and 2.3 mm Hg for DBP. Furthermore, approximately 24% of the children who were normotensive at baseline developed at least one measured BP at or above the 95th percentile for normal in Study 178-CL-206A, and HTN (in large part, Grade 1) was sustained in approximately 60% of these children. There were no TEAEs reported that were related to hypertension. Additionally, the single TEAE categorized a cardiovascular TEAE of interest (increased heart rate, tachycardia, atrial fibrillation, or palpitations) was bradycardia which, after reading the narrative and examining the data, we determined to have been reported in error. Finally, no evidence of increased risk of prolonged QT interval was observed, as most cases reported as QTc prolongation were related to inappropriate correction for heart rate using Bazett's correction, and several identified cases of QTcF prolongation represented isolated measurements of prolonged QTcF that reflect normal QT interval variability.

The single neoplasm case and the 5 hypersensitivity cases were determined to be unassessable or not related to mirabegron treatment. The high incidence of UTI was thought to reflect the high background incidence of UTI in the patient population, and the two SAEs of pyelonephritis acute and *E.coli* UTI were not drug-related. The single TEAE case of seizure was also considered not related to the study drug. The TEAE (worsening of talipes, a congenital condition unrelated to the study drug) of fetal disorders after exposure during pregnancy was miscategorized as there was no pregnancy. There were no TEAEs to suggest increased risk for syncope nor risks related to concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated. Finally, no TEAEs of urinary retention were reported, and a review of selected eDiary catheterization volumes and narratives for patients with abnormal upper urinary tract ultrasound showed all but one were not clinically significant. Although the single case of worsening hydronephrosis could not be explained and may be considered possibly related, clinical information was lacking. PVR measured in the two Phase 1 studies showed no evidence of urinary retention.

8.9 Safety Analyses by Demographic Subgroups

Aside from differences in the blood pressure effect, overall, no differences between children and adolescents were apparent in the safety profile of mirabegron. The overall incidences of TEAEs,

SAEs, and common TEAEs (even within SOC) were similar between the two age groups. For blood pressure specifically, mirabegron treatment caused a mean increase of 4.3 mm Hg in SBP and 1.7 mm Hg in DBP in children (aged less than 12 years of age). Increases in BP were less pronounced in adolescents.

Subgroup analyses of safety results indicate that sex, race, and ethnicity have no effect on patient safety.

8.10 Specific Safety Studies/Clinical Trials

There were no specific safety studies included in this submission.

8.10.1 Interdisciplinary Review Team for QT Studies Consult

A consultation was requested from the IRT-QT in DCN for a QTc evaluation of several reported QT prolongation cases. The most salient IRT-QT observations, with respect to the analysis of prolonged ECG QT interval TEAEs and specifically identified patients with prolonged QTcB and QTcF measurements, have been noted several times previously in this review. In summary, IRT-QT concluded that there was no increased risk of prolonged QT interval associated with mirabegron therapy. For a complete summary of the IRT-QT consultation, the reader is referred to section 8.7.7.

8.10.2 DPMH Consult

A consultation was requested from the DMPH team to assist in the assessment of vital signs (blood pressure and heart rate) data submitted for this NDA and sNDA. For a thorough summary of their consultation comments and recommendations, the reader is referred to section 8.7.6.

8.11 Additional Safety Explorations

8.11.1 Human Carcinogenicity or Tumor Development

No new carcinogenicity studies were conducted for this efficacy supplement.

8.11.2 Human Reproduction and Pregnancy

There were no pregnancies during the study.

8.11.3 Pediatrics and Assessment of Effects on Growth

No adverse effects on growth and development, based on changes from baseline to final visit in height, weight, or BMI, were detected in the phase 3 study included in this submission.

Of note, the Pediatric Exclusivity Board met on February 10, 2021 to discuss the adequacy of the Sponsor's pediatric development program to fulfill the PREA requirements as specified in the WR.

After careful consideration, the Pediatric Exclusivity (PedEx) Board determined that the Sponsor had completed the required studies to fulfill the terms of the Pediatric Written Request (WR) for pediatric studies as issued by FDA. A topic discussed at the PedEx meeting was whether the Sponsor had submitted the required study reports according to the timeline indicated in the WR.

The WR stated that Study 2, the pediatric Phase 3 study, would not be initiated until:

- Preliminary results from the neoplasm post-marketing requirement (PMR) study in adults had been submitted and reviewed by the Agency.
- Results from Study 1, the pediatric PK and tolerability study, and results from an adult bioavailability study comparing the 2 mg/mL and 8 mg/mL suspensions had been submitted and reviewed by the Agency

Study 2 was intended to refer to study 178-CL-206, the planned US-based Phase 3 study. However, for purposes of the WR, studies 178-CL-206A (non-US) and 178-CL-206 were to be considered a single study that would fulfill Study 2 (PMR 1898-2), with just one study report for both studies together. These two studies were originally intended to be parallel studies with identical protocols and would be conducted concurrently. The study results that were required to be submitted before initiating Study 2 included the interim report for the adult neoplasm epidemiology study (to fulfill PMR 1898-4) and the CSRs for studies 178-CL-202 and 178-CL-203 (together making up Study 1, to fulfill PMR 1898-1) and 178-CL-208 (the adult bioavailability study comparing the 2 mg/mL and 8 mg/mL suspensions).

However, Study 2 was not conducted as originally planned. Enrollment for 178-CL-206A (non-U.S.) started first, and it enrolled more than enough patients to meet the PREA and WR requirements. Although 178-CL-206A is a non-IND, non-U.S. study, its findings are applicable to the U.S. pediatric population with NDO because there is no reason to believe that the study population or clinical treatment methods differ by region. Furthermore, the Division confirmed for the Sponsor, at the pre-NDA meeting in November 2019, that the mirabegron pediatric development program as conducted (including the non-IND, non-U.S. study 178-CL-206A *without* the 178-CL-206 U.S. study) was sufficient to support the NDA and sNDA in pediatric patients. Study 178-CL-206 was never conducted.

The start date for the non-IND study 178-CL-206A, which became the sole study performed as Study 2, was June 17, 2016. The submission dates for the results of the studies required to be submitted before initiating Study 2 as per the pediatric WR were as follows:

- The neoplasm epidemiology study interim report was submitted on October 30, 2017
- Study 1: the 178-CL-202 CSR was submitted on February 24, 2016 and the 178-CL-203 CSR was submitted on March 31, 2017
- The 178-CL-208 CSR was submitted on March 31, 2017

Thus, the WR terms were not met exactly because the clinical study reports for 178-CL-203 and 178-Cl-208 and the interim report for the adult neoplasm epidemiology study (to fulfill PMR 1898-4) were not submitted prior to commencement of Study 2 (the non-IND study 178-Cl-206A), as the WR stipulated. However, the study reports for Studies 178-CL-203 and 178-CL-208 did provide complete information to support the dose and formulation used in Study 178-CL-206A**,** and the interim results of the adult neoplasm epidemiology PMR study did not suggest an association between mirabegron and neoplasms. Taking all into consideration, the Pediatric Exclusivity Board voted to grant pediatric exclusivity according to Prong 2.

On February 23, 2021, the Pediatric Review Committee met and reviewed the PeRC assessment. They offered no objection to our planned approval and agreed that pediatric PMRs of the original NDA approval had been fulfilled.

8.11.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No reports of overdose have been reported in the pediatric population. No specific studies have been designed to evaluate withdrawal and/or rebound effects of mirabegron. There are no suggestions from the nonclinical or clinical data that withdrawal or rebound could be expected. Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure and ECG monitoring is recommended.

8.12 Safety in the Postmarket Setting

8.12.1 Safety Concerns Identified Through Postmarket Experience

The Sponsor submitted two safety reports that contained postmarketing safety data for mirabegron tablet use in pediatric patients: a Postmarketing Safety Report (including safety data received from market launch through June 30, 2019) and the 120-Day Safety Update (including safety data received between July 1, 2019 and June 30, 2020). Each safety update submission was comprised of the following components:

- an analysis of postmarketing data and adverse events
- a review of the published literature

In the Postmarketing Safety Report reporting period, there were 323 post marketing pediatric case reports. The SOCs with the most reported postmarketing cases were injury, poisoning and procedural complications; general disorders and administration site conditions; nervous system disorders; and psychiatric disorders.

Of these 323 reports, 314 were nonserious (6 infants, 190 children, and 118 adolescents), and 9 were serious (2 children and 7 adolescents).

In the infant age group, (age 29 days to <2 years), 2 cases reported accidental exposure via breast milk from mothers taking mirabegron, and no adverse drug events were noted in the infants. Accidental ingestion was reported in the remaining 4 cases. In 3 of these 4 cases, the infants

took 1 tablet each, and in the fourth case, the infant ingested 3 tablets of mirabegron. All infants vomited soon after the intake and underwent precautionary medically evaluation with no further complications reported.

The Sponsor provided narratives for each of the 9 serious pediatric case reports.

Table 58 Serious Adverse Events Received for Pediatric Patients until 30 Jun 2019

Case Number	Report Type	Medically Confirmed	Age/Sex	SAE (PTs)	Reported Causality
Child (5 to < 12 years)					
(b) (6)	Spontaneous	Yes	7 years/Male	Fecaloma	Not assessed
Child (age unspecified)					
(b) (6)	Invalid case†	Yes	Unknown/ Unknown	Hypertension	Possible
Adolescent (12 to < 18 years)					
(b) (6)	Spontaneous	Yes	15 years/Female	Hypersensitivity	Not assessed
	Spontaneous	No	12 years/Female	Sinus tachycardia Hypertension	Possible Possible
	Spontaneous	Yes	17 years/Male	Mania	Not related
	Authority	Yes	12 years/Female	Urinary retention	Not assessed
	Authority	Yes	17 years/Female	Pain in extremity Inflammation Hypoesthesia Vasculitis Peripheral swelling	Not assessed Not assessed Not assessed Not assessed Not assessed
	Authority	Yes	16 years/Female	Lethargy Depressed mood	Not assessed Not assessed
	Authority	Yes	15 years/Female	Suicidal ideation Anhedonia Lethargy Depressed mood Somnolence Asthenia Fatigue Product use issue	Not assessed Not assessed Not assessed Not assessed Not assessed Not assessed Not assessed Not assessed

Source: Postmarketing Safety Report, p.6.

In the 192 postmarketing case reports for children (2 to < 12 years), only 11 case reports included adverse drug events. Of these 11 cases, 9 reported nonserious adverse drug events (constipation, headache, nausea/vomiting, somnolence/dizziness, vision blurred, pain in extremity, feeling jittery, decreased micturition frequency and atopic dermatitis), and 2 cases (b) (6) reported serious adverse drug events.

Case (b) (6) involved a 7-year-old boy who experienced severe constipation leading to fecaloma that developed at an unspecified time after initiation of treatment with mirabegron. The patient's constipation required treatment.

Case (b) (6) involved 6 children with spina bifida who were treated with mirabegron for neurogenic bladder and experienced adverse drug events. The SAE of hypertension was reported in one child and was considered drug related by the reporter. Mirabegron was discontinued and, an unspecified time later, the values of the patient's blood pressure returned to normal. No other medical history or concomitant medications were reported. The other 5 children experienced nonserious events of constipation and headache.

In the 125 postmarketing case reports for adolescents (12 to <18 years), only 20 reported adverse drug events. Of these 20 cases, 13 reported nonserious adverse drug events (including dysuria, mood altered, crying, irritability, headache, swelling of face, swelling of eyelid, insomnia, thirst, nausea, nasopharyngitis and heart rate increased), and 7 cases reported serious adverse drug events and are presented below:

- Case (b) (6) (hypersensitivity) involved a 15-year old girl who developed a hypersensitivity reaction after the second dose of mirabegron and was admitted to the emergency room. The treating physician considered the event as a 'classic' drug hypersensitivity reaction; however, no other information was reported in this case.
- Case (b) (6) (sinus tachycardia and hypertension) involved a 14-year-old girl with myelomeningocele and hydrocephalus who switched from solifenacin to mirabegron. An unspecified time after starting mirabegron, the patient developed moderate sinus tachycardia above 100 beats/min and moderate hypertension (150/100 mm Hg). Although the report indicated the patient did not take other medications at the time of the events, she was reportedly a wheelchair user and had concurrent conditions that were 'too extensive to report' including fluid in pericardium and 'ventricular valve.' The patient's co-morbid conditions could provide an alternative etiology for the reported events.
- Case (b) (6) (mania) concerned a 17-year old male patient who was under psychiatric consult with a history of 'school issues' and was taking fluvoxamine and another unknown tranquilizer. Four days after the switching from solifenacin to mirabegron for pollakiuria of psychogenic etiology, the patient became manic, was treated with hydroxyzine, and mirabegron was discontinued. Three days later, the patient experienced a second manic episode that was again treated with hydroxyzine. Although the reporting physician considered the manic episodes possibly related to the administration of mirabegron, concomitant medications and the patient's underlying condition confound the causality assessment.
- Case (b) (6) (urinary retention) involved a 12-year old girl who developed urinary retention approximately 1 month after initiation of mirabegron. The dose of mirabegron was ultimately discontinued and the event resolved. The update states "it was unclear whether this symptom was part of the underlying condition." No underlying conditions were mentioned in the update. The implication that medical information was lacking in this case makes the case unassessable.
- Case (b) (6) (pain in extremity, inflammation, hypoesthesia, vasculitis and peripheral swelling) involved a 17-year old patient who, on her first day of mirabegron, developed inflammation of small blood vessels in her hand and later developed hand

pain, numbness and inflammation. No further information was reported, thus precluding a meaningful medical assessment of the events in this case.

- Case (b) (6) (lethargy and depressed mood) involved a 16-year old patient who experienced low mood and lethargy an unspecified time after initiation of mirabegron. Administration of mirabegron was discontinued and both events resolved at a later, unspecified date. The lack of further information prevents a meaningful medical assessment of the events in this case.
- Case (b) (6) (suicidal ideation, anhedonia, lethargy, depressed mood, somnolence, asthenia, fatigue and product use issue) involved a 15-year old patient who developed lethargy, depressed mood, sleepiness, loss of energy, fatigue, anhedonia, and suicidal ideation an unspecified time after initiation of mirabegron 25 mg a day. No other information was reported, except that most events, including suicidal ideation, were known to have resolved an unspecified time after discontinuation of mirabegron. The lack of further information, especially on latency, prevents a meaningful medical assessment of the events in this case.

Reviewer's Comments:

1. *For Case (b) (6) (pain in extremity, inflammation, hypoesthesia, vasculitis and peripheral swelling) involving a 17-year old patient, who, on her first day of mirabegron, developed "inflammation of small blood vessels" in her hand, hand pain, numbness and inflammation that did not resolve after discontinuing mirabegron, we sought additional information from Sponsor. A complete MedWatch form was submitted and reviewed, providing scant additional detail (patient was taking ranitidine concomitantly). Based on the temporal relationship to taking mirabegron, and the reporting of a case of leukocytoclastic vasculitis in an adult clinical trial subject in the original NDA, we requested that "vasculitis" be added to the Postmarketing Experience section of the mirabegron PI.*

   The Sponsor declined our request and explained that (b) (4) they had closely monitored cases of ANCA and vasculitis. Initially, the Sponsor had performed a cumulative review of individual case reports including vasculitis PTs retrieved from their global safety database from market approval in 2012 through 30 Jun 2017. Since Jun 2017, they have provided interval reviews for vasculitis PTs in each annual PSUR. In the latest PSUR from 2020, vasculitis is monitored as a TME.

   To complete our review, we evaluated the cases the Sponsor judged as informative cases (using the modified Edwards criteria) from all the PSURs to date. In total, we reviewed N=2, N=4, and N=3 from the PSURs covering 01 July through 30 June of 2019-2020, 2018-2019, and 2017-2018, respectively. Additionally, we reviewed the available case reports (N=9) of the 13 informative cases identified in the PSUR from 2017 (from market approval through 30 June 2017).

Overall, the cases included patients that were for the most part elderly (adults ranging from 61 to 93 years old, with the exception of the single 17-year old noted above), female, with extensive past medical conditions, and taking multiple concomitant medications. Several patients had known autoimmune disease diagnoses or allergic/hypersensitivity related-conditions, and many were taking medications for which vasculitis is a listed ADR. In some, the temporal relationship was unclear or the time to onset seemed implausible. While none of the cases noted a rechallenge, many cases reported a negative dechallenge. For some cases, it appeared that the reported symptoms pre-dated medication treatment and for others, the events resolved with treatment despite ongoing mirabegron therapy. Finally, many cases lacked important information and were confounded by concomitant medications, pre-existing conditions, and concurrent illnesses. In summary, although a few cases reported a positive dechallenge, the current evidence does not indicate a causal relationship between mirabegron and vasculitis. Surveillance will continue post-approval in adults and children.

2. *For Case* (b) (6) *(suicidal ideation, anhedonia, lethargy, depressed mood, somnolence, asthenia, fatigue and product use issue) involving a 15-year old patient who developed lethargy, depressed mood, sleepiness, loss of energy, fatigue, anhedonia, and suicidal ideation an unspecified time after initiation of mirabegron 25 mg a day, with no other information except that most events, including suicidal ideation, were known to have resolved an unspecified time after discontinuation of mirabegron, we sought additional information from the Sponsor. A complete MedWatch form was submitted and reviewed, providing no additional detail. In this case, the lack of fundamental case information, such as when mirabegron was taken, the temporal relationship of drug to the events and the patient's medical history, as well as the lack of reports of depressed mood or suicidality in previous adult or pediatric clinical trials, or in the postmarketing experience of which we are aware, precludes a meaningful assessment of relationship of the events to mirabegron.*

During the 120-Day Safety Update reporting period, for all age groups, there were 85 case reports received from the following sources: sponsored studies (39), spontaneous cases (35 cases), unsponsored study, published (3 cases), spontaneous, published (2 cases) and authority (2 cases). Four cases had unidentifiable patients and were considered invalid, and in none of these was a safety concern identified.

In these 81 case reports, 126 adverse events were reported which primarily included PTs related to product use issues (44), off-label use (40), and clinical AEs (17). The remaining PTs included dosing issues (exposure in utero (via father or during pregnancy), social issues (inability to afford medication and insurance issues), and a variety of other events.

The Sponsor provided very brief narratives for the 4 cases that reported SAEs. The table below provides a summary of the SAEs.

Table 59 SAEs reported in the 120-Day Safety Update

Case Number	Report Type	Medically Confirmed	Age/Sex	SAE (PTs)	Reported Causality*
Child (5 years to < 12 years)					
(b) (6)	Spontaneous, published	Yes	10 years/Male	Hydronephrosis	Not related
	Spontaneous	Yes	11 years/Female	Hypertension	Unknown
Child (age unspecified)					
(b) (6)	Unknown	No	Unknown/ Female	Weight reduced	Not assessed
	Unknown	No	Unknown/unknown	Seizures	Possible

*source of assessment unclear.
Source: 120-Day Safety Update , Table 2, p. 5.

- **Case** (b) (6) was a case from the literature in which a 10-year old male with spina bifida taking solifenacin and mirabegron for an unspecified duration, developed hydronephrosis and pyuria. The events were considered by the reporting physician to be a likely complication of the patient's spina bifida condition.
- **Case** (b) (6) concerned an 11-year-old female patient with nephropathy, ureterocele, and only 1 kidney, who developed hypertension an unspecified time after initiation of mirabegron. A negative dechallenge following discontinuation was reported. The Sponsor states that "based on the available information and given this backdrop information, the event of hypertension could be associated with the patient's underlying medical conditions." No further information was provided.
- **Case** (b) (6) is an exposure during pregnancy case, with reported AEs for the mother, included weight reduced. No further information was provided. Based on the plausible temporal relationship, the Sponsor stated that that the causal relationship to mirabegron could not be excluded.
- **Case** (b) (6) was a case from the literature in which a child of unspecified age and medical history developed 'increased seizures' during treatment with mirabegron, implying that seizure was a pre-existing condition. No other information was reported, other that the mirabegron was withdrawn with unknown results for the event of interest. The Sponsor indicated that an assessment was not possible given the lack of information available.

As a result of the search of the scientific literature for mirabegron in pediatric patients during the Postmarketing Safety Report reporting period, the Sponsor identified a single retrospective study in 66 pediatric patients with NDO in South Korea who received mirabegron 50 mg once daily for at least 6 weeks. AEs were reported in 6 patients and included constipation (4.5% of patients), headache (3.0%) and hypertension (1.5%). During the reporting period covered by the 120-Day Safety Update, one article which examined the efficacy of electromotive drug administration in delivering botulinum toxin in 14 children with NDO was identified. The authors found that no improvements were demonstrated through cystometric parameters. The description mentioned that one patient subsequently went on mirabegron therapy.

Reviewer's Comment: The cases, as presented in the Postmarketing Safety Report and in the 120-Day Safety Update, either lacked critical information for assessing causality or were confounded by concomitant mediations or underlying conditions. The literature searches did not provide articles with further insight regarding mirabegron safety. The postmarketing safety reports and 120-day safety update do not provide evidence of additional safety concerns for use of mirabegron in pediatric patients.

8.12.2 Expectations on Safety in the Postmarket Setting

There are 10 years of postmarket experience with the tablet dosage form of mirabegron, which was approved for use in Japan in 2011 and in the United States in 2012. As of June 30, 2019, approximately 14.02 million patients had been exposed to mirabegron since its launch, with an estimated 3946 patients less than 18 years of age. Based on the experience of mirabegron in adults with OAB and the comparability of mirabegron systemic exposure between adult and pediatric patients, we anticipate no additional potential safety issues in the postmarket setting for mirabegron in pediatric patients.

8.13 Integrated Assessment of Safety

The Phase 3 study 178-CL-206A as well as the two (2) Phase 1 studies 178-CL-202 and 178-CL-203 conducted by the Sponsor in support of mirabegron for the treatment of NDO in pediatric patients provided a robust safety assessment in the indicated population. The safety findings were further supported by safety data from OAB patients in the Phase 1 studies noted above. Data from the three studies were analyzed separately given differences in study design.

In regard to the patient exposure and demographics in the three studies provided in this submission:

- 129 pediatric patients aged ≥ 3 years (with NDO or symptoms of OAB) received mirabegron tablets or oral suspension in clinical trials (Phase 1 and 3 studies). Of those, 103 patients had NDO.
- In the Phase 3 study in patients with NDO, the duration of treatment for the majority of patients (56 [65.1%]) was ≥ 364 days and was similar across the two pediatric age groups.
- For all but 4 patients who completed the Phase 3 study, the treatment doses were up-titrated to pediatric equivalent dose PED50 by week 8 in the treatment period.
- The mean duration of treatment for all Phase 3 Study patients was 302.6 ±134.6 days (Mean±SD).

In regard to deaths, SAEs, and TEAEs leading to discontinuations in the major clinical studies:

- There were no deaths reported in the development program.
- In the Phase 3 pediatric NDO population, 19 SAEs were reported by 14 of 86 (16.3%) patients; 10 occurred in 9 children and 9 occurred in 5 adolescents. SAEs included device malfunction (n=3), talipes/talipes correction (n=2), and colitis, pyrexia, appendicitis, bronchitis, *E.coli* UTI, pneumonia bacterial, pyelonephritis acute, viral infection, benign neoplasm of skin, convulsion/seizure, hydrocephalus, urethral perforation, epididymitis,

rash generalized (n=1 each). None of these SAEs appeared to be drug-related. No SAEs were reported in the Phase 1 studies.

- In the Phase 3 study, TEAEs leading to discontinuation occurred only in 3 (3.5%) patients and included increased aspartate aminotransferase (AST), urinary incontinence, and allergic dermatitis, none of which, in our opinion, were drug-related.

In regard to commonly reported TEAEs:

- In the Phase 3 study, TEAEs reported by ≥ 2% of patients were *E.coli* urinary tract infection (UTI) (8 [9.3%] patients), and nasopharyngitis, pyrexia and UTI bacterial (5 [5.8%] patients each). UTI TEAEs were thought to reflect the high annual incidence of UTI in pediatric patients with NDO practicing CIC
- The most commonly reported adverse reactions were UTI (24.4%, which includes *E.coli* urinary tract infection, UTI bacterial, UTI, and UTI Pseudomonal), nasopharyngitis (5.8%), constipation (4.7%), and headache (3.5%).
- The most commonly reported (investigator determined) drug-related TEAEs in the Phase 3 study were UTI bacterial (3[3.5] patients), nausea and constipation (2[2.3%] patients each).
- In the Phase 1 studies, only 4 TEAEs were reported.

In regard to TEAEs of special interest and special safety issues:

- UTI was the most commonly reported TEAE, reported in 21 (24.4%) patients. The high incidence was thought to reflect the high background incidence in the patient population. We assessed the two SAEs, pyelonephritis acute and *E.coli* UTI, as not drug-related.
- Two cardiovascular TEAEs were reported in the Phase 3 study: QT prolongation (n=1, children's group) and bradycardia (n=1, adolescent group). The report of QT prolongation was determined to be not clinically relevant (QTcB only), and we concluded the report of bradycardia was in error. In the Phase 1 study 178-CL-202, the two TEAEs of QT prolongation were single isolated measurements and were not clinically meaningful.
- Of the 5 patients who reported hypersensitivity TEAEs of special interest, the dermatitis allergic and dermatitis cases were unassessable, and the rash generalized, allergic rhinitis, and urticaria were considered to be not related to the study drug.
- The seizure event resulted from hydrocephalus was deemed related to the shunt malfunction and was considered not related to the study drug.
- The fetal disorder after exposure during pregnancy events was worsening of talipes, a congenital condition, and was determined to be not related to the study drug. There was no pregnancy reported.
- No TEAEs were reported for the remaining TEAEs of special interest: urinary retention, syncope, and concomitant treatment with CYP2D6 substrates with narrow therapeutic indices or individually dose-titrated.

In regard to laboratory findings, vital signs, ECGs, and Urinary Tract Ultrasounds:

- AST increased and blood creatine phosphokinase increased were the only two TEAEs reported that were related to clinical laboratory testing. They were considered not related to the study drug.
- Mean increases in SBP and DBP in patients <12 years of age was 4.3 and 1.7 mm Hg, respectively. The mean blood pressure increase in patients less than 8 years of age was 5.9 mm Hg for SBP and 2.3 mm Hg for DBP. BP changes in adolescents were similar to those in adults with OAB. Twenty-four percent (24%) of normotensive children at baseline had at least one subsequent SBP above the 95th percentile based on the NHLBI Fourth Report criteria, and a for a majority, this shift was sustained at the end of the study.
- ECG findings of prolonged QT (n=3 in 178-CL-206A, n=1 in 178-CL-203, and n=7 in 178-CL-202) were reviewed and in none of the cases was the average QTcF prolonged. We agree with the Sponsor that these findings are not clinically significant.
- All but one of 19 abnormal upper urinary tract ultrasound findings were confirmed to be not clinically significant. A single case of worsening hydronephrosis cannot be explained, but the available information was limited, and did not indicate bladder dysfunction related to mirabegron therapy.

In regard to Postmarket experience:

- Four cases of SAEs were presented in the 120-Day Safety Update and contained very little information. All were considered unassessable.
- Nine cases of SAEs were presented in the Postmarketing Safety Report and these also contained very little information or were confounded by concomitant mediations or underlying conditions. Our review of the current evidence does not indicate a causal relationship between mirabegron and reports of vasculitis. Surveillance will continue post-approval in adults and children.

Overall, mirabegron was generally well tolerated in pediatric patients. The safety profile of mirabegron tablets and oral suspension in pediatric patients with NDO is consistent with the safety profile of approved mirabegron tablets in adults with OAB. There are no new or unresolved safety issues.

9 Advisory Committee Meeting and Other External Consultations

There were no issues that required advice from an FDA Advisory Committee and an Advisory Committee meeting was not held for this application.

10 Labeling Recommendations

10.4 Prescription Drug Labeling

Labeling discussions were held with the entire review team on February 4, 5, 10, 11, 16, and 18, 2021 and March 10, 2021. The Division's edited labels (PI and PPI) were conveyed to the Sponsor on February 24, 2021 and March 16, 2021, respectively. The Sponsor accepted most of the Division PI edits and returned the PI document with minor revisions on March 5, 2021. Several minor division edits were conveyed to the Sponsor on March 12, 2021. Thus, at the time this Clinical review was finalized, while final labeling had not been agreed-upon, the majority of labeling discussions with Sponsor had been completed with success.

10.5 Nonprescription Drug Labeling

Mirabegron is available by prescription only.

11 Risk Evaluation and Mitigation Strategies (REMS)

There was no reason to require a REMS for this product, and none was requested.

12 Postmarketing Requirements and Commitments

Neither a postmarketing requirement nor commitment is needed for this product.

13 Appendices

13.4 References

13.5 Financial Disclosure

Covered Clinical Study (Name and/or Number): 178-CL-206A

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 39 (but 6 of these did not enroll patients)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0*		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

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

* Based on the information submitted, in which no investigator in any of these clinical studies had a disclosable financial interest, we conclude that no investigator was a Sponsor employee.

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

/s/

ELENA N BOLEY
03/18/2021 06:24:18 PM

MARK S HIRSCH
03/18/2021 06:36:19 PM
I concur.