Clinical trial results:
A multicentre, open-label, extension study, evaluating the safety and tolerability and the efficacy of ADV7103 at long term in distal renal tubular acidosis patients.

Summary

EudraCT number	2013-003828-36
Trial protocol	SK
Global end of trial date	17 May 2018

Results information

Result version number	v1
This version publication date	16 September 2021
First version publication date	16 September 2021

Trial information

Trial identification

Sponsor protocol code	B22CS

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	21 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2018
Global end of trial reached?	Yes
Global end of trial date	17 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability as measured by adverse events of ADV7103 at long term.

Protection of trial subjects:

In this extension study, if needed, and in particular for children a local anaesthetic patch was applied prior to blood sample collection.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
Long term follow-up duration	3 Years
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: 28
Country: Number of subjects enrolled	Serbia: 1
Worldwide total number of subjects	30
EEA total number of subjects	29

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)	3
Children (2-11 years)	13
Adolescents (12-17 years)	8
Adults (18-64 years)	6
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients who had participated in and completed study B21CS

Period 1

Period 1 title	24 Months study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Long term ADV7103

Arm description: -

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

Dosage and administration details:

The daily dose of ADV7103 was provided in two doses per day (one dose in the morning and one dose in the evening) taken orally before meal, directly in the mouth then swallowed with water or mixed with some semi-liquids foods.

Number of subjects in period 1	Long term ADV7103
Started	30
Completed	29
Not completed	1
Personal reasons	1

Baseline characteristics

Reporting groups	
Reporting group title	24 Months study

Reporting group description: -

Reporting group values	24 Months study	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	3	3	
Children (2-11 years)	13	13	
Adolescents (12-17 years)	8	8	
Adults (18-64 years)	6	6	
Gender categorical Units: Subjects			
Female	17	17	
Male	13	13	

End points

End points reporting groups

Reporting group title	Long term ADV7103

Reporting group description: -

Primary: The number/proportion of patients presenting AEs throughout the course of the study, including the incidence and severity of these events

End point title	The number/proportion of patients presenting AEs throughout the course of the study, including the incidence and severity of these events[1]

End point description:

End point type	Primary

End point timeframe:

throughout the course of the study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were performed. Descriptive statistics of the number/proportion of patients presenting adverse events during the course of the study (One arm)

End point values	Long term ADV7103			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percent				
number (not applicable)	30			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Comprehensive assessments of any apparent toxicity experienced by the subject will be performed throughout the course of the study from the time of subject's signature of the informed consent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Long term ADV7103

Reporting group description: -

Serious adverse events	Long term ADV7103		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Wisdom teeth removal			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis rotavirus			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Long term ADV7103		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 30 (90.00%)		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Ear infection			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		

Nasopharyngitis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Tinea infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2 2 / 30 (6.67%) 2 2 / 30 (6.67%) 2 2 / 30 (6.67%) 2		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Vitamin D deficiency subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3 12 / 30 (40.00%) 15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2016	-New primary and secondary packaging will be used: the new primary packaging is a sachet (also named stickpack) instead of a pillbox and the new secondary packaging is a cardboard box of 60 units instead of 30. - Operation of packaging of the sachets and pharmaceutical certification done by Ivers-Lee - Change of IMP denomination" according to the CHMP statement on the 4th Apr 2014: "mini-tablets" is replaced by "prolonged-release granules" and all documents are updated with this new denomination. - Homogenisation of the wording for the strength of the doses (use "8 mEq" and "24 mEq", rather than the dose in mg of active principles or in mg of granules) - Change of the IMP labelling: the mention of trial reference code is not any more indicated in the label and the mentions on primary packaging do not include anymore the treatment number. - Modification of the number of subjects included: "Up to 32 subjects may be enrolled in order to have 24 subjects fully evaluable" - Modification of study duration: extension from 33 to 40 months with 16 months for inclusion part. - Modification of the compliance evaluation: "to allow the investigator evaluating the patient compliance according to several factors: number of unused monodoses, questioning of the patient and/or his parents, observation of the subject's laboratory results, at each study visit". - Centralisation of analysis for the 1α,25-dihydroxy-vitamin D, parathyroid hormone and bone alkaline phosphatases with delegation of this activity to a central lab. - Modification of the bone marker to be analysed: "TRAP-5b" is replaced by "a new bone marker ". - Analysis of calcitonine removed - Clarification of the ECG and vital signs exams schedule - Precision done on the definition of an SAE: "any inpatient hospitalisation planned before the study enrolment of the patient or required as part of the usual medical management of the patient's disease will not be considered as a SAE"
09 March 2016	- Modification in the IMP process: the primary packaging will be done packaged by Ivers-lee, the secondary packaging will be done by Ivers-lee or Amatsi, and released by IL-CSM, and they will be released and supplied to the centres by Amatsi, in accordance with the GMP.
09 February 2017	- The study duration is extended up to marketing authorisation and provision of the ADV7103 product in France. - Addition of study visits after the initial end of study according to medical practice and on a regular basis at least every 12 months - Addition of exploratory objective: o To explore the ADV7103 treatment acceptability at long term. - Addition of exploratory endpoints: o Treatment acceptability that will be evaluated with Visual Analogue Scales (VAS), to be filled in by the patient or the caregiver (depending of the age), to be scored at M24 o Quality of life of the parents that will be evaluated with a VAS, to be filled in by one of the parents at M24 - Addition of new data to be collected "Disease history": collection of biological parameters and demographic data in the 4 years prior to B21CS

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported