# A Phase 3, Double blind, Randomized, Multicenter, Parallel Group, Placebo controlled Sequential Dose Titration Study to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Pediatric Subjects from 5 to < 18 Years of Age with Overactive Bladder

Published: 01-07-2020
Last updated: 17-01-2025

ObjectivesPrimary* To evaluate the efficacy of mirabegron in children (5 to < 18 years of age) with OABSecondary* To evaluate the efficacy of mirabegron in children (5 to < 18 years of age) with OAB* To evaluate the safety and tolerability of...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Bladder and bladder neck disorders (excl calculi) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON49390

**Source**
ToetsingOnline

**Brief title**
Dolphin Study

### Condition

- Bladder and bladder neck disorders (excl calculi)

**Synonym**
Overactive Bladder (OAB)

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Astellas Pharma
**Source(s) of monetary or material Support:** Farmaceutische industrie

## Intervention

**Keyword:** Mirabegron, Overactive Bladder, Pediatric Subjects, Phase 3

## Outcome measures

### Primary outcome

Endpoints

Primary

* Change from baseline at the end of the 12 week treatment period:

* Mean number of micturitions per 24 hours

### Secondary outcome

Endpoints

Secondary

* Change from baseline at the end of the 12 week treatment period:

* Mean volume voided per 24 hours

* Maximum volume voided

* Mean number of daytime incontinence episodes per 24 hours

* Mean number of nighttime incontinence episodes per 24 hours

* Mean number of daytime micturitions per 24 hours

* Number of dry (incontinence free) days per 7 days at the end of the 12 week

treatment period

* Nature, frequency and severity of AEs

* Clinical laboratory tests (hematology, biochemistry and urinalysis)

* Vital signs (blood pressure and pulse)

* Routine 12-lead ECG

* PVR volume

* Acceptability and palatability questionnaire

* Appropriate pharmacokinetic parameters will be calculated based on the population pharmacokinetic model used

Table continued on next page

Exploratory

* Percentage of subjects with a reduction in daytime incontinence episodes (< 50% reduction [nonresponder], 50% [partial responder] and 100% [responder])

* Improvement from baseline in worst incontinence grading

* Change from baseline at the end of the 12 week treatment period adjusted for fluid intake:

* Mean number of micturitions per 24 hours

* Change from baseline at the end of the 12 week treatment period (adolescents only):

* Mean number of daytime micturitions per 24 hours

* Mean volume voided per 24 hours

* Mean number of incontinence episodes per 24 hours

* Number of dry (incontinence free) days per 7 days at the end of the 12 week treatment period (adolescents only)

* Mean number of daytime grade 3 or 4 (PPIUS) urgency episodes per 24 hours

(adolescents only)

# Study description

**Background summary**

Background
The present study is designed to evaluate efficacy, safety and pharmacokinetics of mirabegron in pediatric subjects with overactive bladder (OAB).
The study is part of the sponsor*s clinical program for development of mirabegron for the treatment OAB in pediatric patients. Current drug therapy for OAB consists of oral antimuscarinics such as oxybutynin. Although the vast majority (approximately 90%) of patients can be treated successfully with this, development of alternative therapy is desirable because of insufficient efficacy and/or the side effects of available therapies.
Mirabegron is a first-in-class, selective human beta 3 adrenergic receptor (AR) agonist, represents a class of drugs for treatment of OAB with a direct mechanism of action. Mirabegron is currently available as 25 mg and 50 mg tablets. An oral suspension is also being investigated for the treatment of OAB and neurogenic detrusor overactivity (NDO) in the pediatric population.
The population for this pediatric clinical efficacy study (Study 178 CL 204) with mirabegron is pediatric patients with OAB.

Treatment of Overactive Bladder in Pediatric Population
Classical treatment of OAB in pediatric patients consists of urotherapy followed by antimuscarinic therapy if the urotherapy is not sufficient. Other therapies for OAB are also described.
Urotherapy
Standard urotherapy includes information on and demystification of the voiding function and dysfunction, instruction on voiding habits (such as regular voiding, voiding posture), life style advice regarding fluid intake, prevention of constipation, recording of symptoms and voiding habits in bladder diaries and support via regular follow-up by a caregiver.
Specific interventions include various forms of pelvic floor training (relaxation, contraction), behavioral modification, electrical stimulation, catherization and biofeedback (use of objective measures, e.g., uroflow or surface electromyography (EMG) to show children how far they relax their pelvic floor during voiding). Urotherapy can also include elements of cognitive behavioral therapy [Nevéus et al, 2006].
Other therapies for OAB
Alternative drug therapy for OAB includes antimuscarinic therapy such as oxybutynin.
Neuromodulation is also used in patients who do not respond adequately to drug therapy.

Nonclinical and Clinical Data
Detailed information from nonclinical and clinical studies conducted with mirabegron can be found in the [Investigator*s Brochure]. Nonclinical and clinical data are also summarized in the current locally-available product information for mirabegron.

Nonclinical Data
The standard nonclinical pharmacology studies as conducted for the use of mirabegron in adult patients with OAB are also relevant for its use in adolescent pediatric patients with OAB or NDO. Primary nonclinical pharmacology data for mirabegron qualitatively but not quantitatively translates to human clinical use in OAB. Other pharmacological effects such as the glucogenolytic effects of mirabegron in rodents did not translate to an effect in humans. These differences relate to species differences in molecular biology of the beta 3 AR, differences in receptor distribution, and differences in coupling to downstream effector mechanisms. From these factors only receptor expression or receptor-effector coupling efficiency are likely to vary by age. No detailed information is available on potential differences in expression for beta 3-AR in humans or animals during maturation. The sparse data available [Derweesh et al, 2000] suggest that any changes in beta-adrenergic responsiveness in rat urinary bladder could be expected at older age rather than at infancy or adolescence.

Clinical Data
The main clinical aspects of mirabegron prolonged release tablets in adults are described in the current locally-available product information for mirabegron.

**Study objective**

Objectives
Primary
* To evaluate the efficacy of mirabegron in children (5 to < 18 years of age) with OAB
Secondary
* To evaluate the efficacy of mirabegron in children (5 to < 18 years of age) with OAB
* To evaluate the safety and tolerability of mirabegron in pediatric subjects with OAB
* To evaluate the pharmacokinetics after multiple dose administration of mirabegron in pediatric subjects with OAB
Exploratory
* To evaluate the efficacy of mirabegron in pediatric subjects with OAB

**Study design**

Study Design

This is a double-blind, randomized, multicenter, parallel group, placebo controlled sequential dose titration study to evaluate efficacy, safety and pharmacokinetics of mirabegron in pediatric subjects with OAB. Male and female pediatric subjects 5 to < 18 years of age with OAB; as defined according to the ICCS [Austin et al, 2014] who have had received 4 weeks of urotherapy prior to randomization.
Planned total number of study sites include approximately 50 study sites across Europe, Latin America, Africa, Middle East and Asia-Pacific.

The study consists of 3 periods with a total duration of 18 weeks.
* Screening period/urotherapy (4 weeks):
This period starts with visit 1/week 4 (screening) and ends with visit 3/week 0 (baseline). After informed consent/assent has been obtained and immediately after eligibility has been confirmed at visit 1/week 4 (screening), subjects using prohibited medication will complete 1 week of washout (if applicable), while beginning 4 weeks of urotherapy.
After a successful screening visit (visit 1/week 4 [screening]), all subjects will need to complete a 2-day bladder e-diary (weekend) to get acquainted with the bladder e-diary and the assessments. Completion of this bladder e-diary should start in the weekend prior to visit 2. All subjects will also complete a 7-day bladder e-diary the week prior to the baseline visit. The 7-day diary will consist of a 5-day weekday bladder e-diary and 2-day weekend e-diary.
* Double-blind, placebo controlled period (12 weeks):
This period starts with the day after visit 3/week 0 (baseline) and ends with visit 7/week 12 (EoT).
At visit 3/week 0 (baseline) inclusion and exclusion criteria will be evaluated. Subjects continuing urotherapy who still meet the OAB entry criteria at baseline will be randomized. Subjects whose symptoms are not satisfactorily controlled with urotherapy and still fulfill the inclusion/exclusion criteria will enter the study. These subjects will be randomized to receive mirabegron in PED25 or placebo using a 1:1 ratio. Subjects with a body weight of >= 35 kg are to receive the tablet unless unable to swallow tablets and would be provided the oral suspension as an alternative. Subjects with a body weight < 35 kg or those who cannot be dosed with the tablet will receive an oral suspension. Daily investigational product (IP) administration will start on day 1 (i.e., the day after this visit) and continue at this dose until visit 5/week 4 (i.e., for 4 weeks). Urotherapy will continue throughout the study treatment period until visit 7/week 12 (EoT).
At visit 5/week 4, dose up-titration to mirabegron in PED50 will be performed unless the investigator determines that the subject is adequately treated for OAB at the PED25 dose or if there are safety concerns identified and considered associated with the use of PED25. Dose down titration from PED50 to PED25 can be done at any time thereafter for safety reasons.
Subjects will start with the subsequent 7-day bladder e-diaries approximately 7 days prior to the indicated visit (or TC).
Pharmacokinetic blood samples will be collected at visit 5/week 4 and visit 7/week 12 (EoT) as indicated in the Schedule of Assessments [Table 1].

* Follow-up period (2 weeks):
This period starts the day after visit 7/week 12 (EoT) and ends with visit 8/week 14 (EoS). The follow up period is applicable to all subjects who have been randomized and received IP.
At visit 7/week 12 (EoT), IP administration will be stopped and a safety observation period of 2 weeks will start.
An independent DSMB will be established. A separate charter will describe the responsibilities of the DSMB.
A blinded interim analysis will be performed after 50% of children planned to be randomized have had their week 12/EoT assessment. The interim analysis will determine if the chance of a positive study with respect to the primary endpoint at the EoS is high enough to justify continuation of the study; otherwise, the study will be stopped for futility.
The IP will not be provided after study completion without written approval from the sponsor.

**Intervention**

Mirabegron tablets 25 mg or 50 mg (test product) and corresponding placebo
Mirabegron oral suspension with 8 mg/ml (test product) and corresponding placebo

**Study burden and risks**

The most common side effects These side effects were experienced by 1 or more in 100 participants in previous studies of mirabegron. They can be light to moderate.

GENERAL
Dizziness headache
LIMBS AND JOINTS
Swelling of joints (joint swelling) SKIN Itching (pruritus) Rash or hives (urticaria)
REPRODUCTIVE
Vaginal infection Itching of the vulva or vagina (vulvovaginal pruritus)
STOMACH AND BELLY
Infection of the bladder (cystitis) Irritation of the stomach (gastritis) Indigestion (dyspepsia) Nausea Constipation Diarrhea HEART Fast or pounding heartbeat (palpitations), Increased heart rate (tachycardia) Raised blood pressure

Rare side effects These side effects were experienced by about 1 in 1,000 participants in previous studies of mirabegron. They can be serious and require you to go to the hospital.

HEART
Irregular heartbeat (atrial fibrillation, QT prolongation) which means that the heart muscle takes longer than normal to charge between beats. BLADDER Unable to completely empty the bladder (urinary retention)
EYES
Swelling of the eyelid (eyelid edema)
MOUTH
Swelling of the lip (lip edema)
SKIN
Swelling under the skin (angioedema) Inflammation of small blood vessels that mainly affect the skin (leukocytoclastic vasculitis) Small purple spots on the skin (purpura)

Very rare side effects These side effects were experienced by about 1 in 10,000 participants in previous studies of mirabegron.
BLOOD VESSEL
Rapid and extreme increase in high blood pressure (hypertensive crisis) Side effects with a frequency that cannot be estimated These side effects cannot be estimated from the available data.

MENTAL
Not being able to sleep (insomnia)
Confusion (confused state)

## Contacts

**Public**
Astellas Pharma

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Illinois 60062
US
**Scientific**
Astellas Pharma

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Illinois 60062
US

## Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

## Inclusion criteria

Inclusion at Visit 1/Week -4 (Screening)
2. Subject has OAB defined according to the ICCS criteria.
4. Subject weighs at least 11 kg at screening.
5. Subject is able to take the IP in accordance with the protocol.
6. Subject agrees to drink an adequate fluid volume during urine collection weekends, as instructed by the investigator.
7. Subject and subject*s parent(s)/legal guardian(s) agree that the subject will not participate in another interventional study while participating in the present study.
8. Subject and subject*s parent(s)/legal guardian(s) are willing and able to comply with the study requirements and with the concomitant medication restrictions.
9. At least 1 of the following conditions apply:
a. Not a woman of childbearing potential (WOCBP)
b. WOCBP who agrees to follow the contraceptive guidance from the time of informed consent/assent through at least 30 days after final IP administration.
10. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 30 days after final IP administration.
11. Female subject must not donate ova starting at first dose of IP and throughout the study period and for 30 days after final IP administration.
12. Male subject with female partner(s) of childbearing potential (including breastfeeding partner[s]) must agree to use contraception throughout the treatment period and for 30 days after final IP administration.
13. Male subject must not donate sperm during the treatment period and for 30 days after final IP administration.
14. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 30 days after final IP administration.

Additional Inclusion at Visit 3/Week 0 (Baseline)
15. Subject must have a micturition frequency of at least 8 times (on average)

per day, in the 7 days prior to visit 3/week 0 (baseline), as recorded in the bladder e-diary.
16. Subject must have at least 1 daytime incontinence episode (on average) per day, during the 7-day period before visit 3/baseline, as recorded in the bladder e-diary.
17. Subject whose symptoms are not satisfactorily controlled with urotherapy and still fulfills the inclusion/exclusion criteria will enter the study.

## Exclusion criteria

Exclusion at Visit 1/Week -4 (Screening)
1. Subject has extraordinary daytime only urinary frequency according to the ICCS definition
* This applies to a toilet-trained child who has the frequent need to void that is associated with small micturition volumes solely during the day
* The daytime voiding frequency is at least once per hour with an average voided volume of < 50% of expected bladder capacity (EBC) (typically 10% to 15%)
* Incontinence is rare and nocturia is absent
Subject has
2. an uroflow indicative of pathology other than OAB
3. monosymptomatic enuresis
4. dysfunctional voiding
5. bladder outlet obstruction, except if successfully treated
6. anatomical anomalies (surgically treated or untreated) that affect lower urinary tract function
7. Subject with hematuria on dipstick test. In the case of hematuria on dipstick test in a female during menstruation, the test can be repeated before randomization (after the end of menstruation)
8. Subject with diabetes insipidus
Subject has
9. kidney or bladder stones
10. suffered from chronic UTI or has had more than 3 UTIs in the 2 months prior to visit 1/week -4 (screening)
11. a pulse > 99th percentile for age
12. stage 2 hypertension or subject has stage 1 hypertension that is not well controlled, as defined by the 2017 American Academy of Pediatrics Clinical Practice Guidelines
13. QTcF > 440 msec on screening ECG or a risk of QT prolongation (e.g., hypokalemia, long QT syndrome [LQTS] or family history of LQTS or exercise-induced syncope)
14. Subject*s aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is >= 2 × upper limit of normal (ULN) or total bilirubin (TBL) is >= 1.5 × ULN according to age and sex (subjects with Gilbert*s syndrome are excepted from the bilirubin threshold)

Subject has
15. mild or moderate renal impairment (estimated glomerular filtration rate according to the modified Schwartz of < 60 mL/min per 1.73 m2)
16. a symptomatic (symptoms can include pain, fever, hematuria, new onset foul-smelling urine) UTI. Note: if the UTI is treated successfully (clinical recovery: confirmed by dipstick test and repeated dipstick test after 14 days [both should be negative]), the subject can be rescreened
17. a history or presence of any malignancy
18. Subject uses any drugs that are sensitive cytochrome P450 2D6 (CYP2D6) substrates with a narrow therapeutic index or sensitive P-glycoprotein (P-gp) substrates after the start of washout
19. Subject is using or has used prohibited prior and/or concomitant medication(s)
Subject has
20. known or suspected hypersensitivity to mirabegron or any components of the formulations used
21. participated in another clinical study (and/or subject has received any investigational therapy within 30 days (or 5 half-lives of the drug, or the limit set by national law, whichever is longer) prior to visit 1/week -4 (screening)
22. Subject received urinary catheterization within 2 weeks prior to screening
23. Constipation as defined by the Rome IV criteria that cannot be successfully treated prior to study entry
24. Female subject who has been pregnant within 6 months prior to screening or breastfeeding within 3 months prior to screening
25. Subject has any condition which makes the subject unsuitable for study participation
Additional Exclusion at Visit 3/Week 0 (Baseline)
Subject has
26. extraordinary daytime only urinary frequency according to the ICCS definition based on the bladder e-diary
27. monosymptomatic enuresis confirmed by the bladder e-diary
28. a maximum voided volume (morning volume excluded) > EBC for age ([age +1] × 30) in mL, based on the bladder e-diary
29. polyuria defined as voided urine volumes of > 40 mL/kg baseline body weight during 24 hours or > 2.8 L urine for a child weighing >= 70 kg (ICCS definition) [Austin et al, 2014], based on bladder e-diary
30. PVR volume > 20 mL (lowest PVR volume result) as measured by ultrasonography
31. Subject suffers from a symptomatic (symptoms can include pain, fever, hematuria, new onset foul-smelling urine) UTI. Note: if a symptomatic UTI is present, all visit 3/week 0 (baseline) assessments must be postponed until the UTI is successfully treated (clinical recovery: confirmed by dipstick test and repeated dipstick test after 14 days [both should be negative]), and the urotherapy should continue. The postponed visit 3/week 0 (baseline) should be within 14 days of the intended visit 3/week 0 (baseline)
32. Subject with hematuria on dipstick test. In the case of hematuria on

dipstick test in a female during menstruation, the test can be repeated before randomization (after the end of menstruation)
33. Subject has a pulse > 99th percentile for age
34. Subject has stage 2 hypertension or subject has stage 1 hypertension that is not well controlled, as defined by the 2017 American Academy of Pediatrics Clinical Practice Guidelines
35. Any reason that makes the subject unsuitable for study participation

# Study design

## Design

| | |
|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 5 |
| Type: | Anticipated |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Mirabegron |
| Generic name: | Myrbetriq |
| Registration: | Yes - NL outside intended use |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 01-07-2020 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 04-11-2020 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 06-06-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 22-09-2021 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 08-10-2022 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 17-10-2022 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 29-03-2023 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 06-04-2023 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 21-05-2023 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2016-001767-37-NL |
| CCMO | NL74008.028.20 |

# Study results

Results posted: 09-08-2024

Actual enrolment: 0

**Summary results**
Trial never started

**First publication**
10-01-2024