1 TITLE PAGE

CLINICAL STUDY REPORT – 48-MONTH DATA SYNOPSIS

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

ADVICENNE

Study/Protocol No.:	**B22CS**
EudraCT No.:	2013-003828-36
Investigational Medicinal Product:	ADV7103
Study Phase:	Phase III, extension study
Sponsor:	**Advicenne SA** 21 Allée Boissy d'Anglas 30000 Nîmes France Tel: +33 466 05 54 20 Fax: +33 466 21 23 35
Coordinating Investigator:	Dr. Aurélia Bertholet-Thomas Hôpital Femme Mère Enfant CHU de Lyon 59 Boulevard Pinel 69677 Bron Cedex France
First Patient First Visit:	06 November 2014
Last Patient Last 48-month Visit:	23 June 2020
Date of Clinical Study Report:	09 August 2021
Clinical Study Report Version:	Final Version

The study was conducted according to the protocol and in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, with the Declaration of Helsinki and with other applicable regulatory requirements.

2 SYNOPSIS

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

TITLE OF STUDY:

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.

INVESTIGATORS:

Dr. Aurélia Bertholet-Thomas (Coordinating Investigator)

A full list of Investigators is available in Section 16, Appendix 16.1.4.

STUDY CENTRES:

Multicentre – 12 centres; 10 in France, 1 in Serbia and 1 in Slovakia

PUBLICATION (REFERENCE):

STUDIED PERIOD:	**PHASE OF DEVELOPMENT:**
FPFV: 06 November 2014 LPLV: 23 June 2020	Phase III, extension study

OBJECTIVES:

Primary Objective

The primary objective of the study was to evaluate the long-term safety and tolerability of ADV7103 as measured by adverse events (AEs).

Secondary Objectives

The secondary objectives of this study were to evaluate:

- The long-term efficacy of ADV7103 on correcting metabolic acidosis as measured by bicarbonataemia,
- The long-term effects of ADV7103 on kalaemia,
- The long-term effects of ADV7103 on citraturia,
- The long-term effects of ADV7103 on calciuria,
- The long-term effects of ADV7103 on phosphaturia,
- The long-term effects of ADV7103 on magnesuria,
- The long-term effects of ADV7103 on crystalluria,
- The long-term paraclinical and biological safety of ADV7103,
- The long-term compliance to ADV7103.

Exploratory Objectives

Exploratory objectives were to explore:

- The long-term effects of ADV7103 on nephrocalcinosis,
- The long-term effects of ADV7103 on nephrolithiasis,
- The long-term effects of ADV7103 on bone remodelling,
- The long-term effects of ADV7103 on rickets and osteomalacia, respectively in the paediatric and adult population,
- The long-term effects of ADV7103 on growth in the paediatric study population,

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

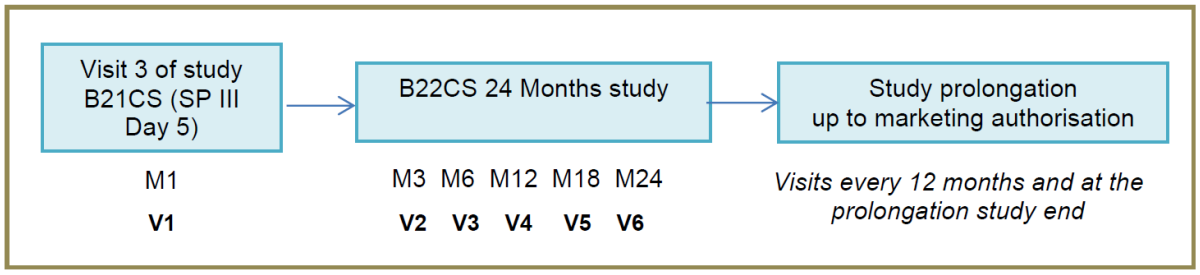
- The long-term effects of ADV7103 on pubertal maturity in the relevant paediatric study population,
- The long-term treatment acceptability of ADV7103,
- The long-term effects of ADV7103 on quality of life (QoL),
- The medical profile of the patient before Study B21CS inclusion, including the distal renal tubular acidosis (dRTA) genetic mutation.

METHODOLOGY:

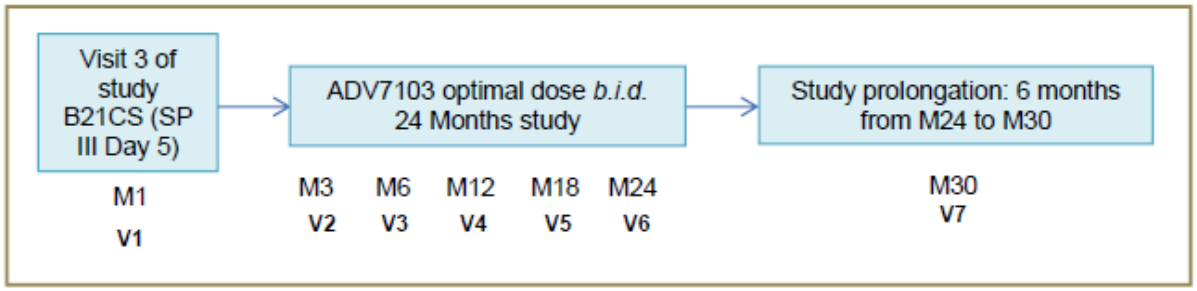
This study was a multicentre, open-label extension (OLE) study of the Phase II/III Study B21CS in patients with dRTA. Study B21CS was a multicentre, open-label, non-inferiority, sequential study comparing the efficacy, safety, tolerability and acceptability of ADV7103 with standard of care (SoC) during two successive phases involving a switch from SoC to ADV7103 in patients with a confirmed diagnosis of dRTA. Patients completing Study B21CS were allowed to enter the OLE study (Study B22CS) and continue their treatment with ADV7103 at the optimal dose determined during Study B21CS (and further adapted if needed) for ≥24 months (originally planned for 24 months but extended in France until market authorisation and availability of ADV7103 and extended for six additional months (30 months in total) in Slovakia and Serbia, until approval of the import licence for ADV7103). A total of 30 patients with inherited dRTA were thus enrolled into Study B22CS after satisfactory completion of Study B21CS.

Six visits were scheduled during the first 24 months of the OLE study. The first visit of Study B22CS at M1 corresponded to Visit (V)3 of Study B21CS (Study Period (SP) III, Day 5) and a further five visits took place at M3, M6, M12, M18 and M24, respectively. One visit every year was scheduled thereafter for patients continuing beyond 24 months in France. For patients in Slovakia and Serbia, there was a further visit 6 months after M24 (M30).

Study design for patients in France



Study design for patients in Slovakia and Serbia



Safety and tolerability were assessed by recording AEs and serious adverse events (SAEs), physical examination (including body weight, height, body mass index [BMI], and Tanner stage [if appropriate]), vital signs and electrocardiograms (ECGs), and urine and blood laboratory tests.

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

Efficacy was assessed by measurement of patients' bicarbonataemia and kalaemia, and by analysis of urine to determine citraturia, calciuria, phosphaturia, magnesuria and crystalluria. Treatment compliance was also assessed.

The exploratory assessments included nephrocalcinosis, calculi, specific bone biochemistry blood parameters, bone mineral density (BMD), osteomalacia and rickets, stature, body weight, estimated adult stature (EAS), growth velocity, physical development of the sexual organs at puberty, treatment acceptability of ADV7103, effects of ADV7103 on patients' and parents' quality of life (QoL) by visual analogue scale (VAS). The impact of dRTA and its treatments on daily life of patients and/or parents was assessed through individual exploratory interviews during the study prolongation period.

A preliminary analysis was performed after all enrolled patients reached the M6 visit (or discontinued treatment). The results of the 6-month analysis are presented in a separate report. Endpoints analysed for the report were those that could be evaluated at M6.

An analysis was performed at M24, which included several additional long-term secondary endpoints and all the long-term exploratory outcomes (nephrocalcinosis, nephrolithiasis, bone remodelling, rickets/osteomalacia and growth, treatment acceptability and patients' QoL).

The current report is based on the first of the annual analyses, at M48. In addition to all the efficacy, safety, tolerability and compliance endpoints analysed at M24, it includes additional exploratory endpoints.

NUMBER OF PATIENTS (PLANNED AND ANALYSED):

Up to 32 patients were planned to be included and 30 participated in the extension study.

Four age groups were planned: infants from 6 months to 4 years old, children from 4 to 12 years old, adolescents from 12 to 18 years old and adults aged over 18 years old.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Main inclusion criteria

- Patient who had participated in and completed Study B21CS,
- Patient for whom the efficacy, safety and tolerability of ADV7103 was satisfactory during Study B21CS,
- Patient and/or parents or legal representative(s) who were willing and able to participate in the study, to understand and to comply with study procedures for the entire length of the study,
- Patient or parents or legal representative(s) who had provided signed written informed consent,
- Patient of ≤17 years of age for whom assent had been collected or had been tried to be collected.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION:

ADV7103: unit-dose (pillboxes then sachets) containing prolonged-release granules of potassium citrate (ADV7103-CK) and prolonged-release granules of potassium bicarbonate (ADV7103-BK), with two strengths 8 milliequivalent (mEq) and 24 mEq.

ADV7103 dose used in the OLE was the one determined by the Investigator during Study B21CS, over two years (i.e. the long-term treatment) and which the Investigator could adapt during the study if needed.

ADV7103 was administered orally twice daily (BID), in the morning and evening.

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

DURATION OF TREATMENT:

The optimal dose of ADV7103 was to be taken for up to and beyond 48 months.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Not applicable.

CRITERIA FOR EVALUATION:

For the 48-month analysis presented in this report, the endpoints assessed included all the safety endpoints, secondary efficacy endpoints and exploratory efficacy endpoints.

SAFETY:

Primary endpoint

The number/percentage of patients presenting AEs throughout the course of the study, including the incidence and severity of these events.

Secondary endpoints

The number/percentage of patients presenting abnormal values after treatment at each study visit, including the incidence and clinical significance when appropriate of these abnormal values, for:

- Physical examination (general appearance, bone system, muscular system, articular system),
- Vital signs (systolic and diastolic blood pressures [SBP and DBP], heart rate [HR] and respiratory rate [RR]),
- ECG parameters (HR, PR interval, QRS interval [QRS], QT interval [QT], QT interval with Bazett's correction [QTcB] and QT interval with Fridericia's correction [QTcF]),
- Laboratory parameters (serum chloride, albumin, proteins, sodium, magnesium, urea, creatinine) and urine bicarbonate, potassium, chloride, proteins, sodium, magnesium,
- Liver function tests (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]),
- Urinalysis (pH, leucocytes, glucose, ketones, proteins, blood and specific gravity) with microscopic examination if required,
- Estimated glomerular filtration rate (eGFR) using the Schwartz formula for children and Cockcroft & Gault formula for adults.

EFFICACY:

Secondary endpoints

- The number/percentage of patients presenting normal ranges at each study visit in the following parameters:
- Bicarbonataemia,
- Kalaemia,
- Citraturia (expressed as urinary ratio of citrate/creatinine [UCi/UCr]),
- Calciuria (expressed as urinary ratio of calcium/citrate [UCa/UCi] and urinary ratio of calcium/creatinine [UCa/UCr]),
- Phosphaturia (expressed as urinary ratio of phosphate/creatinine [UPh/UCr], tubular reabsorption of phosphorous [TRP] and ratio of renal tubular maximum reabsorption of phosphorous [TmP] to glomerular filtration rate [TmP/GFR]),
- Magnesuria (expressed as urinary ratio of magnesium/creatinine [UMg/UCr]),
- The number/percentage of patients at each study visit presenting crystalluria positive, including urine environment,
- Compliance to the treatment including the incidence of events of non-compliance at M3, M6, M12, M18, M24, M30 (for patients in Slovakia and Serbia) and for patients in France, at annual visits in the prolongation

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

period and at the end of study, presented as number/percentage of patients compliant for >90%, 75% included to 90% excluded, 50% included to 75% excluded and <50% of the time.

Exploratory efficacy endpoints:

The following endpoints were assessed:

- Nephrocalcinosis,
- Calculi,
- Bone remodelling (including biochemistry blood parameters and BMD),
- Rickets and osteomalacia,
- Evaluation of growth in children (including stature and body weight measurement, EAS balanced by the genetic target structure (GTS), and growth velocity),
- Physical development of the sexual organs at puberty,
- Treatment acceptability of ADV7103
- Patients' and parents' QoL (evaluated with a VAS to be filled in by the patient or the caregiver, depending on age),
- Impact of dRTA and its treatment on daily life of patients and/or parents through individual exploratory interviews after M24, during prolongation period,
- Medical history (disease history of the patient for the 4 years before Study B21CS in relation to their medical profile for the 4 years during Study B22CS: results of bicarbonataemia, kalaemia, blood creatinine, urine calcium, urine creatinine, urine citrate, eGFR, number of hospitalisations and any visits to hospital emergency service, number of renal calculi, anthropometric data, doses of alkalising treatment used and dRTA genetic mutation),
- Most exploratory efficacy endpoints were assessed at M1 and M24, and at annual visits during the prolongation period and at end of study, except biochemistry blood parameters, stature, body weight, growth velocity and physical development of the sexual organs at puberty (assessed at each study visit), treatment acceptability (assessed at M24 only), and patients' and parents' QoL (assessed at M6 and M24).

STATISTICAL METHODS:

The following analysis sets were defined:

- Included Set: all patients included in Study B22CS,
- Safety Set: all patients receiving at least one dose of study drug in the Study B22CS,
- Efficacy Analysis Set: all patients receiving at least one dose of study drug, with at least one efficacy assessment in Study B22CS,
- Treatment acceptability and/or QoL Analysis Set: all patients receiving at least one dose of study drug, with at least one treatment acceptability and/or QoL assessment.

Data were organised by age group and overall as follows, with age group derived from the age of inclusion in Study B22CS:

- Adults (≥18 years old),
- Adolescents (12 to 18 years old),
- Children (4 to 12 years old),
- Infants (0.5 to 4 years old).

Subgroup analyses planned by type of dRTA and on pregnant women were not performed as all patients presented primary type of dRTA and no pregnancy was reported.

The Included Set was used for the analysis of baseline data and for presentation of listings. For all parameters, unless stated otherwise, baseline was defined as the last available measurement prior to the first administration of investigational medicinal product (IMP) in the B22CS study and referred to the assessment obtained at V1 in

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

Study B22CS. If the endpoint had been assessed in Study B21CS, the baseline referred to the appropriate last observation prior to the first ADV7103 dosing occasion in Study B21CS or the appropriate last observation prior to the ADV7103 dosing occasion in the study B22CS. As V4 of Study B21CS lasted from 0 to 24 hours and could overlap two successive days with two different dates depending on patient, the time-point of the blood and urine collections considered as baseline for Study B22CS was either the last time-point collection done for a patient or the time-point where all the blood and urine parameters needed for Study B22CS were assayed.

Primary Safety Assessment:

The primary endpoint was the number/percentage of patients presenting AEs during the course of the study, including the incidence and severity of these events. The safety analyses were performed on the Safety Set.

Adverse events were analysed within each age group and overall and corresponding numbers and percentages were tabulated by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0. The number and percentage of patients with at least one AE/treatment-emergent adverse event (TEAE)/related TEAE/SAE/related SAE were summarised in tables (overall and by SOC and PT). Summary tables of TEAEs by causality and intensity were also presented (overall and by SOC/PT). The number of patients with at least one AE/TEAE for a given PT corresponded to the number of AEs/TEAEs, whatever the number of occurrences in the studied period. A patient with multiple AEs within an SOC was counted only once towards the total of this SOC. In cases of change of intensity or causality for an event during the treatment period, the intensity was the highest recorded intensity, and the causality was the highest likelihood recorded. All AEs and TEAEs were listed as well as AEs leading to death, SAEs and AEs leading to study withdrawal.

Secondary Safety Assessments:

Secondary safety assessments included vital signs, ECG, physical examination, laboratory parameters and estimation of eGFR; data were listed by age group, patient, and visit/time. If ranges were available, abnormalities were flagged. Summary statistics were provided by age group and overall by visit/time.

Secondary Efficacy Assessments:

The secondary efficacy endpoints (excluding crystalluria parameters), including number/percentage of patients according to normality status and mean (standard deviation [SD]) and change from baseline at each visit, were summarised by age group and overall using tabular and graphical displays. Crystalluria was evaluated qualitatively, quantitatively or semi-quantitatively, considering the low number of quantitative values.

Exploratory Efficacy Assessments:

Summary tables were presented with the number/percentage of patients with nephrocalcinosis, nephrolithiasis, and other parameters by normality status including bone biochemistry blood parameters, Z-score values for BMD, stature/weight/EAS, growth velocity and pubertal maturity. All summaries were presented by age group and overall by measurement time. Specific listings of patients with abnormal findings were presented, raw data were listed and out of normal values were flagged. Summary tables with the number/percentage of patients with treatment acceptability scores ≥50 and ≥75 were presented by age group and measurement time. Graphs of mean±standard error of the mean (SEM) over time were presented for the values of VAS of treatment acceptability and VAS of QoL (rated by the patient only). Raw data for VAS of treatment acceptability and raw data with change from M6 (if applicable) for VAS of QoL were listed. Statistical analysis of the data recorded in interviews regarding the impact of dRTA and its treatments on the daily life of patients and/or parents during the prolongation period after V6 [M24] was performed by Icon.

SUMMARY – CONCLUSIONS

The results presented in this report are from the full final 48-month data analysis of safety (AEs, vital signs, ECGs, clinical laboratory tests and physical examinations), efficacy (levels of bicarbonataemia, kalaemia, calciuria (UCa/UCr; UCa/UCi), citraturia (UCi/UCr), phosphaturia (UPh/UCr), magnesuria (UMg/UCr) and

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

crystalluria, and treatment compliance), and exploratory efficacy parameters (nephrocalcinosis, nephrolithiasis, bone remodelling, osteomalacia and rickets, growth, pubertal maturity, treatment acceptability and patients' QoL). The present report includes all study endpoints.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

A total of 30 patients (six adults, eight adolescents, 13 children and three infants) entered the OLE study and 29 of these had data collected up to M24. One adult withdrew from the study after M12 for personal reasons, and one adolescent and one child completed the study at M30 as per the country-specific protocol. All patients were included in the safety, efficacy and QoL analyses.

Overall, a majority of patients (56.7%) were female, although in the infant group all three patients were male. The mean±SD age overall was 10.6±6.0 years, with patients ranging from 2 to 21 years of age.

The majority of patients overall (23 patients, 76.7%), had a genetic diagnosis. One child was not genetically tested since his older brother presented a genetically diagnosed dRTA. Eighteen patients (60.0%) had a clinical and/or biochemical diagnosis (in the absence of or before genetic diagnosis).

All of the patients assessed had inherited dRTA (one child had missing genetic data to confirm the aetiology of dRTA).

All patients had past presence of metabolic acidosis and the majority had nephrocalcinosis (86.7%) and hearing impairment (66.7%), regardless of age. Some patients (13.3%) presented nephrolithiasis. Muscle weakness, cramp, periodic paralysis, nephrolithiasis, renal impairment, fractures/pseudofractures, growth impairment (in children), short stature (in adults) and other clinical symptoms were only seen in small numbers at baseline (≤four patients). One infant had hypokalaemia, two patients (one adult and one child) had osteopenia and one child had polyuria. There were no cases of rickets, osteomalacia or bone pain at baseline.

Overall, 29 of the 30 patients (96.7%) were taking concomitant medications. The medication classes with the highest frequency were vitamins (21 patients; 70.0%), analgesics (15 patients; 50.0%), systemic anti-bacterials (seven patients; 23.3%), drugs for functional gastrointestinal (GI) disorders (seven patients; 23.3%), anti-diarrheals, intestinal anti-inflammatory/anti-infective agents (five patients; 16.7%). blood substitutes and perfusion solutions (five patients (16.7%),

The majority of patients taking vitamins as concomitant medications (overall and in all age groups) were receiving calciferol or equivalent (indicated in prevention or treatment of vitamin D deficiency): cholecalciferol (20 patients; 66.7%), calcifediol (one patient; 3.3%), and alfacalcidol (one patient; 3.3%).

SAFETY RESULTS

A total of 188 TEAEs were experienced by 27 patients overall (90.0%); 23 TEAEs in four adult patients (66.7%), 66 TEAEs in eight adolescents (100.0%), 72 TEAEs in 12 children (92.3%) and 27 TEAEs in three infants (100.0%).

The most common TEAEs were Metabolism and nutrition disorders (35 TEAEs in 18 patients (60.0%) overall, including 13 patients with vitamin D deficiency, five patients with hypokalaemia, four patients with iron deficiency, and two with decreased appetite. Common TEAEs were also GI disorders (known as an adverse effect of alkalising products). Forty-four TEAEs were reported in 16 patients (53.3%) overall, including eight patients (26.7%) with vomiting, five patients (16.7%) with abdominal pain, and five patients (16.7%) with diarrhoea. TEAEs were quite common in Infections and infestations; 43 TEAEs were reported in 11 patients (36.7%) overall and were very varied. In the urine sphere (known as site of infections in dRTA patients), four patients had a urinary tract infection, pyelonephritis or an asymptomatic bacteriuria. More limited TEAEs were Renal and urinary disorders (while nephrocalcinosis and nephrolithiasis are known to be the main complications of dRTA),

with 17 TEAEs reported in nine patients overall (30.0%) including three patients (10.0%) with renal colic, and two patients (6.7%) with nephrolithiasis.

In general, TEAEs were of mild intensity: 26 patients overall (86.7%) reported 135 TEAEs of mild intensity. There were 49 TEAEs of moderate severity reported in 14 patients (46.7%) overall. The TEAEs of moderate severity were most commonly from the SOC of Renal and urinary disorders; nine TEAEs of moderate severity were reported in five patients (16.7%) overall. Three patients (10.0%) (one adult and two children) reported three episodes of renal colic, one adult reported three episodes of nephrolithiasis, one child reported two episodes of haematuria, and one adolescent reported one episode of anuria.

There were four severe TEAEs affecting three patients in the study: one case of decreased appetite in the adolescent group, two cases of unilateral deafness affecting one child, and one case of gastroenteritis rotavirus in the infant group. None of the severe TEAEs was considered related to treatment.

Eleven TEAEs in five patients (16.7%) were considered treatment-related, all in the SOC of GI disorders. One adolescent had three episodes of diarrhoea, one episode of GI disorder, and one episode of GI pain. One child had one episode each of abdominal pain, abdominal pain upper, and dyspepsia. One adolescent had one episode of abdominal pain upper, one child had one episode of abdominal pain, and one adult had one episode of dyspepsia.

Thirteen SAEs were reported in 10 patients overall (33.3%), all considered unrelated to treatment. All SAEs were resolved/recovered within the following days. The SAEs included deafness unilateral, sudden hearing loss, food poisoning, gastritis, vomiting, gastroenteritis rotavirus, gastroenteritis viral, migraine, renal colic, and wisdom teeth removal.

There were no TEAEs leading to study drug discontinuation or death, and no suspected unexpected serious adverse reactions (SUSARs).

Clinical laboratory evaluations in the study included full blood and urine chemistry and urinalysis. There was no obvious pattern in the percentage of abnormalities over time whatever the blood or urine parameter and most abnormal results were considered to be NCS. Of the abnormalities that were considered to be CS, most were cases of abnormally low eGFR in one adult, three adolescents and 5 children at one or several visits. No episodes of hyperkalaemia were reported and, more specifically, there were no observed abnormalities on ECGs that are classically associated with hyperkalaemia. One infant had a CS high urinary pH at M30 and M36, but this had resolved to a NCS level at M48. One child had raised leucocytes and erythrocytes on microscopic analysis at M24 (related to the TEAE pyelonephritis).

Physical examination findings over the 48 months of the study were all normal apart from five patients with isolated abnormal findings during their physical examination. One adolescent had a NCS increase of weight at M36, and a child had a NCS increase of weight at M18. One child had a molluscum contagiosum at M12 and M18 declared as unrelated AE, and one adolescent had an abnormal articular system finding at M36 which was NCS. One adolescent had an abnormal finding of general health/overall appearance at M48 related to the worsening of anorexia declared as an unrelated AE.

There were no CS abnormalities in vital signs over the 48 months of the study. There were no CS abnormalities in ECG parameters over the first 24 months of the study, and no observed abnormalities known to be linked to hypokalaemia or hyperkalaemia (such as modification of T wave, prolongation of PR interval or broadening of QRS) on the ECG.

The ADV7103 dose was fairly stable over the course of the study, with an increase in mean±SD dose (mEq/day) from 107.7±57.4 at M1 to M3 to 117.0±67.6 at M24 to M30, then decreased to 109.0±49.0 at M36 to M42 and 93.9±36.7 at M42 to M48. Mean doses as mEq/day were generally highest in the adolescent group or the adult group, followed by the child group and the infant group who had the lowest daily doses.

Overall, the mean±SD dose as mEq/kg/day decreased gradually over time, from 3.39±1.70 at M1 to M3 to 2.37±1.35 at M42 to M48. This decrease was more pronounced in both child and infant age groups. By M36 to M42, this represented a dose (mEq/kg/day) of 2.36±1.15 in the adult group, 1.98±1.05 in the adolescent group, 2.88±0.96 in the child group and 4.19±1.84 in the infant group. As expected, the alkali doses expressed in mEq/kg/day decreased with age and varied in general (mean doses as mEq/kg/day were highest in the infant group, followed by the child group, the adolescent group, and the adult group).

The safety data reported over 48 months in the OLE study were consistent with the known safety profile of ADV7103 and also with observations made in the B21CS study. The safety analysis did not raise any new safety concerns regarding the use of ADV7103 in patients with the indication of dRTA. Overall, the safety of ADV7103 was very good and the cases of GI-related TEAEs, known to be related to the drug mechanism, were

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

mostly mild in severity and were reported in only few patients (16.7%). Of note, there were no cases of hyperkalaemia observed and no observed abnormalities known to be linked to hyperkalaemia on the ECG. The good safety profile of the product was maintained long-term and did not evolve with exposure.

Secondary efficacy parameters

Results on the secondary efficacy parameters that were assessed in the OLE study demonstrated good efficacy of ADV7103 after 48 months of treatment (where patients were entered into the study with an initial optimal dose of ADV7103 as determined in the previous pivotal Study B21CS), with well controlled metabolic acidosis and kalaemia and positive effects on some urine parameters (particularly citrate and calcium):

- Plasma bicarbonate

Overall, when blood tests were done before study drug intake, 13 patients (52.0%) at baseline, 21 patients (91.3%) at M3, 12 patients (63.2%) at M6, 14 patients (77.8%) at M12, 16 patients (84.2%) at M18, 14 patients (60.9%) at M24, 18 patients (81.8%) at M36, and 13 patients (68.4%) had plasma bicarbonate levels above the lower limit of the normal range. For all patients including blood tests not done before morning dose, equivalent figures were reported.

There was, overall, a mean±SD increase from baseline in plasma bicarbonate of 1.98±3.43 mmol/L at M3, 1.30±3.92 mmol/L at M6, 1.56±2.94 mmol/L at M12, 0.82±3.26 mmol/L at M18, 0.93±2.86 mmol/L at M24, 0.95±4.57 mmol/L at M36, and 0.69±4.68 mmol/L at M48 overall, when blood tests were done before study drug intake, with the highest increase in the adult group. The adolescent and infant groups were the only groups showing a decrease at some visits.

Mean plasma bicarbonate was in the normal range over time. By M48, the mean±SD (mmol/L) plasma bicarbonate level was 23.07±3.44 in the adult group, 23.54±3.35 in the adolescent group, 22.08±5.45 in the child group, 22.00 in the infant group and 22.61±4.23 overall, when blood tests were done before study drug intake.

In general, ADV7103 allowed very good control of the metabolic acidosis, which is the main characteristic of dRTA and the main goal for the treatment of this condition, with the majority of patients showing normal values of bicarbonataemia over time up to 48 months.

ADV7103 ensures satisfactory long-term control of metabolic acidosis as evaluated with plasma bicarbonate over a four-year period.

- Kalaemia

Overall, for non-haemolysed blood samples done before study drug intake, 16 patients (84.2%) at baseline, 20 patients (95.2%) at M3, 19 patients (95.0%) at M6, 17 patients (94.4%) at M12, 17 patients (89.5%) at M18, 21 patients (91.3%) at M24, 20 patients (90.9%) at M36, and 17 patients (89.5%) at M48 had clinically normal plasma potassium levels. For the larger group of patients, including non-haemolysed samples not done before morning dose, similar figures were reported.

By M48, the mean±SD non-haemolysed plasma potassium (mmol/L) from blood tests done before study drug intake was 3.60±0.20 in the adult group, 3.56±0.35 in the adolescent group, 3.88±0.40 in the child group, 4.25 (no SD) in the infant group and 3.79±0.40 overall.

Plasma potassium was within the normal range in the majority of patients, and generally only slightly below the lower limit level for the remaining patients at some timepoints. Results were similar for non-haemolysed samples not done before morning dose, haemolysed and non-haemolysed samples analysed together and for results when blood tests were done before study drug intake compared with all samples.

ADV7103 allowed very good control of hypokalaemia, one of the major signs of the disease together with metabolic acidosis.

- Citraturia

Overall, seven patients (35.0%) had citraturia (expressed as UCi/UCr) in the normal ranges at baseline, 10 patients (52.6%) at M3, nine patients (40.9%) at M6, seven patients (29.2%) at M12, 14 patients (51.9%) at M18, 10 patients (41.7%) at M24, nine patients (42.9%) at M36, and four patients (20.0%) at M48.

The general trend on treatment with ADV7103 was maintenance of the number of patients with UCi/UCr in the normal ranges between 29 to 53% throughout the 48 months of treatment except at the M12 and M48 timepoints.

Reducing hypocitraturia induced by the disease is one of the goals of treating the patient and ADV7103 produced a stabilisation of citraturia as exemplified by UCi/UCr and by the number of patients with normalised citraturia.

- Calciuria

Urine calcium/creatinine ratio

All patients had UCa/UCr within the normal range at all visits, except for one to two patients who presented abnormally high values at M3 and subsequent visits up to M48, when there were 4 patients with abnormally high values of Uca/UCr.

There was a stable number of patients with UCa/UCr in the normal range throughout the 48 months of treatment.

Reducing hypercalciuria induced by the disease is one of the goals of treating the patient and ADV7103 allowed maintaining calciuria in the normal ranges, with a stabilisation or a decrease of UCa/UCr throughout the 48 months of follow-up, particularly for paediatric groups.

Urine calcium/citrate ratio

Nine patients overall (45.0%) at baseline, 11 patients (57.9%) at M3, nine patients (47.4%) at M6, 10 patients (43.5%) at M12, 10 patients (38.5%) at M18, nine patients (37.5%) at M24, nine patients (42.9%) at M36, and five patients (25.0%) at M48 had UCa/UCi in the normal range.

Nine patients overall (45.0%) at baseline, 12 patients (63.2%) at M3, 10 patients (52.6%) at M6, 11 patients (47.8%) at M12, 13 patients (50.0%) at M18, 12 patients (50.0%) at M24, 12 patients (57.1%) at M36, and six patients (30.0%) at M48 had UCa/UCi below the threshold associated with risk of lithogenesis.

The trend was a stabilisation of UCa/UCi and of the number of patients with a UCa/UCi in the normal range and below the threshold used to evaluate the risk of lithogenesis at about 50% throughout the 48 months of follow-up, though the data at the M48 visit showed more patients with an increased risk.

Consistent with the observed maintenance of citraturia and maintenance or reduction of calciuria, ADV7103 demonstrated a maintenance or reduction of UCa/UCi, potentially reducing the lithogenic risk for the patient in the long-term.

As stated above, it is important to adapt the dose in proportion to the growth of the children in order not only to maintain the plasma bicarbonate level but also the citraturia and calciuria in the normal range.

- Phosphaturia

Twenty paediatric patients (90.9%) overall had UPh/UCr in the normal range at baseline, 19 patients (95.0%) at M3, 20 patients (90.9%) at M6, 22 patients (95.7%) at M12, 21 patients (100%) at M18, 20 patients (95.2%) at M24, 18 patients (94.7%) at M36, and 15 patients (100%) at M48.

TRP levels were normal for all patients, when considering both the plasma phosphate level (which was normal for all patients, except for some isolated and NCS low or high values). Most patients had a normal eGFR (no medical history of renal impairment was reported and a normal eGFR was reported for all patients during the study, except for some isolated low values and three patients with eGFR mildly decreased for a 12 to 24 month period).

Reducing hyperphosphaturia induced by the disease is one of the goals of treating the patient and ADV7103 maintained UPh/UCr in normal ranges, in conditions of normal TRP and TmP/GFR.

- Magnesuria

Most paediatric patients overall had UMg/UCr in the normal range from M1 to M48, except one to five patients who had UMg/UCr above the normal range at baseline at some timepoints. These patients were all in the adolescent and child groups except for one infant with UMg/UCr above range at M18.

- Crystalluria

Overall, 25 (83.3%) patients had crystals during the 48 months study, 16 out of these 25 patients (64.0%) had amorphous carbonated calcium phosphate (ACCP) crystals in the study.

The incidence of urine crystals was stable during the 48-month study, and between 30% and 50% of the patients had positive crystalluria depending on the study yearly visit. The incidence did not increase in line with exposure. Most of these patients had ACCP crystals, and the incidence of ACCP crystals did not increase with exposure.

The majority of patients (between 57% to 77% depending on study visit) had urine pH between 7.0 and 8.0. Depending on study visit, some patients (between 18% to 39%) had urine pH >8.0, and few patients (between 0 and 12%) had urine pH <7.0. The incidence of high urine pH did not increase with exposure.

Together, crystalluria and urine pH were stable, no increase of the occurrence of ACCP crystals and of urine pH were observed with the ADV7103 treatment or with increased exposure, despite the intake of alkalising products. ADV7103 does not increase the risk of occurrence of ACCP. Notably the absence of an increase of ACCP crystals is of great importance since these crystals may be a consequence of the treatment for dRTA.

- Treatment compliance

Overall, during the 48 months of the study, compliance was generally good (between 67% and 93% of patients depending on study period) in all age groups and maintained at a high level (usually ≥75% for >80% of the patients except at M18 and M48) confirming a good acceptance of ADV7103 treatment. Only four patients (13.3%) had treatment compliance below 50% recorded. This was for a two-month period for one adolescent, for a six-month period for one adolescent and one infant, and for an 18-month period for one adolescent.

Exploratory efficacy parameters

Results on the exploratory efficacy parameters that were assessed in the OLE study suggested quite positive effects of ADV7103 after 48 months of treatment on renal and bone markers, growth, treatment acceptability and QoL.

- Nephrocalcinosis

Overall, most patients evaluated presented with nephrocalcinosis at baseline (25 patients; 86.2%), M24 (28 patients; 96.6%), M36 (24 patients; 92.3%), and M48 (20 patients; 90.9%).

One adolescent patient developed nephrocalcinosis during the 48 months of follow-up, while they were fully compliant to the treatment.

- Nephrolithiasis

Overall, nephrolithiasis was only seen in small numbers of patients, and the percentage of patients presenting with nephrolithiasis was similar at baseline (six patients; 20.7%), M24 (five patients; 17.2%), M36 (seven patients; 26.9%), and M48 (seven patients; 31.8%). Cases of nephrolithiasis were reported in each group of age.

- Bone Remodelling

Biochemistry blood parameters

- **1α,25-dihydroxy-vitamin D:** Overall during the 48 months of treatment, most patients (from 80% to 100% of the patients, according to the study visit) had blood 1α,25-dihydroxy-vitamin D levels in the normal range. No low blood 1α,25-dihydroxy-vitamin D levels were recorded apart from one adult at M24 + 10 weeks. High blood 1α,25-dihydroxy-vitamin D levels were recorded in one adult at M36, and the adolescent and child groups had cases of high blood 1α,25-dihydroxy-vitamin D levels at certain visits only.
- **25-hydroxy-vitamin D:** Overall during the 48 months, between 32% and 60% of the patients according to the study visit had blood 25-hydroxy-vitamin D levels in the normal range, and between 43% and 57% of the patients at most visits. No high blood 25-dihydroxy-vitamin D levels were recorded. Low blood 25-hydroxy-vitamin D levels were recorded in 40% to 68% of the patients depending on the study visit.

  Some patients (21/30; 70.0%) received doses of vitamin D at some time-points during the study, in prevention or for treatment of hypovitaminosis D. For almost all these patients at all time-points, the 1α,25-dihydroxy-vitamin D (which is the active form of vitamin D) was always in the normal ranges. The exception was for one adolescent who had high values of 1α,25 dihydroxy-vitamin D at baseline, M3, and M12 while receiving vitamin D treatment. The 25-hydroxy-vitamin D reflects the state of the

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

reserves. Even when vitamin D reserves are low, 1α,25-dihydroxy-vitamin D was maintained in the normal ranges. No trend about the 25-hydroxy-vitamin D level can be drawn but there is a seasonal variation of blood 25-hydroxy-vitamin D questioning the interpretation of the change from baseline data.

- **Blood bone alkaline phosphatase:** Overall, most patients (from 75% to 96%, according to the study visit) had blood bone alkaline phosphatase (ALP) levels in the normal range, during the 48 months of treatment. All cases of high levels of blood bone ALP occurred in the adult and adolescent and child groups. All infants presented normal levels of this bone blood marker.
- **Phosphate:** Overall, most patients (between 83% to 97% depending on study visit) had blood phosphate levels in the normal range during the 48 months of treatment. Low blood phosphate levels were recorded as isolated values. There was a consistent decrease from baseline in blood phosphate level (mmol/L) with the highest decrease in the adolescent group.
- **Calcium:** Overall, almost all patients (between 93% to 100% depending on study visit) had blood calcium levels in the normal range during the 48 months of treatment, without any noticeable trend of an increase or decrease in blood calcium levels.
- **Parathyroid hormone**: Overall, most patients (from 84% to 100% depending on study visit) had blood parathyroid hormone (PTH) levels in the normal range during the 48 months of treatment, with no noticeable trend of an increase of decrease in PTH levels.

Bone mineral density

The majority of paediatric and adult patients had normal Z-scores for the spine (>-2.0) at all four visits: baseline (18 patients; 72.0%), M24 (23; 85.2%), M36 (18; 78.3%), and M48 (18; 85.7%). Spine BMD abnormalities (Z-scores ≤-2.0) were reported for seven patients (28.0%) overall at baseline, four (14.8%) at M24, five (21.7%) at M36, and three (14.3%) at M48. Spine BMD abnormalities defined by a Z-score of ≤-2.5 were reported for one child patient at all four visits; all other patients had normal Z-scores (> -2.5).

All adult patients had normal Z-scores for the hip (>-2.0) at all four visits (baseline, M24, M36 and M48). No hip BMD abnormalities defined by a Z-score of ≤-2.5 were reported for any patient. The Z-score of the BMD of the hip showed a positive change from baseline, with mean±SD Z-score from -0.89±0.61 at baseline to -0.17±0.91 at M48.

The majority of patients had normal Z-scores for body (> -2.0) at all visits: baseline (12/16 patients, 75.0%), M24 (13/18 patients, 72.2%), M36 (10/15 patients, 66.7%) and M48 (11/16 patients, 68.8%).

Overall, the Z-score of the BMD of the spine (the relevant skeletal area for evaluating the BMD in both paediatric and adult populations) showed a continuous and significant clinical improvement after 48 months of treatment with ADV7103.

Hip data relevant only for adult patients cannot be statistically analysed in a meaningful way due to the limited number of patients, however, the Z-score of the BMD of the hip showed a continuous improvement after 48 months of treatment with ADV7103.

Body data are difficult to interpret due to skeletal area not always being fully respected (whole body with head), and missing data.

- Rickets and Osteomalacia

No adults presented with osteomalacia and one infant presented with rickets with ankle pain at baseline. By M24, no patients presented with either osteomalacia or rickets. By M36, two adolescents and two children had developed rickets, but by M48 this had resolved for one adolescent and one child. The two others had normal

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

and improved growth, did not present any rickets specific clinical signs or any abnormal values for the blood bone parameters, but one of them had a forearm fracture during the study.

- Growth in Children

Stature and body weight

The majority of patients in all age groups and at all visits were in the ±2SD range and in the ±3SD range for weight, height and BMI. This is expected as treatment with alkalising treatment was started a long time before study enrolment.

All but two patients were in the ±2SD range for height for all visits. All but one patient had height in the ±3SD range at baseline. One adult patient with a height below -2SD at baseline was not further improved since her growth was ended before study entry. The other patient, a 4.5-year female child, had a height below -3SD at baseline, followed by an improvement above +3SD and below -2SD at M3 and M6, then in the ±2SD range from M12 to M48. Her EAS increased from baseline (141.5 cm) to M48 (151.5 cm) for a GTS of 165 cm (range 156 to 174 cm). Improved control of metabolic acidosis with ADV7103 allows the patient with severe stunted growth to reach normal ranges and get closer to the GTS before end of puberty.

Overall, the majority of patients had a normal EAS. The percentage of patients with a normal EAS increased over time from 20 patients (76.9%) at baseline to 23 patients (88.5%) at M48.

Most patients were in the ±2SD range for weight for all visits, and most patients had a normal BMI throughout the study.

Growth velocity

Growth velocity was normal (i.e. in the 3 to 25th centile or ≥25th centile range) for the majority of paediatric patients overall. There were up to five patients with a growth velocity below the 3rd centile throughout the study, and a single patient with a growth velocity below the 3rd centile at M48. Most patients had a growth velocity ≥25th centile, between 11 (57.9%) and 16 (72.7%) paediatric patients throughout the study.

For female patients, the growth velocity ranged from 0.11±0.62 cm/6-month to 2.80±4.44 for adolescents, and remained relatively constant during the study, with values between 2.17±1.39 and 3.52±2.18 cm/6 month for children. For male patients, the growth velocity generally increased over time for the two adolescents, remained relatively constant during the study, with values between 2.12±1.74 and 4.11±2.39 cm/6 month for children, and with values between 2.89±1.58 and 4.51±2.27 cm/6 month in infants.

ADV7103 appeared to have a positive effect on growth velocity, which is slowed down in dRTA patients with the risk of dwarfism at adult age if patient remains untreated.

- Pubertal Maturity

There were two adolescents with late pubertal maturity; one female patient aged 14 at study entry with late development at M18 and M24, and one male patient aged 12 at study entry with late development at M18. There were no cases of early pubertal maturity.

Overall, pubertal maturity was normal in boys and girls. ADV7103 treatment had no impact on the pubertal maturity after 48 months of follow-up.

- Treatment Acceptability

Treatment acceptability scores were taken from data at the M24 visit. Overall, high mean 100 mm VAS scores were obtained for improvement in efficacy (91.2%), improvement in safety (72.2%), more appropriate formulation (83.9%), more convenient number of daily dose intakes (90.2%) and improvement in taste (68.6%).

Overall, good acceptability of ADV7103 was confirmed throughout the long-term treatment, irrespective of the parameter or the answerer. More than 80% of the patients had a score above 75% for improvement of efficacy,

NAME OF COMPANY: ADVICENNE PHARMA	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: NOT APPLICABLE		
NAME OF ACTIVE INGREDIENT: ADV7103		

formulation and number of daily doses. About 60% of the patients had a score above 75% for improvement of safety and taste even if some discrepancies were observed between answerers (children or parents).

- Quality of Life

Quantitative evaluation

Consenting patients (n=19) were interviewed to gather their impressions about disease, treatment and their impacts on the QoL, after an extensive, long-term experience with ADV7103 (over 48 months).

The four main QoL domains impacted by dRTA and its treatment were difficulties studying, social challenges, and negative emotional and physical impacts. Difficulties associated to hearing impairment remained but switching from previous SoC to ADV7103 was experienced as “life changing” by patients/parents.

The perceived emotional burden of disease was relieved in the absence of treatment-related invasive questions from others. Difficulties at school due to burdensome administrative issues and need to explain disease and treatment disappeared, facilitating parents who had stopped working to return to work. Social/family issues improved: travel and holidays became easier to organise, patients/parents stopped thinking about managing treatment daily/nightly, reducing tension in the family/couple. Bad taste, bad breath and GI AEs improved with ADV7103. Better compliance led to milder physical impacts and less fear of being hospitalised.

Mean satisfaction score with ADV7103 vs. SoC was 9 out of 10 and ADV7103 exceeded or met the expectations of 82% patients.

Overall, dRTA and its treatment have a significant impact on QoL of patients and parents and ADV7103 helped improve day-to-day life and reduces treatment burden, resulting in greater overall patients’ and parents’ satisfaction.

CONCLUSION

In conclusion, the results from this 48-month data analysis of the OLE study corroborate the results of Study B21CS and confirm that ADV7103 has a very good safety profile after long-term treatment. ADV7103 does not induce hyperkalaemia or increase the occurrence of ACCP crystals or lithiasis. Results showed that ADV7103 allows a sustained control of metabolic acidosis and hypokalaemia, since plasma bicarbonate and potassium levels are well controlled. Compared to SoC treatment (taken in Study B21CS), ADV7103 allows a reduction of the number of patients with hypocitraturia, with abnormally high UCa/UCi and with a risk of lithogenesis, which are important in avoiding future nephrocalcinosis and renal impairment. Treatment compliance with this twice daily treatment is good in the long-term. ADV7103 allows a continuous and significant clinical improvement of the Z-score of the BMD of the spine after 48 months of treatment. ADV7103 allows to restore a normal growth of the child with a severe stunted growth at study entry. Finally, compared to their usual SoC, patients’ QoL is improved after 48 months of ADV7103 treatment.

DATE OF THE REPORT: 09 August 2021