Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 2a, Proof-of-Concept Study of ASP8302 in Subjects With Underactive Bladder

Summary

EudraCT number	2017-003693-13
Trial protocol	SK PL NL DE GB
Global end of trial date	28 April 2020

Results information

Result version number	v1 (current)
This version publication date	22 April 2021
First version publication date	22 April 2021

Trial information

Trial identification

Sponsor protocol code	8302-CL-0201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03702777
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe B.V. (APEB)
Sponsor organisation address	Sylviusweg 62, 2333 BE Leiden, Netherlands,
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V. (APEB), astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V. (APEB), astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study objectives of this study are to evaluate the efficacy of ASP8302 compared with placebo in participants with underactive bladder (UAB), to investigate the safety and tolerability of ASP8302 compared with placebo in participants with UAB, to investigate the pharmacokinetics of ASP8302 in participants with UAB and to support the development of the UAB - Patient Reported Outcome (PRO).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Japan: 60
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Slovakia: 11
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	135
EEA total number of subjects	74

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	66
From 65 to 84 years	68
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Adult male and female participants diagnosed with underactive bladder (UAB), who were able to void spontaneously, with or without clean intermittent catheterization (CIC), without severe overactive bladder (OAB) and without significant bladder outlet obstruction (BOO) were enrolled in this study.

Pre-assignment

Screening details:

Prior to randomization, participants entered a single-blind placebo run-in period for 2 weeks and completed a 3-day micturition diary. After the placebo run-in period, participants' eligibility criteria were re-confirmed and participants were then randomized into the double-blind treatment period of the study.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received ASP8302 matching placebo orally once daily for up to 4 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received ASP8302 matching placebo orally once daily for up to 4 weeks.

Arm title	ASP8302 100 mg

Arm description:

Participants received ASP8302 100 mg capsules orally once daily for up to 4 weeks.

Arm type	Experimental
Investigational medicinal product name	ASP8302
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received ASP8302 100 mg capsules orally once daily for up to 4 weeks.

Number of subjects in period 1	Placebo	ASP8302 100 mg
Started	70	65
Completed	65	62
Not completed	5	3
Consent withdrawn by subject	2	2
Adverse event, non-fatal	1	-
Miscellaneous	1	-
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received ASP8302 matching placebo orally once daily for up to 4 weeks.	
Reporting group title	ASP8302 100 mg
Reporting group description:	
Participants received ASP8302 100 mg capsules orally once daily for up to 4 weeks.	

Reporting group values	Placebo	ASP8302 100 mg	Total
Number of subjects	70	65	135
Age categorical Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	35	31	66
From 65-84 years	34	34	68
85 years and over	1	0	1
Age Units: years			
arithmetic mean	61.4	62.7	
standard deviation	± 13.1	± 10.9	-
Sex Units: Participants			
Female	30	26	56
Male	40	39	79
Race Units: Subjects			
ASIAN	31	29	60
WHITE	39	36	75
Post Void Residual Urine Volume (PVR) after standardized bladder filling measured by catheterization			
Volume of urine in the bladder after standardized bladder filling measured by catheterization (PVRc2).			
Units: milliliter (mL)			
arithmetic mean	369.3	374.7	
standard deviation	± 234.6	± 248.6	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received ASP8302 matching placebo orally once daily for up to 4 weeks.	
Reporting group title	ASP8302 100 mg
Reporting group description:	
Participants received ASP8302 100 mg capsules orally once daily for up to 4 weeks.	

Primary: Change From Baseline in PVR After Standardized Bladder Filling Measured by catheterization (PVRc2) at Week 4

End point title	Change From Baseline in PVR After Standardized Bladder Filling Measured by catheterization (PVRc2) at Week 4
End point description:	
Volume of urine in the bladder after standardized bladder filling measured by catheterization (PVRc2). The FAS-PVR Population (FAS-PVR) comprised of all randomized participants who took at least 1 dose of double-blind study medication and had a nonmissing PVRc2 value at baseline and end of trial (EoT).	
End point type	Primary
End point timeframe:	
Baseline and week 4	

End point values	Placebo	ASP8302 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	61		
Units: mL				
median (inter-quartile range (Q1-Q3))	-35 (-130 to 40)	-40 (-125 to 25)		

Statistical analyses

Statistical analysis title	Placebo versus ASP8302 100 mg
Comparison groups	Placebo v ASP8302 100 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96 [1]
Method	Stratified rank ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-5

Confidence interval	
level	90 %
sides	2-sided
lower limit	-42
upper limit	34

Notes:

[1] - The stratified rank analysis of covariance (ANCOVA) was used to compare the median change between placebo and ASP8302 treatment group.

Hodges-Lehmann method was used to obtain an estimate in the median (and 90% CI).

Secondary: Voided Volume After Standardized Bladder Filling (VV_St) at Week 4

End point title	Voided Volume After Standardized Bladder Filling (VV_St) at Week 4

End point description:

VVst is thought to increase as the bladder emptying is improved. Standardizing the bladder filling is thought to increase accuracy in comparison with normal spontaneous bladder filling which will differ between time points.

No multiplicity correction was performed.

FAS-PVR Population

End point type	Secondary

End point timeframe:

Week 4

End point values	Placebo	ASP8302 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	61		
Units: mL				
median (inter-quartile range (Q1-Q3))	306 (185 to 409)	368 (265 to 456)		

Statistical analyses

Statistical analysis title	Placebo vs ASP8302 100 mg
Comparison groups	Placebo v ASP8302 100 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17 [2]
Method	Stratified rank ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	62
Confidence interval	
level	90 %
sides	2-sided
lower limit	8
upper limit	112

Notes:

[2] - The stratified rank ANCOVA was used to compare the median between placebo and ASP8302 treatment group.

Hodges-Lehmann method was used to obtain an estimate in the median (and 90% CI).

Secondary: Bladder Voiding Efficiency Calculated With PVRc2 and VV-St (BVEc2) at Week 4

End point title	Bladder Voiding Efficiency Calculated With PVRc2 and VV-St (BVEc2) at Week 4

End point description:

Bladder voiding efficiency (BVE) is defined as the percentage of the total bladder capacity (BC) that is voided using the following formula: BVE = [volume voided (VV) / (PVR + VV)] x 100.
BVEc2: BVE calculated for PVRc2 parameter i.e. BVEc2 = [VV_St / (PVRc2 + VV_St)] x 100.

FAS-PVR Population

End point type	Secondary

End point timeframe:

Week 4

End point values	Placebo	ASP8302 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	61		
Units: percentage of BVE				
median (inter-quartile range (Q1-Q3))	54.60 (28.40 to 76)	53.10 (40.20 to 70)		

Statistical analyses

Statistical analysis title	Placebo vs ASP8302 100 mg
Comparison groups	Placebo v ASP8302 100 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.489 [3]
Method	Stratified rank ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	3.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.9
upper limit	10.6

Notes:

[3] - The stratified rank ANCOVA was used to compare the median between placebo and ASP8302 treatment group.

Hodges-Lehmann method was used to obtain an estimate in the median (and 90% CI).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to end of study (6 weeks)

Adverse event reporting additional description:

The SAF consisted of all participants who took at least 1 dose of double-blind study medication, and was used for safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v21.0

Reporting groups

Reporting group title	ASP8302 100mg

Reporting group description:

Participants received ASP8302 100 mg capsules orally once daily for up to 4 weeks.

Reporting group title	Placebo

Reporting group description:

Participants received ASP8302 matching placebo orally once daily for up to 4 weeks.

Serious adverse events	ASP8302 100mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)	2 / 70 (2.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 63 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 63 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ASP8302 100mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 63 (6.35%)	6 / 70 (8.57%)	
Infections and infestations			
Cystitis			
subjects affected / exposed	4 / 63 (6.35%)	0 / 70 (0.00%)	
occurrences (all)	4	0	
Urinary tract infection			
subjects affected / exposed	0 / 63 (0.00%)	6 / 70 (8.57%)	
occurrences (all)	0	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2018	The chnages included: 1) Updated informed consent process to delete the possibility of the obtaining informed consent from a legally authorized representative. 2) Revised the inclusion criterion 5 to remove the specification that females are heterosexually active.Updated the concomitant medications to include information on how to treat urinary tract infections. 3) Updated the criteria for discontinuation of treatment based on liver function test abnormalities to specify that treatment was to be discontinued for certain liver function test abnormalities. 4) Updated the definition of adverse event (AE) so that it may or may not be considered related to the underlying disease. 5) Added the definition and reporting of suspected unexpected serious adverse reactions (SUSARs). 6) Added a section containing subject confidentiality and privacy to the protocol appendix.
22 July 2019	The changes included: 1) The number of participants enrolled in the placebo run-in period was increased to 163. This increased number provided 130 randomized participants (65 in each arm) in order to achieve 98 evaluable participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported