A Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 2a, Proof-of-Concept Study of ASP8302 in Subjects with Underactive Bladder

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•To evaluate the efficacy of ASP8302 compared with placebo in subjects with Underactive Bladder (UAB)•To investigate the safety and tolerability of ASP8302 compared with placebo in subjects with UAB•To investigate the pharmacokinetics of ASP8302 in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON48804

Source
ToetsingOnline

Brief title
Astellas ASP8302 / NIAGARA study

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
bothersome chronic incomplete bladder emptying, underactive bladder

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma

Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: ASP8302, Phase 2 study, Underactive Bladder, Urinary free flow

Outcome measures

Primary outcome

•Change from baseline to visit 4 in PVR after standardized bladder filling

measured by

catheterization (PVRC2)

Secondary outcome

•The volume voided of standardized bladder filling at site visits (VVST)

•Bladder voiding efficency C2 (i.e. bladder voiding efficiency calculated with

PVRC2 and VVST)

Study description

Background summary

The target disease indication for ASP8302 is underactive bladder (UAB), which is a bothersome chronic condition that is due to incomplete bladder emptying. Underlying mechanisms of storage symptoms are diverse and are often related to a significant post void residual urine volume.

There are currently no approved drugs for UAB. In a limited number of countries, bethanechol is available for related conditions; however, its efficacy is not convincingly demonstrated and systemic cholinergic side effects are common. When conservative management is insufficiently effective additional treatment is required, which is directed at bladder drainage, i.e., clean intermittent catheterization or indwelling catheters (urethral or suprapubic). Any form of urinary
catheterization is time consuming, socially restricting, psychologically burdensome for the subject catheterization can cause complications of varying severity.

ASP8302 is a novel positive allosteric modulator for the muscarinic M3 receptor. The
pharmacological principle of positive allosteric modulator is to enhance activation of the target only when the target is stimulated by its endogenous ligand, thereby avoiding tonic cholinergic activation. Therefore, ASP8302 is expected to improve voiding dysfunction by enhancing bladder contraction during the voiding phase of the micturition cycle. It should be relatively inactive during the storage phase resulting in fewer side effects and greater efficacy than existing cholinergic agents.

Study objective

•To evaluate the efficacy of ASP8302 compared with placebo in subjects with Underactive Bladder (UAB)
•To investigate the safety and tolerability of ASP8302 compared with placebo in subjects with UAB
•To investigate the pharmacokinetics of ASP8302 in subjects with UAB
•To support the development of the UAB - Patient Reported Outcome (PRO)

Study design

Design
This is a multinational, multicenter, randomized, double-blind, parallel group, placebo-controlled
phase 2a/proof-of-concept study. The study will comprise a single-blind, 2-week placebo run-in
period, followed by a randomized, double-blind, placebo-controlled, 4-week treatment period and a
2-week follow-up period. Subjects will visit the clinic at screening (visit 1), following a 2-week
placebo run-in period (visit 2), after 2 and 4 weeks of double-blind treatment (visits 3 and 4,
respectively), and after a 2-week follow-up period (visit 5). During the course of the study, visits and
assessments will be performed as defined in the Schedule of Assessments.
Screening
Informed consent will be obtained before performing any study related procedures. Subjects will
undergo eligibility screening, including safety labs, pregnancy test for female subjects of childbearing
potential, vital signs, electrocardiogram (ECG), urinalysis and physical examination, which includes
for females: assessment of uterus prolapse and cystocele, and for males, a trans-rectal ultrasound or trans-abdominal ultrasound for prostate volume (PV) measurement. If recent urodynamic pressure
flow study (PFS) data is available (i.e., within 12 months before screening)

then PV measurement is
not necessary. If the subject fails exclusion criterion #21 (urinary tract infection [UTI]) on visit 1, the
subject can be rescreened once after successful treatment of the UTI (2 weeks of cure), and if eligible
at rescreening enroll in the study.
Uroflowmetry with a void following natural spontaneous bladder filling (i.e., with bladder perceived
to be full and when a clear desire to void is experienced by the subject) will be performed to measure
flow, Volume Voided (VV) and Post Void Residual urine volume (PVR). PVR will be measured by
2D transabdominal ultrasound (PVRUS1) after the void. The functional bladder capacity (BC) will be
calculated (VV + PVRUS1). The highest of the BC at visits 1 and 2 is also to be used as the filling
volume for standardized bladder filling at randomization (visit 2) and at End of Treatment (EoT;
visit 4), see below.
Run-in Period
Subjects meeting all eligibility screening criteria can enter into a single-blind, 2-week placebo run-in
period. During this period, subjects will be asked to complete a micturition diary during the 3 days
preceding randomization (visit 2), collecting data on voiding frequency, urgency, urine volume and
incontinence.
Treatment Period
Randomization
At visit 2, subjects fulfilling inclusion and exclusion criteria will be randomized to 1 of the following
double-blind treatment arms using a 1:1 ratio:
•*ASP8302 100 mg once daily (qd)
•*Placebo to match (PTM)
Randomization will be stratified by region (Europe, Japan) and sex.
Drug intake on the day of visit 2 must be done after uroflowmetry and PVR assessments (and PFS, if
applicable).
At visit 2, PVR will be measured in 4 ways: after natural spontaneous and standardized bladder
filling, with ultrasound, as well as catheterization:
1. V2_PVR US1: PVR measurement with ultrasound following void and uroflowmetry after natural
spontaneous bladder filling as at screening; also V2_BC will be calculated.
2. V2_PVRC1: PVR measurement with catheterization following V2_PVRUS1. With the same
catheter, the bladder will be filled to BC (highest BC of visit 1 and visit 2

[V1_BC or V2_BC],
i.e., standardized bladder filling). The catheter used to assess V2_PVRC1 should be of small
caliber (8 Ch/Fr) to reduce effects to the urethra and to measurements with standardized bladder
filling (see inclusion criterion #12). For the same reason the filling rate for standardized bladder
filling should not exceed 20 mL/min.
3. V2_PVR US2: PVR measurement with ultrasound following void and uroflowmetry after
standardized bladder filling (after catheter for assessing V2_PVRC1 is removed) will be used to
calculate the bladder voiding efficiency (BVE) for randomization (see inclusion criterion #13).
4. V2_PVRC2: PVR measurement with catheterization following V2_PVRUS2. The VV of the void
following standardized bladder filling (VVST) and the V2_PVRC2 will be used to calculate the
bladder voiding efficiency (BE) for randomization (see inclusion criterion #13): V2_BVE =
[VVST/(V2_PVRC2 + VVST)] x 100
A Pressure Flow PFS sub-study will be performed in 40 subjects maximally in approximately
7 selected sites (in Europe and Japan) for evaluation of urodynamic parameters. Standardized PFS
(details will be described in a separate PFS manual) will be conducted at randomization (baseline) and
EoT for all subjects at these selected sites. A PFS review committee, consisting of urodynamic
experts, will be installed to assess the PFS results after the study.
Double-Blind Treatment Period
The duration of the double-blind treatment period will be 4 weeks. Subjects will be asked to complete
a micturition diary during the 3 days preceding visit 3 (week 2) and visit 4 (week 4).
At visit 3, uroflowmetry and measurement of PVR will be performed with ultrasound only
(V3_PVRUS1) following natural/spontaneous bladder filling.
End of Treatment Assessments
Subjects will be asked to complete their micturition diary 3 days prior to visit 4, as stated above.
At visit 4, following completion (or early termination) of the treatment period, subjects will perform
the assessment of the EoT visit. Uroflowmetry and the 4 PVR measurements will be performed as at
visit 2, i.e., with a void following natural/spontaneous bladder filling (assessment of V4_PVRUS1 and

V4_PVRC1), and a void following standardized bladder filling using the same filling volume and rate
as on visit 2 (assessing V4_PVRUS2 and V4_PVRC2).
Uroflowmetry and PVR assessment (and PFS if applicable) must be performed 2 to 4 hours after drug
intake on the day of visit 4.
Follow-up Period
A follow-up visit (visit 5) will be performed 2 weeks after visit 4 (EoT). Three days preceding the
visit, the micturition diary will be completed. At visit 5, uroflowmetry and PVR measurement will be
performed with ultrasound following natural/spontaneous bladder filling (i.e., assessment of
V5_PVRUS1).
Population Pharmacokinetic Analysis
Blood samples for population pharmacokinetics (PPK) will be collected at visit 3 and/or 4.

Intervention

Subjects will receive multiple capsules (i.e., ASP8302 100 mg / placebo) once a day for a period of 6 weeks.

Study burden and risks

In general, study participants may experience physical or psychological discomfort from study tests, study procedures and questionnaires. In addition, study participants may experience side effects from the study medication.

The study burden consists of (maximum):
- Visits to the doctor: 5 visits
- Physical exam: 3 times
- ECG: 4 time
- Questionnaires: 2 times
- Complete diary: 35 times
- Venipuncture: 5 times, and during this procedure, blood can be drawn at several time points during the visit via a cannula.
- Urine samples: 5 times
- Measure urine free flow: 5 times
- Measure PVR: 5 times
- Measure PFS: 2 times (only applicable for some hospitals)

Contacts

Public
Astellas Pharma

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

At Study Entry - Screening (visit 1):
1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation at the time of signing the informed consent form (ICF).
3. Subject is diagnosed with UAB, defined as a bothersome chronic incomplete bladder emptying:
• clinical condition is present for >= 6 months before screening, and
• subject has a PVR >= 75 mL (measured by ultrasound after uroflowmetry; V1_PVRUS1).
4. Subject on CIC should have been on CIC for at least 1 month and should be able to void spontaneously and not be completely dependent on CIC.
5. Female subject must either:

•Be of non-childbearing potential:
-Post-menopausal (defined as at least 1 year without any menses for which there is no other obvious pathological or physiological cause) prior to screening, or
-Documented surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
•Or, if of childbearing potential:
-Agrees not to try to become pregnant during the study and for 28 days after the final study drug administration
-Agrees to have a serum pregnancy test on all visits
-And have a negative serum pregnancy test at the screening visit
-And agrees to consistently use 1 form of highly effective birth control* starting at screening and throughout the study period and for 28 days after the final study drug administration.
6. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for 28 days after the final study drug administration.
7. Female subject must not donate ova starting at screening and throughout the study period, and for 28 days after the final study drug administration.
8. A sexually active male subject with female partner(s) of childbearing potential is eligible if he agrees to use a male condom starting at screening and continue throughout study treatment and for 90 days after the final study drug administration.
9. Male subject must not donate sperm starting at screening and throughout the study period and for 90 days after the final study drug administration.
10. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 28 days after the final study drug administration.
*Highly effective forms of birth control include:
• Consistent and correct usage of established hormonal contraceptives that inhibit ovulation
• Established intrauterine device or intrauterine system
• Bilateral tubal occlusion
• Vasectomy (a vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
• Male is sterile due to a bilateral orchiectomy
• Sexual Abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
11. Subject agrees not to participate in another interventional study while participating in this study., At Randomization (visit 2):
12. Subject has a PVR >= 100 mL (measured by catheterization, i.e., PVRC2).
13. Subject has a VVST >= 50 mL and a BVE (V2_BVE) >= 10%. The VVST and V2_PVRC2 will be used to calculate V2_BVE = [VVST/(V2_PVRC2 + VVST)] *100.

Waivers to the inclusion criteria will NOT be allowed.

Exclusion criteria

At Study Entry - Screening (visit 1):
Related to lower urinary tract:
1. Subject has significant BOO:
•Clinically significant urethral stricture in the opinion of the investigator.
•Female subject has uterine prolapse >= Grade 2 Shaw*s system (down to or outside the introitus), moderate or severe cystocele (reaches or protrudes outside the introitus).
•Male subject has a bladder outlet obstruction index (BOOI) >= 40 on PFS (either performed on screening or within 12 months of the screening visit), or -if PFS is not available-a PV of > 40 mL (Europe) > 30 mL (Japan) on ultrasound (either performed on screening or within 6 months of the screening visit). Note: if PFS is available and PV is above the cut-off level, the subject is not to be excluded if BOOI is < 40.
• Other condition that in the opinion of the investigator constitutes significant BOO.
2. Urgency urinary incontinence clinically significant in the opinion of the investigator.
3. 1 or more bladder diverticuli clinically significant in the opinion of the investigator.
4.Vesico-ureteral/renal reflux clinically significant in the opinion of the investigator.
5. Urinary catheter in situ.
6. 1 of the following conditions as a primary cause for their UAB, or a condition that could potentially influence treatment outcome:
•Neurological lesion or condition, including cerebrovascular accident, spinal lumbar disc hernia, spinal cord injury, multiple sclerosis, Parkinson*s disease, Guillain-Barré syndrome, pudendal, hypogastric or pelvic nerve lesion. Diabetes mellitus is allowed if controlled with or without medical treatment.
•Increased pelvic floor muscle activity during voiding (e.g., dyssynergic striated sphincteric activity/striated sphincteric activity during voiding, Fowler syndrome and pelvic floor muscle spasm).
•Previous bladder surgery. Prior Benign Prostatic Obstruction surgery is allowed if performed more than 6 months prior to screening.
•Previous implant surgery for incontinence still in situ.
•Significant active urological pain syndrome
•Previous pelvic radiation therapy
7. Dependence on use of a manual assistance method intended to improve bladder emptying., Related to (previous or current) treatment and/or study drug:
8. 1 or more of the following non-medication therapies:
•Electrostimulation therapy.
•Intravesical or injection based treatment.

•An ongoing bladder training program and/or pelvic floor muscle exercises, which started within 6 weeks prior to visit 1.
•Muscle-derived stem cell injection in the bladder or urethra or bladder transplantation at any time prior to screening.
9. Prohibited medications or subject is using restricted medications under conditions different to those specified in the concomitant medication section.
10. Known or suspected hypersensitivity to ASP8302 or any of the inactive ingredients.
11. Inflammatory bowel disease or clinically significant diarrhea.
12. Subject is known to be immunocompromised due to conditions such as human immunodeficiency virus/acquired immune deficiency syndrome or hepatitis C.
13. Diagnosed with clinically significant cardiovascular or cerebrovascular diseases within 6 months prior to visit 1.
14.Diagnosed with clinically significant asthma, chronic bronchitis and/or chronic obstructive pulmonary disease.
15. Mean Fridericia corrected QT interval (QTcF) > 430 ms for males or > 450 ms for females, a pre-existing long QT syndrome or hypokalemia.
16. Clinically significant abnormal 12-lead ECG.
17. Current or previous malignant disease of the pelvis. Subjects with a history of (non-pelvic) cancer are considered eligible if the subject has undergone therapy and the subject has been considered disease free for at least 5 years. Subject with completely excised basal cell carcinoma or squamous cell carcinoma of the skin and completely excised cervical cancer in situ are also considered eligible.
18. Moderate to severe hepatic impairment.
19. Severe renal impairment defined as estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2.
20 Current or history of alcohol and/or drug abuse within the last 24 months prior to screening.
21. Evidence of a UTI confirmed by a urine culture containing > 100,000 cfu/mL in midstream urine. If a UTI is confirmed in the visit 1 sample, the run-in period should be stopped. After successful treatment of the UTI, the subject can be rescreened and if eligible enroll in the study.
22. Any of the following abnormal liver or kidney function parameters (as assessed in visit 1 sample):
•ALT, AST or bilirubin increased to > 1.5 times the ULN.
•γ-GT increased to >3 times the ULN.
•eGFR < 45 mL/min/1.73 m2 based on the Modification of Diet in Renal Disease formula.
23. Received investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to screening.
24. Employee of the Astellas Group, third parties associated with the study, or the clinical study site team.
25. To have any condition, which in the opinion of the investigator makes the subject unsuitable for study participation., At randomization (visit 2):
26. Subject meets any of the exclusion criteria of visit 1.
27. Severe OAB, i.e., experienced 3 or more episodes of urgency (Patient

Perception of Intensity of Urgency Scale [PPIUS] Grade 3 or 4), during the 3-day micturition diary period prior to visit 2.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-04-2019
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ASP8302
Generic name:	ASP8302

Ethics review

Approved WMO

Date:	09-08-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	10-12-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-11-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-11-2019
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	EUCTR2017-003693-13-NL
CCMO	NL66244.028.18

Study results

Date completed:	28-04-2020
Results posted:	16-02-2021
Actual enrolment:	11

Summary results
Trial is onging in other countries

First publication
01-01-1900