Clinical trial results:
A multicentre, open-label, non-inferiority sequential study, evaluating the efficacy, safety, tolerability and acceptability of ADV7103 compared to standard of care in distal renal tubular acidosis patients.

Summary

EudraCT number	2013-002988-25
Trial protocol	SK
Global end of trial date	20 May 2016

Results information

Result version number	v1 (current)
This version publication date	21 July 2021
First version publication date	21 July 2021

Trial information

Trial identification

Sponsor protocol code	B21CS

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Advicenne SA
Sponsor organisation address	2 rue Briconnet, Nimes, France, 30000
Public contact	Director of Clinical Affairs, Advicenne Pharma, 33 466 05 54 23, cguittet@advicenne.com
Scientific contact	Director of Clinical Affairs, Advicenne Pharma, 33 466 05 54 23, cguittet@advicenne.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001357-PIP01-12
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	26 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the relative efficacy of ADV7103 and standard of care on correcting metabolic acidosis as measured on pre-morning dose blood bicarbonate levels during 3 days of treatment at steady state (Day 2 to Day 4)

Protection of trial subjects:

A Data Safety Monitoring Board, DSMB, will be constituted and will get together when at least 4 subjects of a defined sub-set of age, according to the planned inclusion’s staggered approach, will have completed the study. Two meetings will be organised in order to review data of at least 4 subjects of Sub-set 1 and Sub-set 2 then data of at least 4 subjects of Sub-set 3. Additional meetings may be organised at any time if any intolerable safety issue related to the study drug occurs during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Serbia: 1
Worldwide total number of subjects	37
EEA total number of subjects	36

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)	2
Children (2-11 years)	18
Adolescents (12-17 years)	10
Adults (18-64 years)	7

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

the screening/inclusion visit will be planned in the investigator site (Visit 1) on Day-1 to perform the baseline evaluations.

Period 1

Period 1 title	Study period 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Standard of care (SoC)

Arm description:

SP I is a steady phase with SoC at the therapeutic dose

Arm type	Active comparator
Investigational medicinal product name	SoC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The daily dose of standard of care (usual alkalising treatment) will be taken as usual by the subject. This dose should be determined at inclusion and the dose regimen should be the same all along the study period, with at least a dose in the morning.

Number of subjects in period 1	Standard of care (SoC)
Started	37
Completed	35
Not completed	2
Consent withdrawn by subject	1
difficulty in swallowing ADV7103	1

Period 2

Period 2 title	Study period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ADV7103 Titration

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ADV7103
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release granules
Routes of administration	Oral use

Dosage and administration details:

The daily dose will be provided in 2 doses a day in the morning and in the evening, to be taken orally before the meal or with some semi-liquid foods for the youngest children. The morning dose will be taken approximately between 7 and 8 am and the evening dose will be taken approximately between 7 and 9 pm. The granules must not be chewed.

Number of subjects in period 2	ADV7103 Titration
Started	35
Completed	32
Not completed	3
Consent withdrawn by subject	2
Lack of efficacy	1

Period 3

Period 3 title	Study period 3
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ADV7103

Arm description:

SPIII is a steady phase with ADV7103 at the optimal dose

Arm type	Experimental
Investigational medicinal product name	ADV7103
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release granules
Routes of administration	Oral use

Dosage and administration details:

The daily dose will be provided in 2 doses a day in the morning and in the evening, to be taken orally before the meal or with some semi-liquid foods for the youngest children. The morning dose will be taken approximately between 7 and 8 am and the evening dose will be taken approximately between 7 and 9 pm. The granules must not be chewed.

Number of subjects in period 3	ADV7103
Started	32
Completed	32

Baseline characteristics

End points

End points reporting groups

Reporting group title	Standard of care (SoC)
Reporting group description: SP I is a steady phase with SoC at the therapeutic dose	
Reporting group title	ADV7103 Titration
Reporting group description: -	
Reporting group title	ADV7103
Reporting group description: SPIII is a steady phase with ADV7103 at the optimal dose	

Primary: Average bicarbonate blood level

End point title	Average bicarbonate blood level
End point description:	
End point type	Primary
End point timeframe: during 3 days of treatment at steady state with ADV7103 and SoC (Day 2 to Day 4).	

End point values	Standard of care (SoC)	ADV7103		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: mmol/L				
arithmetic mean (standard deviation)	21.7 (± 3.06)	23.1 (± 1.62)		

Statistical analyses

Statistical analysis title	Paired t-test
Comparison groups	Standard of care (SoC) v ADV7103
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	t-test, 1-sided

Notes:

[1] - Analysis performed on 30 subjects as subjects switched from Study period 1 to Study period 3

Adverse events

Adverse events information	
Timeframe for reporting adverse events: during the course of the study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	Standard of care steady state
Reporting group description: -	
Reporting group title	ADV7103 titration
Reporting group description: -	
Reporting group title	ADV7103 steady state
Reporting group description: -	

Serious adverse events	Standard of care steady state	ADV7103 titration	ADV7103 steady state
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	1 / 34 (2.94%)	0 / 32 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 34 (2.94%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Standard of care steady state	ADV7103 titration	ADV7103 steady state
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 37 (8.11%)	19 / 34 (55.88%)	0 / 32 (0.00%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 37 (0.00%)	3 / 34 (8.82%)	0 / 32 (0.00%)
occurrences (all)	0	3	0
pyrexia			

subjects affected / exposed	0 / 37 (0.00%)	2 / 34 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 37 (8.11%)	6 / 34 (17.65%)	0 / 32 (0.00%)
occurrences (all)	3	7	0
Abdominal pain upper			
subjects affected / exposed	0 / 37 (0.00%)	5 / 34 (14.71%)	0 / 32 (0.00%)
occurrences (all)	0	6	0
Vomiting			
subjects affected / exposed	0 / 37 (0.00%)	3 / 34 (8.82%)	0 / 32 (0.00%)
occurrences (all)	0	3	0
Diarrhoea			
subjects affected / exposed	0 / 37 (0.00%)	2 / 34 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	0 / 37 (0.00%)	2 / 34 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2014	i. Bicarbonataemia analysis no longer performed in a centralised laboratory but taken directly to the nearest local laboratory. ii. Additional urinary and blood parameters added without change of number or volume of samples. iii. Patients presenting a moderate renal impairment excluded in addition to those presenting severe renal impairment. iv. Ethnic origins removed from demographic data to be collected. v. Volume of blood to be drawn modified to allow 4 samples for participation in the fluctuation evaluation. Samples planned to be 1 ml will be 2 ml for adolescents and adults. vi. New version of the IMPDs established for ADV7103-CK and ADV7103-BK. Loading rates of ADV7103-CK and ADV7103-BK slightly different to ones in previous batches. Error regarding alkalising power of ADV7103 corrected. Expiry period of ADV7103 modified in protocol following stability study. vii. Secondary packaging introduced for ADV7103. viii. Pharmacovigilance and data management activities delegated to external organisations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported