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Efficacy and safety of mirabegron in children and adolescents with neurogenic detrusor overactivity: An open-label, phase 3, dose-titration study

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Abstract

Aims: To evaluate the efficacy and safety of mirabegron in children and adolescents (aged 3 to <18 years) with neurogenic detrusor overactivity (NDO) using clean intermittent catheterization.

Methods: In this open-label, multicenter, baseline-controlled, Phase III study (NCT02751931), participants received once-daily mirabegron at an adult dose equivalent of 25 mg. Dose was increased to 50 mg equivalent unless there were safety/tolerability concerns. The primary efficacy endpoint was change from baseline to Week 24 in maximum cystometric capacity (MCC). Secondary urodynamic assessments, Pediatric Incontinence Questionnaire (PIN-Q), Patient Global Impression of Severity (PGI-S), Clinician Global Impression of Change (CGI-C), and Acceptability questionnaires were included.

Results: Overall, 86 participants (55 aged 3 to <12 years, 31 aged 12 to <18 years) received treatment; 68 were included in efficacy assessments. A statistically significant increase in MCC from baseline to Week 24 was observed (87.20 ml, 95% confidence interval: 66.07, 108.33; $p < .001$); this increase was apparent from Week 4. Significant increases in bladder compliance, bladder volume until first detrusor contraction, average volume per catheterization, maximum daytime catheterized volume and number of dry days per week. Significant decreases in detrusor pressure and number of leakage episodes per day were also observed. Significant improvement in PGI-S but not PIN-Q was observed. Most participants reported their condition had either much or very much improved using the CGI-C. Mirabegron was well tolerated in this population with a profile aligned with that in adults.

Conclusions: Mirabegron was effective and well-tolerated in the treatment of pediatric patients with NDO.

KEYWORDS

children, muscarinic antagonists, neurogenic, neurogenic bladder, overactive detrusor, overactive urinary bladder, urinary bladder

1 | INTRODUCTION

Neurogenic detrusor overactivity (NDO) is defined as involuntary detrusor contractions during bladder filling, where a relevant neurological cause is present.[1] The most common cause of NDO is congenital spinal defects; other causes include spinal cord injuries or central nervous system abnormalities.[2]

If left untreated, NDO may lead to decreased bladder compliance and deterioration of the upper urinary tract.[3] A main objective of treatment is to maintain low bladder pressure during bladder storage and voiding and therefore avoid associated complications such as urinary tract infections (UTIs), bladder stones, fibrosis, trabeculation, and autonomic dysreflexia.[4] Treatment for NDO conventionally consists of clean intermittent catheterization (CIC) with or without pharmacological treatment with antimuscarinic drugs.[5] Other potential treatments include botulinum toxin, which has shown improvements in clinical and urodynamic parameters in this population.[6] Few antimuscarinics are currently approved for the treatment of NDO. Oxybutynin is currently the gold-standard pharmacological treatment for NDO and the majority of patients are treated successfully with the combination of oxybutynin and CIC.[7] Solifenacin and tolterodine have also been evaluated in this population.[8,9] However, antimuscarinic drugs are associated with a number of anticholinergic adverse events (AEs), such as dry mouth, constipation, and urinary retention,[10] which may limit adherence. Of particular concern in pediatric patients is the potential for impairment of cognitive development and learning, especially as anticholinergic central nervous system AEs are reportedly more common in pediatric patients compared with adults.[11]

Mirabegron, a *β3*-adrenoreceptor agonist, is an alternative treatment option to antimuscarinics, with proven efficacy and safety in adults with overactive bladder.[12,13] As mirabegron has a distinct mechanism of action, and is generally devoid of antimuscarinic AEs, it generally has a favorable safety profile. Notably, mirabegron was not associated with drug-related cognitive AEs in elderly patients.[14] Mirabegron has also shown positive effects on urodynamic parameters in adult patients with NDO.[15–17]

This study aimed to evaluate the efficacy and safety of mirabegron in children and adolescents with NDO.

2 | MATERIALS AND METHODS

2.1 | Study design

This open-label, multicenter, baseline-controlled, phase III study (NCT02751931) conducted at 32 sites in Europe, Asia/Pacific, the Middle East, and Mexico included children and adolescents with NDO confirmed by urodynamic investigation at baseline, aged 3 years to less than 18 years (grouped into two age groups, children [here defined as 3 to <12 years] and adolescents [12 to <18 years]). Inclusion criteria included weight ≥11 kg, CIC for ≥4 weeks before screening, and a current indication for drug therapy to manage NDO. Exclusion criteria included other known genitourinary conditions that could cause overactive contractions or incontinence, gastrointestinal problems such as partial or complete obstruction, decreased motility such as paralytic ileus, risk of gastric retention, indwelling catheter less than 4 weeks of screening, and symptomatic UTI.

The study consisted of three investigational periods: a pretreatment period for a maximum of 28 days before baseline (including screening, washout [if applicable], and baseline); the efficacy treatment period, which began the day after baseline and continued to Week 24; and the long-term safety period, which began after Week 24 and continued to Week 52. Patients who completed the pretreatment period received mirabegron. The initial dose was based on categories of weight and was selected to achieve plasma concentrations equivalent to the steady-state exposure expected with 25 mg mirabegron once daily in adults (PED25, Tables S1 and S2). Doses were increased to a dose equivalent to 50 mg in adults (PED50, Table S1) at Weeks 2, 4, or 8 unless the patient was considered to be effectively treated with PED25 or if there were safety or tolerability concerns precluding dose escalation. Down titration to PED25 was permitted at any time in the case of safety concerns. Mirabegron was given once daily with food at the same time each day. Patients with body weight more than 35 kg and able/willing to take tablets received mirabegron tablets while those with body weight ≤35 kg or who could not or did not want to take tablets received mirabegron as an oral suspension.

The study was approved by the Independent Ethics Committee/Institutional Review Board for each site. The patient's parent(s)/legal guardian(s) provided informed consent, and where appropriate, the patient provided written assent. The studies were conducted in accordance with the International Council for Harmonization, Good Clinical Practice, and the Declaration of Helsinki.

2.2 | Efficacy assessments

Urodynamic assessments were performed at baseline, Weeks 4 and 24. Other assessments were measured using a bladder e-diary. The primary efficacy endpoint was change from baseline in maximum cystometric capacity (MCC) after 24 weeks of treatment. Secondary endpoints

included change from baseline in urodynamic measures (bladder compliance, number of overactive detrusor contractions, detrusor pressure at end of filling and filling volume until first overactive detrusor contraction) and bladder volume and leakage measures (average catheterized volume per catheterization, maximum catheterized volume, maximum catheterized daytime volume, average morning catheterized volume, mean number of leakage episodes per day, and number of dry [leakage-free] days).

Computerized urodynamic equipment was used for all urodynamic assessments. Steps were taken to ensure the rectum was free of stool. The patient was placed in the same position for each assessment at each visit. The bladder was filled with room temperature saline at a rate of 10% of the mean baseline catheterized volume. If the filling rate was accidentally too high or too low then this rate was used at all visits. Variations of ≤2 ml/min in filling rate were accepted.

In addition, patient- and clinician-reported questionnaires (change from baseline in the Pediatric Incontinence Questionnaire [PIN-Q] and Patient Global Impression of Severity [PGI-S]; Clinician Global Impression of Change [CGI-C] and Acceptability) were used. The PIN-Q measured quality of life via an e-diary using a score ranging from 0 (no effect) to 80 (worst effect); a decrease indicates improvement. For the PGI-S, patients rated how they felt about their bladder condition during the past three days as "Really Bad" (0), "Bad" (1), "Not Bad, Not Good" (2), "Good" (3) and "Really Good" (4); an increase indicates improvement.

2.3 | Pharmacokinetic (PK) assessments

For PK analysis, four samples of venous blood at steady state at the optimal dose (after 10 days at the same dose) were collected over 2 sampling days (Day 1: predose trough sample, Day 2: one predose trough sample and two postdose samples separated by at least 1 h). Since PK sampling was sparse and skewed towards the early phase of the profile, the data from this study were pooled with two phase I studies in patients with NDO or overactive bladder aged 5 to less than 18 years (NCT02211846) and aged 3 to less than 12 years (NCT02526979).[18] The PK profile of mirabegron was then characterized using a population PK modeling approach for maximum (peak) plasma drug concentration (C_{max}), time to reach maximum (peak) plasma concentration following drug administration (t_{max}), area under the plasma concentration-time curve from time 0 to 24 h (AUC_{24}), trough plasma concentration (C_{trough}), apparent total clearance of the drug from plasma (CL/F), and apparent volume of distribution (Vz/F).

2.4 | Safety assessments

Safety assessments included incidence of treatment-emergent AEs (TEAEs), vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate), 12-lead electrocardiogram (ECG) parameters, laboratory variables (hematology, biochemistry, and urinalysis), and ultrasound assessments.

Potentially clinically relevant changes for SBP and DBP were based on the Fourth Report of the National Institutes of Health National Heart, Lung and Blood Institute [19] and the 2017 American Academy of Pediatric Clinical Practice Guidelines (CPG).[20] Briefly, using the Fourth Report, potentially clinically relevant changes were defined as any SBP or DBP value above the 99th percentile + 5 mmHg or change in category (e.g., pre-hypertension to Stage 1). Using the CPG, potentially clinically relevant changes were defined as change in hypertension category from baseline; SBP above the 95th percentile + 12 mmHg or ≥140 mmHg for patients aged 3 to less than 13 years and 140 mmHg for patients ≥13 years; or DBP above the 95th percentile + 12 mmHg or ≥90 mmHg for patients aged 3 to less than 13 years and ≥90 mmHg for patients ≥13 years. Potentially clinically relevant changes in pulse rate were defined as any values above the 99th percentile compared with age-related norms[21] or ≥15 beats per minute change from baseline.

2.5 | Statistical analysis

A sample size of 63 enrolled patients was calculated to be sufficient (assuming 30% of patients discontinued or were not evaluable) to provide the 44 evaluable patients necessary to detect a statistically significant change from baseline in MCC (90% power).

Safety assessments were performed in all patients who received at least one dose of study drug (safety analysis set [SAF]). The full analysis set (FAS) consisted of all patients who received at least one dose of study drug and who had valid MCC measurements at baseline and postbaseline and was used for all efficacy assessments.

All statistical analyses used SAS version 9.3 or higher. Demographics and baseline characteristics, and efficacy and safety data, were summarized by descriptive statistics. All statistical comparisons were made using two-sided tests at $\alpha = 0.05$ significance level unless specifically stated otherwise. Missing primary efficacy endpoint

values were analyzed using the last observation carried forward (LOCF) method at Week 24.

3 | RESULTS

Of 91 patients enrolled, 86 (55 children and 31 adolescents) took at least one dose of mirabegron and were included in the SAF (Figure S1). Of these, 68 children and adolescents were included in the FAS. Sixteen patients discontinued treatment, of which three discontinued due to an AE (two during dose titration and one during the fixed-dose assessment period). Other reasons for discontinuation were: four cases of no signs of NDO on baseline urodynamic assessment; seven cases of technical issues with baseline urodynamic assessment; and two cases of withdrawal due to QTcB prolongation at baseline.

Patient demographics are presented in Table 1. Mean age was 7.9 and 14.0 years in children and adolescents, respectively. Overall, the most commonly used NDO medications were oxybutynin (32.6%) and solifenacin (22.1%).

3.1 | Efficacy assessments

A statistically significant increase in MCC from baseline was observed in the total population (mean change from baseline 87.20 ml, 95% confidence interval: 66.07, 108.33; $p < 0.001$; Figure 1) and in both age groups ($p < 0.001$). The increase in MCC was apparent from Week 4 in both children and adolescents and overall (Figure S2). An increase of more than 30 ml in MCC was observed from Weeks 4–24. Week 24 results were consistent using LOCF.

Change from baseline in all secondary endpoints are summarized in Table 2. In the overall population, a significant increase in bladder compliance compared with baseline was observed at Week 24; detrusor pressure was significantly decreased from Week 4 and remained significant at Week 24. There was a significant increase in bladder volume until first detrusor contraction >15 cmH_2O from baseline in all age groups. The increase from baseline in average volume per catheterization of 47.99 ml (*SD*: 67.62) at Week 24 was statistically significant from Week 2 (data not shown). This decreased to 42.68 ml (*SD*: 66.22) at Week 52 but remained significant. A similar pattern of significant

TABLE 1 Patient baseline demographics and characteristics (safety analysis set)

Parameter	Children (3 to <12 years) *N* = 55	Adolescents (12 to <18 years) *N* = 31	Total *N* = 86
Sex, male, *n* (%)	22 (40.0)	17 (54.8)	39 (45.3)
Mean age, years (*SD*)[a]	7.9 (2.5)	14.0 (1.7)	10.1 (3.7)
Mean weight, kg (*SD*)[a]	29.83 (13.41)	50.96 (13.78)	37.45 (16.90)
Mean height, cm (*SD*)[a]	124.77 (18.69)	152.91 (12.06)	134.91 (21.40)
Mean BMI, kg/m^2 (*SD*)	18.18 (3.94)	21.96 (6.02)	19.55 (5.10)
Mean duration of NDO, years (*SD*)	5.80 (3.33)	9.44 (5.18)	7.11 (4.43)
Closure of spina bifida, *n* (%)	43 (78.2)	24 (77.4)	67 (77.9)
Shunt for hydrocephalus, *n* (%)	23 (41.8)	17 (54.8)	40 (46.5)
Wheelchair bound, *n* (%)	19 (34.5)	19 (61.3)	38 (44.2)
NDO medication therapy, *n* (%)[b]			
Oxybutynin	21 (38.2)	7 (22.6)	28 (32.6)
Solifenacin	11 (20.0)	8 (25.8)	19 (22.1)
Mirabegron	3 (5.5)	3 (9.7)	6 (7.0)
Propiverine	3 (5.5)	2 (6.5)	5 (5.8)
Tolterodine	3 (5.5)	1 (3.2)	4 (4.7)
Trospium	3 (5.5)	1 (3.2)	4 (4.7)
Botulinum toxin type A	1 (1.8)	2 (6.5)	3 (3.5)
Fesoterodine	0	3 (9.7)	3 (3.5)

Abbreviation: NDO, neurogenic detrusor overactivity.

[a]At screening.

[b]More than 5% of any age group.

TABLE 2 Change from baseline in urodynamic and leakage parameters (secondary endpoints; full analysis set)[a]

	Children (3 to <12 years) $N = 43$	Adolescents (12 to <18 years) $N = 25$	Total $N = 68$
Bladder compliance, ml/cmH_2O, mean (*SD*)			
Baseline	14.53 (50.75)	11.02 (10.05)	13.21 (40.42)
Change from baseline to Week 4	−4.09 (50.78)	15.16 (22.69)*	2.85 (43.59)
Change from baseline to Week 24	14.62 (42.09)	13.59 (15.02)*	14.22 (33.99)*
Number of overactive detrusor contractions >15 cmH_2O, mean (*SD*)			
Baseline	3.07 (3.88)	2.04 (2.97)	2.70 (3.59)
Change from baseline to Week 4	0.44 (5.82)	−0.64 (2.94)	0.06 (5.01)
Change from baseline to Week 24	−1.86 (4.16)	−0.77 (3.87)	−1.45 (4.05)*
Detrusor pressure (cmH_2O) at end of bladder-filling, mean (*SD*)			
Baseline	42.25 (26.27)	38.65 (17.97)	40.94 (23.51)
Change from baseline to Week 4	−12.38 (19.56)*	−6.48 (30.70)	−10.32 (23.96)*
Change from baseline to Week 24	−18.11 (19.97)*	−13.19 (19.91)*	−16.24 (19.92)*
Bladder volume (ml) until first detrusor contraction >15 cmH_2O, mean (*SD*)			
Baseline	115.82 (86.97)	185.17 (121.25)	141.31 (105.56)
Change from baseline to Week 4	56.09 (96.23)*	73.80 (117.21)*	62.45 (103.68)*
Change from baseline to Week 24	93.09 (88.14)*	121.33 (159.84)*	104.02 (120.57)*
Average catheterized volume per catheterization, ml, mean (*SD*)			
Baseline	236.73 (70.52)	278.98 (91.96)	251.87 (80.80)
Change from baseline to Week 4	30.08 (49.50)*	51.96 (64.71)*	38.04 (56.03)*
Change from baseline to Week 24	41.63 (58.03)*	59.31 (82.22)*	47.99 (67.62)*
Change from baseline to Week 52	42.84 (65.31)*	42.40 (69.25)*	42.68 (66.22)*
Maximum catheterized volume per catheterization, ml, mean (*SD*)			
Baseline	302.41 (107.29)	364.63 (111.27)	324.69 (112.00)
Change from baseline to Week 4	46.69 (80.29)*	73.25 (103.98)*	56.35 (89.77)*
Change from baseline to Week 24	49.88 (103.70)*	84.39 (121.98)*	62.28 (110.91)*
Change from baseline to Week 52	53.51 (96.72)*	54.30 (104.74)*	53.80 (98.88)*
Maximum catheterized daytime volume, ml, mean (SD)			
Baseline	300.16 (105.71)	367.52 (119.03)	324.29 (114.49)
Change from baseline to Week 4	37.71 (83.33)*	70.35 (113.98)*	49.58 (96.06)*
Change from baseline to Week 24	44.20 (98.31)*	81.37 (117.77)*	57.56 (106.32)*
Change from baseline to Week 52	53.76 (100.24)*	49.13 (117.23)*	52.07 (105.84)*
Average morning catheterized volume, ml, mean (*SD*)			
Baseline	272.23 (102.40)	305.00 (102.40)	283.82 (102.82)
Change from baseline to Week 4	19.81 (89.04)	75.25 (105.72)*	38.29 (97.64)*
Change from baseline to Week 24	40.76 (116.41)*	86.66 (96.55)*	57.15 (111.07)*
Change from baseline to Week 52	31.83 (94.25)*	38.14 (108.06)	34.04 (98.44)*
Number of leakage episodes per day (day and night time), mean (*SD*)			
Baseline	3.16 (3.71)	1.79 (1.70)	2.59 (3.10)
Change from baseline to Week 4	−1.76 (2.81)*	−0.95 (1.48)*	−1.41 (2.35)*

TABLE 2 (Continued)

	Children (3 to <12 years) $N = 43$	Adolescents (12 to <18 years) $N = 25$	Total $N = 68$
Change from baseline to Week 24	−1.97 (3.17)*	−0.98 (1.08)*	−1.53 (2.49)*
Change from baseline to Week 52	−2.19 (3.41)*	−1.05 (1.61)*	−1.68 (2.79)*
Number of dry (leakage-free) days per 7 days (day and night time), mean (*SD*)			
Baseline	0.83 (2.08)	1.56 (2.41)	1.09 (2.21)
Change from baseline to Week 4	0.68 (1.69)*	1.36 (1.91)*	0.92 (1.79)*
Change from baseline to Week 24	1.34 (2.18)*	2.17 (2.38)*	1.65 (2.27)*
Change from baseline to Week 52	1.38 (2.65)*	2.14 (2.51)*	1.67 (2.60)*

Note: *$p < 0.05$.

[a]In patients with baseline and postbaseline measurements.

increase to Week 24 followed by a reduction by Week 52 (but remaining significant) was observed in maximum daytime catheterized volume.

There was also a significant decrease in the mean number of leakage episodes per day at all timepoints, in both age groups and in the whole cohort. There was a significant increase in the number of dry days per week at all timepoints and in the whole cohort, including both age groups.

3.2 | Patient- and clinician-reported outcomes

Patients reported an improvement in their quality of life as measured by the PIN-Q, although no changes were statistically significant (Figure 2). Mean change from baseline in PGI-S was significant in the overall population, indicating an improvement (Figure 2). Using the CGI-C, the majority of patients reported that their condition had either much or very much improved (47.7%, and 24.6%, respectively) at Week 24. Minimal improvement was reported by 16.9% of patients. No change or minimal worsening was reported by 7.7% and 3.1%, respectively. No patients reported that their condition was much worse or very much worse.

The vast majority of patients (92.5%) indicated in the acceptability questionnaire at Week 24 that the taste of the tablets was really good, good, or not bad/not good. Swallow acceptability was rated as "really easy" by 57.5% of all patients. Smell and taste of the oral suspension was rated as really good, good, or not bad/not good by 84% and 92% of patients, respectively. Ability to take and to prepare the oral suspension was reported as "really easy" or "easy" by 84% of patients.

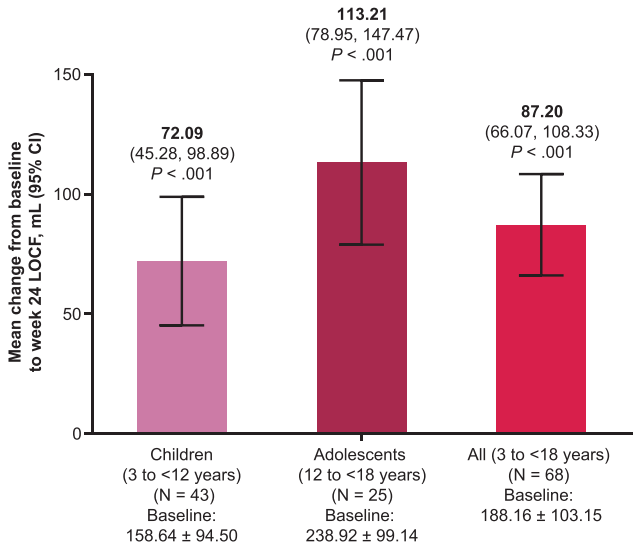

FIGURE 1 Change in maximum cystometric capacity from baseline to Week 24 LOCF (primary endpoint; full analysis set). CI, confidence interval; LOCF, last observation carried forward

3.3 | PK assessment

A total of 114 patients from three studies[18] were included in the pooled population PK analysis. A two-compartment model with transit compartment absorption and first-order elimination was considered to adequately characterize the concentration-time profile of mirabegron in children and adolescents. Summary statistics for PK parameters in this study are provided in Table S1.

3.4 | Safety assessments

In the SAF ($n = 86$), TEAEs were reported by 59.3% of all patients (Table 3). The most common TEAEs (occurring in >2% of all patients) were UTI (23.3%) and nasopharyngitis and pyrexia (each 5.8%). The majority of TEAEs

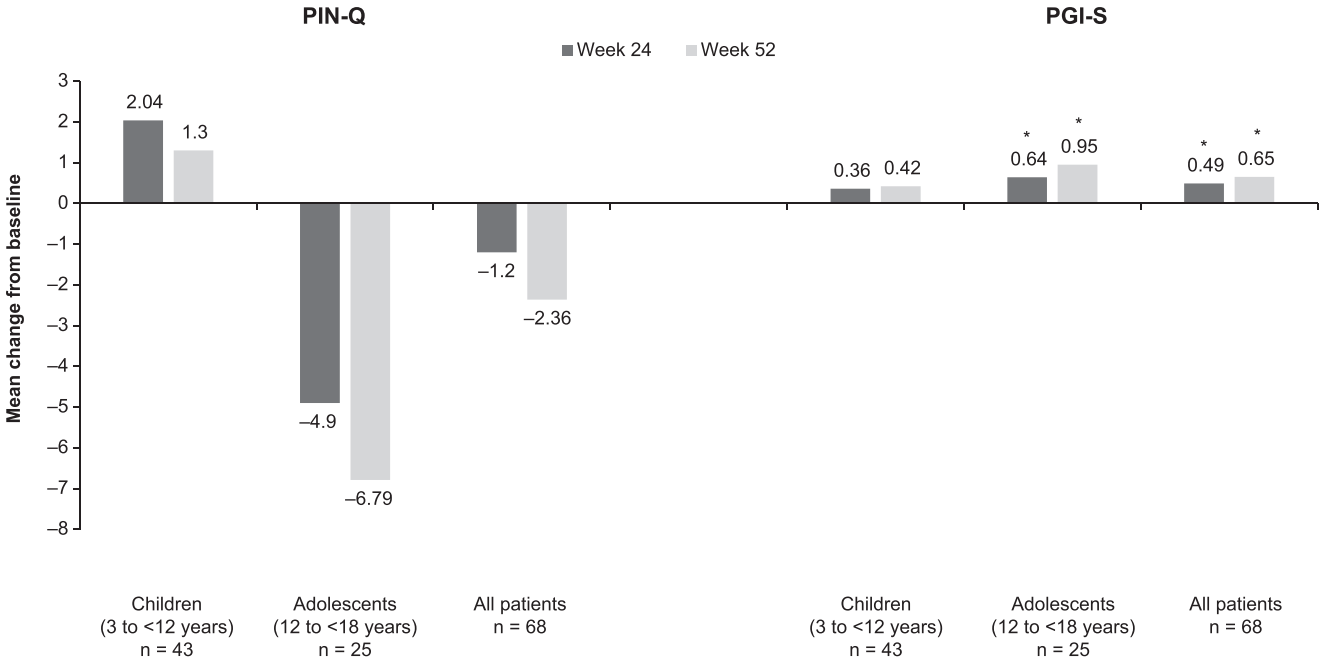

FIGURE 2 Patient-reported questionnaire endpoints (secondary endpoints; full analysis set)[a] *$p < 0.05$. [a]In patients with baseline and postbaseline data. PGI-S, Patient Global Impression of Severity; PIN-Q. Pediatric Incontinence Questionnaire

were not considered to be related to treatment and TEAEs considered possibly or probably related to treatment were reported in 13 (15.1%) and 1 (1.2%) patients, respectively. Serious TEAEs were reported in 14 (16.3%) patients, none was considered to be related to treatment. There were no deaths.

Mean change in SBP in the overall population from baseline at Weeks 24 and 52 was 4.94 and 6.35 mmHg, respectively. Changes in hypertension category from baseline were observed in 20.0% of children and 21.4% of adolescents using the CPG and 20.0% of children and 17.9% of adolescents using the Fourth Report. One adolescent had a potentially clinically relevant change in SBP from baseline (using either definition). Mean change from baseline in DBP at Weeks 24 and 52 was 3.00 and 0.27 mmHg, respectively. Changes in DBP category from baseline were observed in 22.0% of children and 21.4% of

TABLE 3 Incidence of treatment-emergent adverse events (safety analysis set)

TEAE, *n* (%)	Children (3 to <12 years) *N* = 55	Adolescents (12 to <18 years) *N* = 31	Total *N* = 86
Any	33 (60.0)	18 (58.1)	51 (59.3)
Possible or probable drug-related TEAE	8 (14.5)	6 (19.4)	14 (16.3)
Serious TEAE	9 (16.4)	5 (16.1)	14 (16.3)
TEAE leading to permanent discontinuation	3 (5.5)	0	3 (3.5)
Most commonly reported TEAEs (>4% in total group)			
Urinary tract infection[a]	12 (21.8)	9 (29.0)	21 (23.3)
Nasopharyngitis	3 (5.5)	2 (6.5)	5 (5.8)
Pyrexia	2 (3.6)	3 (9.7)	5 (5.8)
Constipation	3 (5.5)	1 (3.2)	4 (4.7)
Respiratory tract infection viral	4 (7.3)	0	4 (4.7)
Upper respiratory tract infection	1 (1.8)	3 (9.7)	4 (4.7)

Abbreviation: TEAE, treatment-emergent adverse event.

[a]Includes the terms *Escherichia* urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal urinary tract infection pseudomonal, and urinary tract infection.

adolescents using the CPG and 18.0% of children and 14.3% of adolescents using the Fourth Report. There were no potentially clinically relevant changes in DBP reported using either definition. There were no pulse rate readings below the reference range. A total of 5 patients (6.4%) had a potentially clinically relevant incidental pulse rate value. There were no clinically significant ECG abnormalities or QTcF findings, but one patient experienced a drug-related TEAE of QT prolongation at Week 24.

One adolescent had a potentially clinically relevant value for total bilirubin (>2 × upper limit of normal) without concomitant elevations in transaminases and one child had TEAEs of increases in aspartate aminotransferase (AST) and blood creatine phosphokinase. The increase in AST led to study discontinuation.

The majority (83.1%) of ultrasound assessments at Week 52 were interpreted as normal; all abnormal results were considered to be not clinically significant.

4 | DISCUSSION

In this open-label study, treatment with mirabegron, a β3 agonist, given as tablets or oral suspension in a pediatric population with NDO, resulted in statistically significant and clinically meaningful reductions in the primary endpoint of MCC as early as Week 4 and these reductions were sustained across the 24-week treatment period. MCC is a reproducible, objective, urodynamic parameter that has been used in a number of clinical studies.[8] Higher MCC is accepted as an indication of reduced risk of high intravesical pressure and associated potential for renal damage.[22] In the current study, the increases in MCC were consistent with the increase in maximum catheterized daytime volume recorded in the outpatient setting, thereby supporting the relevance of urodynamic assessments to "real-world" settings. However, urodynamic assessment in children is a challenging endeavor. In younger patients, excellent "negotiation" skills are required from the physician to get a compliant child during the examination.

Bladder compliance reflects the relationship between bladder volume and pressure.[1] In this study, bladder compliance was improved over 24 weeks of mirabegron treatment. In addition, bladder filling volumes were significantly increased, which is consistent with increased bladder compliance. These results suggest that increased MCC in this study was likely due to increased bladder compliance. Lower bladder compliance is associated with vesicoureteral reflux, radiographic upper tract abnormality, pyelonephritis and upper tract stones.[23] An increase in bladder compliance with antimuscarinic therapy has also been noted in some studies.[8,24,25]

In addition to significant improvements in urodynamic parameters, there were significant improvements in average catheterized volume per catheterization, maximum catheterized volume per catheterization, maximum catheterized daytime volume and average morning catheterized volume. There was also a benefit on number of leakage episodes per day (significant decrease from baseline at all timepoints) and number of dry days (significant increase from baseline at all timepoints).

The efficacy of mirabegron was sustained over 52 weeks of treatment with similar magnitude of treatment effects at Weeks 24 and 52. However, the increase in average catheterized volume per catheterization was lessened at Week 52 compared with Week 24 (mean change 42.68 and 47.99 ml, respectively) although still significant at both timepoints.

Although there were no significant improvements in PIN-Q scores, patients and clinicians reported that patients' symptom severity significantly improved by Week 24 and this improvement was sustained to Week 52.

Mirabegron was well tolerated in a pediatric population and no new safety concerns were identified. The tolerability profile observed in this study was aligned with the profile observed in adults. The PK profile of mirabegron predicted by population PK modeling indicates that clearance and volume of distribution of mirabegron increases with increasing body weight but patient age did not substantially affect PK parameters after accounting for body weight.

Adherence and persistence with antimuscarinic drugs are known to be suboptimal. While adherence may be of a lesser concern in younger patients, the fact that the vast majority of patients in this study found the tablets and oral solution to be good in terms of taste, smell and swallow acceptability is reassuring.

This study is limited by the lack of a placebo group. However, the majority of endpoints were objective urodynamic measures and therefore less prone to bias. In addition, the applicability of these urodynamic results is supported by their concordance with patient- and clinician-reported outcomes.

5 | CONCLUSIONS

The results of this open-label Phase III study show that mirabegron was effective and well-tolerated in children and adolescents with NDO.

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CONFLICT OF INTERESTS

Cristian Persu and David T Bolong report no relevant conflicts of interest. Małgorzata Baka-Ostrowska received an investigator's fee for this study. Camilla Tøndel's institution received an investigator's fee for this study. Achim Steup, Nancy Martin and Christopher Lademacher are employees of Astellas.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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