14 September 2023
EMA/481595/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aqumeldi

International non-proprietary name: enalapril maleate

Procedure No. EMEA/H/C/005731/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Administrative information

Name of the medicinal product:	Aqumeldi
Applicant:	Proveca Pharma Limited Dublin Landings 2 North Wall Quay Dublin 1 D01 V4A3 IRELAND
Active substance:	enalapril maleate
International Non-proprietary Name/Common Name:	enalapril maleate
Pharmaco-therapeutic group (ATC Code):	ACE inhibitors, plain (C09AA02)
Therapeutic indication(s):	Aqumeldi is indicated for the treatment of heart failure in children from birth to less than 18 years.
Pharmaceutical form(s):	Orodispersible tablet
Strength(s):	0.25 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	100 tablets + 1 scoop, 200 tablets + 1 scoop and 50 tablets + 1 scoop

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List of abbreviations

ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor
API	Active Pharmaceutical Ingredient
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the EP
CHD	Congenital heart diseases
CHMP	Committee for Medicinal Products for Human use
DCM	Dilated cardiomyopathy
DS	Drug Substance
DSM	Drug Product Manufacturer
DP	Drug Product
DPM	Drug Product Manufacturer
DoE	Design of Experiments
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EP/ Ph. Eur.	European Pharmacopoeia
FPS	Finished Product Specifications
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
HDPE	High Density Polyethylene
HF	Heart failure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPA	Isopropyl alcohol
IPC	In-Process Control
KF	Karl Fischer titration
LC-MS	Liquid chromatography mass spectrometry
LDPE	Low Density Polyethylene
LOD	Loss on Drying
LOD	Limit of Detection
LOQ	Limit of Quantitation
NLT	Not Less Than
NMT	Not More Than
PDCO	Paediatric Committee
PDE	Permitted Daily Exposure

PHF	Paediatric heart failure
PIP	Paediatric Investigation Plan
Ph. Eur.	European Pharmacopoeia
PP	Polypropylene
PUR	Polyurethane
PVC	Polyvinyl chloride
PSD	Particle Size Distribution
QbD	Quality by Design
QTPP	Quality Target Product Profile
ROA	Route of Administration
RPM	Revolutions Per Minute
RSD	Relative Standard Deviation
SmPC	Summary of Product Characteristics
USP/NF	United States Pharmacopoeia / National Formulary
UV	Ultraviolet
XRD	X Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Proveca Pharma Limited submitted on 7 March 2022 an application for a Paediatric Use marketing authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Aqumeldi, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 July 2020.

The applicant applied for the following indication: Aqumeldi is indicated for the treatment of heart failure in children from birth to less than 18 years.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Renitec
- Marketing authorisation holder: NV Organon (previously held by Merck Sharp & Dohme)
- Date of authorisation: 1985-09-06

Marketing authorisation granted by: Sweden

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0093/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0093/2021 was completed.

The PDCO issued an opinion (EMEA-C-001706-PIP01-14-M03) on compliance for the PIP P/0093/2021.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 June 2011	EMEA/H/SA/2119/1/2011/PED/SME/III	Norbert Benda and Mair Powell

The Scientific advice pertained to the following non-clinical and clinical aspects:

The need for further preclinical studies, new paediatric pharmacokinetic (PK), pharmacodynamic (PD), or clinical efficacy/safety studies to support a Paediatric Use Marketing Authorisation (PUMA) Application.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: John Joseph Borg Co-Rapporteur: Fátima Ventura

The application was received by the EMA on	7 March 2022
The procedure started on	24 March 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 June 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	21 July 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 December 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and	30 January 2023

PRAC members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 February 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2023
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	25 May 2923
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 June 2023
The CHMP agreed on a 3rd list of outstanding issues in writing to be sent to the applicant on	22 June 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 August 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Aqumeldi on	14 September 2023

2. Scientific discussion

2.1. Problem statement

Enalapril was the second angiotensin-converting enzyme (ACE) inhibitor to become widely available for therapeutic use after captopril, the first registered oral ACE inhibitor (ACEI). In children, whilst in clinical practice enalapril is used for similar indications as adults, in the European Union it is only licensed for use in children with hypertension and a body weight over 20 kg. In particular, in the harmonised SmPC for enalapril following Art 30 Referral for Renitec and associated names (CPMP/3175; 4 Dec 2003) it was agreed to include a statement in section 4.4 that enalapril is not recommended in children in indications other than hypertension. Current dose recommendations in children with heart failure (HF) are based on empirical evidence combined with data extrapolated from adult studies. A further challenge regarding dosing of ACE-I in paediatrics is the lack of authorised age-appropriate formulations licensed for use in paediatric HF throughout Europe.

The importance of pharmacological treatment in children with HF, especially dilated cardiomyopathies (DCM), is emphasized by the low availability of donor hearts. Owing to this scarcity, mortality within the first year of presentation remains extremely high, highlighting the need for optimal treatment in children to prevent or to postpone heart transplantation.

To address the unmet medical need for a licensed enalapril product for children with heart failure, a Framework 7 project ("Labeling of Enalapril from Neonates up to Adolescents", LENA) was conducted between November 2013 and April 2019.

2.1.1. Disease or condition

Paediatric heart failure (PHF) represents an important cause of morbidity and mortality in childhood. Etiology and pathogenesis are different between adults and children: the first mainly relates to ischemia, the latter is a consequence of congenital heart diseases (CHDs) or cardiomyopathies in most cases.

2.1.2. Epidemiology

Although the estimated incidence of heart failure is relatively low at 0.9–7.4 per 100,000 children, it is a disease that carries a high burden of morbidity and mortality, with an in-hospital mortality rate of 7–26%. Infants account for the majority (64%) of heart failure admissions in patients ≤18 years of age (Burstain DS at all; Am Heart J 2019, 209: 9 – 19; Rossano JW J Card Fail 2012; 18: 459 – 70).

2.1.3. Aetiology and pathogenesis

In children, cardiac failure is most often due to CHDs and cardiomyopathies. The underlying pathophysiology of the PHF in CHD could be left to right shunt with volume overload, valvular regurgitation, outflow tract obstruction or coronary insufficiency. In cardiomyopathies the pathophysiology is related often to systolic dysfunction with low cardiac output or to diastolic dysfunction with elevated pulmonary capillary pressure. Other causes of HF in children could be arrhythmias or infection resulting in systolic dysfunction.

2.1.4. Clinical presentation, diagnosis

In infant and young children the typical presentation is characterized by difficulty in feeding, cyanosis, tachypnea, sinus tachycardia, and diaphoresis.

Older children and adolescence often present symptoms of fatigue, shortness of breath, tachypnea, and exercise intolerance. Abdominal pain, oliguria, and leg pitting edema may also be present. The severity of HF in children is usually staged according to the Ross modified classification that recognizes four functional classes with increasing severity of clinical features from I to IV.

The diagnostic approach in patients with PHF is based on noninvasive clinical investigations: electrocardiography, chest radiography, echocardiography, laboratory investigation. These can be followed in some more complex cases by cardiac magnetic resonance, cardiac catheterisation and endomyocardial biopsy.

2.1.5. Management

Currently, there are well-established guidelines for the management of heart failure in the adult population. Due to the lack of research trials in children, the clinical guidelines for the treatment of PHF have historically been reliant on expert consensus, and the extrapolation of data from trials performed in adults.

In the clinical setting, diuretics and angiotensin-converting enzyme inhibitors (ACE-I) are used, with beta-blockers and devices for electric therapy as other options. In the end-stage disease, heart transplantation is the best choice of treatment, while a left ventricular assist device can be used as a bridge to transplantation (due to the difficulties in finding organ donors), recovery (in the case of myocarditis), or destination therapy (for patients with systemic disease). In adults, enalapril is licensed for the treatment of hypertension and heart failure, as well as for reducing proteinuria in chronic kidney disease (CKD). The SmPC for Renitec reference medicinal product states that there is only limited experience of the use of enalapril in hypertensive paediatric patients in greater than 6 years of age. The mechanism of action of enalapril and its potential pharmacodynamic interactions are believed to be similar in adults and paediatric patients.

The importance of pharmacological treatment in PHF, especially dilated cardiomyopathies, is emphasized by the low availability of donor hearts. Owing to this scarcity, mortality within the first year of presentation remains extremely high, highlighting the need for optimal treatment in children to prevent or postpone transplantation. In children, whilst in clinical practice enalapril is used for similar indications as adults, in the European Union (EU) it is only licensed for use in children with hypertension and a body weight over 20 kg. In children with heart failure the doses of enalapril used (off-label) are based on empirical evidence combined with data extrapolated from adult studies. A further challenge regarding dosing of ACE-I in paediatrics is the lack of authorised age-appropriate formulations licensed for use in paediatric heart failure throughout EU.

Therefore, there is an unmet medical need for a licensed medicinal product for children with heart failure that could be administered with age-appropriate formulations.

2.2. About the product

Enalapril is an ethyl ester pro-drug, and its pharmacological effects are mediated by its active metabolite, enalaprilat (also known as MK422). The main effect of enalaprilat is the inhibition of ACE, a key component in the renin angiotensin aldosterone system (RAAS). This leads to a decrease in the formation of angiotensin II and thereby to peripheral vasodilation. This is followed by a diminished

secretion of aldosterone, causing less sodium and fluid retention. These two mechanisms cause a decrease in blood pressure (BP), and a decreased preload and afterload of the heart as summarised by Brunner (1981). In addition to its stimulatory effect on aldosterone secretion, angiotensin II is able to directly increase the activity of the epithelial sodium channel (Zaika 2013). This leads to maximum sodium reabsorption, a process that is also reduced by ACE inhibitors. In adults, enalapril is licensed for the treatment of hypertension and heart failure, as well as for reducing proteinuria in chronic kidney disease (CKD). In addition to their BP lowering effect, ACE inhibitors have a role in the treatment of patients with heart failure, because they prevent (further) cardiac remodelling, as shown by Konstam (1993). In CKD the beneficial effect of enalapril is mostly the result of a decrease in glomerular pressure due to a relaxation of the efferent arterioles (Zhang 2017).

In children, whilst in clinical practice enalapril is used for similar indications as adults, in the European Union it is only recommended for use in children with hypertension and a body weight over 20 kg. In the harmonised SmPC for enalapril (CPMP/3175; 4 Dec 2003) a statement was included that enalapril is not recommended in children in indications other than hypertension. Despite a positive benefit/risk ratio of enalapril in the treatment of hypertension in children over 20kg, an evaluation by the European Medicines Agency concluded that data on the pharmacokinetics (PK) and pharmacodynamics (PD) of enalapril in this population appear scarce (CPMP/3175; 4 Dec 2003). In children below the weight of 20 kg, even less data is available.

Current dose recommendations in children with HF are based on empirical evidence combined with data extrapolated from adult studies. A further challenge regarding dosing of ACE-I in paediatrics up until now was the lack of authorised age-appropriate formulations licensed for use in paediatric HF throughout Europe.

2.3. Type of application and aspects on development

This is a Paediatric Use Marketing Authorisation (PUMA) application for Aqumeldi 0.25 mg oro-dispersible tablets (ODMT). The applicant applied initially for registration of both enalapril ODMT strengths: 0.25mg and 1 mg. The 1 mg strength was withdrawn during the procedure.

The proposed indication was:

Aqumeldi is indicated for the treatment of heart failure in children from birth to less than 18 years.

The applicant submitted four clinical studies WP07-WP10. WP07 is a relative bioavailability trial between Aqumeldi ODMTs and one of the current enalapril medicinal products in the market. Relative bioavailability was demonstrated for the Aqumeldi ODMT formulation in two methods of administration: swallowing or dispersing in the voluntary's tongue.

Studies WP08 and WP09 had similar design and conduct but directed to different patient conditions, dilated cardiomyopathy (DCM) and congenital heart disease (CHD), respectively. PK data generated underwent non-compartmental analysis aimed at the comparison between treatment status (naïve or pre-treated patients) and between age groups. On the basis of these results the applicant proposed a joint population PK (popPK) analysis of the whole data with covariates such as sex, age, weight, height, disease score, GFR, aetiology of disease and further relevant covariates. The two studies provided relevant data to support dosing recommendations in all the proposed population except neonates. Further extrapolation exercise permitted to agree the dosing for the youngest age group.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as orodispersible tablets containing 0.25 of enalapril maleate (equivalent to 0.19 mg of enalapril) as active substance.

Initially, the strength of 1 mg of of enalapril maleate (equivalent to 0.76 mg of enalapril) was also applied but this strength was withdrawn during evaluation.

Other ingredients are: mannitol (E421), crospovidone, poly(vinyl acetate), povidone, sodium laurilsulfate, sodium stearyl fumarate, and silica, colloidal anhydrous

The product is available in a high density polyethylene bottle with polypropylene cap equipped with a child-resistant, tamper evident closure system and a silica desiccant and one scoop to allow extraction of the tablets from the bottle as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of enalapril maleate is (2S)-1-[(2S)-2-[[(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid hydrogen (Z)-butenedioate corresponding to the molecular formula $C_{24}H_{32}N_2O_9$. It has a relative molecular weigth of 492.5 and the following structure:

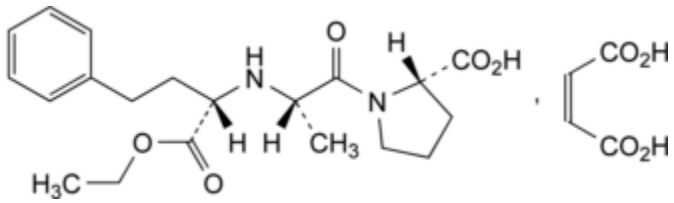


Figure 1: Active substance structure

As there is a monograph of the active substance in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

The chemical structure elucidation of the active substance is subject to CEP.

The active substance is a white or almost white, crystalline powder, sparingly soluble in water, freely soluble in methanol and practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides. Its hygroscopicity is low.

Enalapril maleate exhibits stereoisomerism due to the presence of three chiral centres. Two polymorphic forms have been observed as per literature: Forms I and II.

Manufacture, characterisation and process controls

The supplier of the active substance enalapril maleate has a CEP used in the MAA.

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The active substance is packaged in a clear low density polyethylene bag which complies with the EC directive 2002/72/EC and EC 10/2011 as amended. This bag is placed inside a low density polyethylene bag and each bag is individually tied. This double polyethylene bag pack is placed in a HDPE container with a lid and this outer container is also sealed. Silica gel is placed between HDPE drum and polythene bag.

Specification

Enalapril maleate complies with the Ph. Eur monograph and is controlled by the suppliers in accordance with the current relevant CEP.

The active substance specification tested by the finished product manufacturer includes tests for appearance (Ph. Eur.), identification (Ph. Eur.), appearance of solution (Ph. Eur.), pH (Ph. Eur.), specific optical rotation (Ph. Eur.), related substances (Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), assay (HPLC), residual solvents (CEP), microbiological contamination (Ph. Eur), and particle size distribution (Laser diffraction).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. In addition to the tests covered by the Ph, Eur. monograph, supplementary tests for a residual solvents have been added to the specification in line with the CEP. All additional methods have been adequately validated and described according to ICH Q2.

Stability

Long-term stability studies were conducted on five active substance batches stored in the proposed packaging in conditions of 25°C / 60% RH. Sixty months' data are available for all batches except for one batch, where 48 months' data are submitted and two batches where 36 months' data are submitted. Studies under accelerated conditions (40°C / 75% RH in line with ICH Q1A) were provided for three batches. One batch was tested at intermediate conditions of 30°C / 75% RH. Parameters tested included: loss on drying, specific optical rotation, related substances, assay and appearance.

All the results are within acceptance limits and no trends of concern were observed.

The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period of 60 months stored at 25°C (excursions allowed between 15°C and 30°C) in the proposed container.

2.4.3. Finished Medicinal Product

The finished product is presented as: white, round, biconvex orodispersible tablets, 2 mm in diameter containing 0.25mg enalapril maleate as the active substance.

The product is provided with a plastic (high impact polystyrene) scoop to facilitate the removal of the orodispersible tablets from the bottle. The scoop is not intended for counting or measuring purposes.

The aim of the pharmaceutical development programme was to develop a stable age-appropriate dosage form that would allow accurate and yet flexible dosing to paediatric patients from birth. Although oral liquids are considered to be acceptable for the whole paediatric age range, including neonates, the development of an age-appropriate flexible solid oral dosage form was required due to the limited aqueous stability of enalapril maleate; mini-tablets offer the advantages of ease of swallowing and dose flexibility and may be produced by conventional manufacturing processes. In addition, mini-tablets (2 mm diameter) have been shown to be accepted by both infants and neonates. Orodispersible mini-tablets which exhibit similar dimensions to mini tablets but disintegrate quickly upon contact with water (or saliva) thereby reducing the potential risk of choking have been developed, and were selected as the dosage form for enalapril maleate.

The quality of the active substance is covered by a Certificate of Suitability (CEP) of the European Directorate of Quality of Medicines (EDQM).

A solubility study using the highest therapeutic dose in 250 mL across a pH range of pH 1.0, pH 4.5, and pH 7.5 was carried out on the active substance. All results comply to the acceptance criteria.

Although two polymorphs of enalapril maleate exist (forms I and II), the relatively high solubility of the material, together with data suggesting the polymorphs exhibit similar pharmaceutical properties negate the value or requirement to control the crystalline form of the enalapril maleate. XRPD analysis confirms the crystalline form II is not altered by the manufacturing process or storage conditions.

The excipients and their concentrations were selected based on their accepted use in orodispersible tablets manufactured by direct compression, their acceptability in the proposed patient population, and through pharmaceutical development studies. A number of concerns regarding the processed material of one of the excipients have been satisfactorily addressed by the applicant. During the assessment the CHMP recommended that additional data on intermediate precision (determination of saponification value and photometric determination of povidone) and accuracy (gravimetric assay of crospovidone) should be provided. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except iron oxide yellow which is controlled for USP/NF. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

In relation to formulation development of the finished product, a Quality Target Product Profile (QTPP) was defined at the beginning of the development programme, and was subsequently updated, following process development studies and the generation of clinical and stability data. The possible variables during various stages involved in manufacturing process were identified and the effect of the critical variables on the performance of the formulation were evaluated. The parameters which form part of the QTPP are considered suitable.

During formulation development different prototypes containing varying amounts of active substance as well as various excipients of different functions were evaluated together in order to determine the most suitable combination. In order to achieve this, the applicant used the principles of Quality by Design but did not claim a full design space.

A dissolution method was developed based upon the USP monograph for enalapril maleate tablets and in accordance with Ph Eur 2.9.3. Comparative dissolution study results between test product and reference product batches all showed more than 85% dissolution in 15 minutes. Furthermore, the applicant developed a disintegration method which showed Enalapril maleate ODMTs disintegrate in no

more than 3 minutes. The CHMP requested as a major objection (MO) the dissolution method .The applicant addressed the issue and the responses were considered satisfactory Therefore, since it has been demonstrated that, due to the BCS classification of the active substance (which has high solubility), dissolution and disintegration are very fast, ensuring the quick release of the active substance, the change from a dissolution to a disintegration method was accepted.

A series of experiments were conducted to investigate the dispersion of the orodispersible tablets in water and the administration of aliquots of the resulting solution to allow the required dosing to the group of patients which require an initial dose less than 0.25 mg (low-weight neonates). Two approaches were investigated: approach using measuring cylinder and approach using syringe. The assay results of doses administered using the measuring cylinder dispersion procedure showed uniform doses of 0.125 mg enalapril maleate could be administered, but not the lower dose of 0.025 mg. In addition, the mean assay results were consistently high. The results for doses administered using the oral syringe dispersion were provided, the application of this dispersion method complied with Ph. Eur. 2.9.6. acceptance criteria for uniformity of content. The syringe method of dispersion was therefore considered to be acceptable, especially since it had the added benefit of being less complex to execute compared to the measuring cylinder approach. The syringe dispersion method was successfully used in the clinical studies for initial dose titration of low-weight neonates.

Patients may require medicine administration via nasogastric tube (NGT) and the feasibility of administering the orodispersible tablets via this route was investigated. Dose recovery and NGT blocking were considered and evaluated with polyurethane (PUR), silicone and polyvinyl chloride (PVC) NGTs. The results showed that no evidence of blockage was observed, showing that the dispersion could be successfully administered through NGTs.

The primary packaging is high density polyethylene bottle with polypropylene cap equipped with a child-resistant, tamper evident closure system. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of a standard dry powder blending and direct compression process. The tablets are then filled into high density polyethylene bottles which are closed with a polypropylene screw cap equipped with a child-resistant, tamper evident closure system and a silica desiccant. The manufacturing process consists of 4 main steps: blending, compression, and packaging. The process is considered to be a standard manufacturing process.

A major objection was raised with respect to the lack of homogeneity of 0.25 mg and 1 mg strengths. The applicant withdrew the 1 mg strength prior to the CHMP opinion and the issue was considered resolved.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process of the 0.25 mg strength is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and shelf life specification include appropriate tests for this kind of dosage form: appearance (visual), diameter, water content (KF), identity (UV, HPLC), assay (HPLC), purity (HPLC, LC-MS), disintegration (Ph. Eur.), and microbial contamination (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested as MO) considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided, nitrosamine impurities were tested for and found in the finished product. However, amounts were less than 10% of the LOQ and therefore no specific control measures are deemed necessary. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 3 commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 13 commercial scale batches of the finished product stored for up to 48 months under long term conditions (25°C / 60% RH), under intermediate conditions (30°C/65% RH) for up 12 months and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, assay, purity, disintegration, dissolution and microbial contamination. The analytical procedures used are stability indicating.

The 0.25 mg showed degradation at the higher temperatures of accelerated and intermediate storage conditions. There was a decreasing trend of assay values with the 6 month data at the accelerated storage conditions for most of batches going out of specification. The assay values showed a degradation at the intermediate storage conditions but stayed within the specification at the 12 month time point. A significant change was observed in the assay values for some of the batches and therefore as per the ICH Q1E Guidelines – Evaluation of Stability data, the shelf life will be based on the long term stability data. Based on the stability data so far, the 0.25mg strength is expected to meet the specification for at least 24 months.

In-use stability studies have been performed to establish a period of time during which the multi-dose product can be used whilst retaining quality within an accepted specification once the container has

been opened. At intervals appropriate quantities of drug product were removed from the primary container by the intended dispensing method and under normal conditions of use.

During investigation of in-use stability at beginning of shelf-life, samples were stored under ambient conditions (15-25°C). Samples to be analysed at end of shelf life are stored under ICH long term conditions of 25°C ± 2°C / 60% ± 5% RH until the start of the in-use stability study and throughout investigation of in-use stability. All the results stayed within the specification parameters over the storage period of 101 days.

Forced degradation studies have been performed to establish the stability indicating nature of the finished product analytical methods and to identify the degradation mechanisms of the finished product. The testing was done at acidic stress (5M hydrochloric acid, 50°C, 60 mins), alkaline stress (1M NaOH solution, RT, 60 mins), peroxidic stress (3% H_2O_2, RT, 10 min) and thermal stress (80°C, 20h) conditions. Subsequent studies were performed under stronger conditions in order to achieve degradation of at least 10% for alkaline stress, peroxidic stress, and thermal stress conditions..The product is specifically sensitive to the acidic and thermal stress and shows resistance to oxidative stress.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Based on the results of the photostability study, exposure to light does not have an impact on the stability, therefore the finished product is photostable.

A bulk hold time stability study was conducted to provide analytical data to support a hold time. The bulk product was sealed in a double-layer PE bag using a bag tie. The sealed PE-bag was transferred into a PE-container and the PE-container was closed with the corresponding lid. The container with the bulk product was stored in a climate-controlled warehouse, 15 to 25°C and humidity NMT 40% R.H. The bulk product was stored for 12 weeks from the date of manufacture. The results from the bulk hold time stability study confirm no significant change when stored in the bulk container closure system stored in warehouse storage conditions of 15-25°C and ≤40% R.H.

Based on available stability data, the proposed shelf-life of 2 years for 0.25 strength and do not store above 25°C as stated in the SmPC (section 6.3) are acceptable. After first opening, use within 100 days.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During evaluation 5 major objections were raised by the CHMP in relation to dissolution results, dissolution test method, lack of homogeneity, proposed limits of impurities and risk assessment of nitrosamines.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product which pertain to provide additional data on intermediate precision (determination of saponification value and photometric determination of

povidone) and accuracy (gravimetric assay of crospovidone) for one excipient. This point is put forward and agreed as recommendations for future quality development.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To provide additional data on intermediate precision (determination of saponification value and photometric determination of povidone) and accuracy (gravimetric assay of crospovidone) for one excipient.

2.5. Non-clinical aspects

2.5.1. Introduction

This is a Paediatric Use Marketing Authorisation (PUMA) Application and no new non-clinical studies were submitted. Instead, only published data were provided. This was considered acceptable. Pharmacodynamic, pharmacokinetic and toxicological properties of enalapril maleate are well known. Furthermore, among others, published non-clinical studies conducted with enalapril included studies with juvenile animals. Information on available non-clinical data was included in the following sections.

2.5.2. Pharmacology

No non-clinical pharmacology studies have been performed with Aqumeldi, which is acceptable. Enalapril (i.e., its active metabolite enalaprilat) is a potent and specific inhibitor of ACE in vitro and in vivo. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to lower vasopressor activity, and to reduced aldosterone secretion.

Following oral administration, enalapril is bioactivated by hydrolysis to enalaprilat, which is the pharmacologically active ACE inhibitor.

Enalaprilat is a potent inhibitor of ACE in vitro (IC50 of 1.2 nM, hog plasma). ACE is identical to kininase II, which degrades bradykinin and other kinins that stimulate production of NO, cyclic GMP, and vasoactive eicosanoids. The inhibition is specific; i.e., enalapril and enalaprilat did not inhibit the in

vitro activity of various proteolytic enzymes such as trypsin, carboxypeptidase A and B, plasmin, chymotrypsin, and renin [FDA (1985)].

The inhibition of the acute pressor response to angiotensin I in anaesthetized and unanaesthetized rats and dogs was used to assess the in vivo ACE inhibitory activity of enalaprilat and enalapril. In anaesthetized rats, single doses of enalaprilat (100 µg/kg i.v.) and enalapril (60 µg/kg i.v.) produced a prolonged inhibition of ACE (over 2 hours). In anaesthetized dogs, the IC50 values for inhibition of the angiotensin I-induced pressor response were 6 µg/kg i.v. for enalaprilat and 278 µg/kg i.v. for enalapril. Oral ACE inhibitory activity of enalapril was demonstrated in rats and renal hypertensive dogs [FDA (1985)].

No formal safety pharmacology studies in accordance to ICH S7A were conducted with enalapril. Enalapril and enalaprilat (each 10 µM) were without activity in radiobinding assays in rat brain for dopamine, neuroleptic, serotonin-1 and -2, alpha-2-adrenergic, beta-adrenergic, muscarinic cholinergic, GABA, and benzodiazepine receptors. In conscious and anesthetized dogs, enalapril (1 mg/kg, p.o. or 0.1-1 mg/kg i.v.) caused a slight increase in cardiac output and a decrease in peripheral resistance. Enalapril displayed no overt signs of central nervous system activity and had no significant effect on the respiratory system or on the gastrointestinal transit time [FDA (1985)]. The toxicity reported with enalapril in neonatal rats is viewed as relevant to humans, but the timing of exposure is a critical factor in the development of altered renal morphology as summarized by Zoetis and Hurtt (2003).

Considering that this is a Paediatric Use Marketing Authorisation (PUMA) application, data from juvenile animal safety studies from the published literature have been included in the non-clinical overview (see below).

Rats

Postnatal days 1-7

Nephrogenesis is normally accompanied by a tightly regulated and efficient vascularization. Yim et al (2016) investigated the effect of angiotensin II inhibition on angiogenesis in the developing rat kidney. Newborn rat pups were treated with enalapril (30 mg/kg/day) or vehicle (control) for 7 days after birth. Renal histological changes were checked using Hematoxylin & Eosin staining. Yim et al (2016) also investigated the intrarenal expression of vascular endothelial growth factor (VEGF)-A, VEGF receptor 1 (VEGFR1), VEGFR2, platelet-derived growth factor (PDGF)-B, and PDGF receptor-β with Western blotting and immunohistochemical staining at postnatal day 8. Expression of the endothelial cell marker CD31 was examined to determine glomerular and peritubular capillary density. Enalapril-treated rat kidneys showed disrupted tubules and vessels when compared with the control rat kidneys. In the enalapril-treated group, intrarenal VEGF-A protein expression was significantly higher, whereas VEGFR1 protein expression was lower than that in the control group ($P<0.05$). The expression of VEGFR2, PDGF-B, and PDGF receptor-β was not different between the 2 groups. The increased capillary CD31 expression on the western blots of enalapril-treated rat kidneys indicated that the total endothelial cell protein level was increased, while the cortical capillary density, assessed using CD31 VEGF-VEGFR signalling and altered capillary repair may play a role in the deterioration of the kidney vasculature after blocking of angiotensin II during renal development.

Postnatal days 1-28

Inhibition of the renin-angiotensin system (RAS) during kidney development produces chronic alterations in renal morphology and function that have been characterized in detail in adult animals. The aim of a study by Guron (2005) was to determine the consequences of neonatal angiotensin-converting enzyme (ACE) inhibition on renal haemodynamics and function in rats at a much earlier age, namely 3-4 weeks. Male Wistar pups received daily intraperitoneal injections of enalapril (10 mg/kg) or isotonic saline from

birth until 24-28 days of age, when renal haemodynamics and function were assessed using clearance techniques under pentobarbital anaesthesia. Enalapril-treated rats showed significant reductions in glomerular filtration rate (GFR; -44 +/- 6%; P < 0.05), effective renal plasma flow (ERPF; -33 +/- 6%; P < 0.05) and filtration fraction (-16 +/- 3%; P < 0.05) compared with saline-treated controls. Although mean arterial pressure tended to be lower in enalapril-treated rats, this group demonstrated a significant increase in renal vascular resistance compared with control rats (RVR; 46 +/- 6 vs 32 +/- 3 mmHg/mL per·min per g·kidney weight, respectively; P < 0.05). In enalapril-treated rats, urine osmolality was reduced (-59 +/- 5%; P < 0.05) and urine flow rate and fractional urinary excretion rates of sodium and potassium were markedly elevated compared with controls (P < 0.05). Enalapril-treated rats showed severe renal histological abnormalities, including wall thickening of cortical arterioles, papillary atrophy and tubulointerstitial alterations, mimicking those described previously in similarly treated rats examined in adulthood. It was concluded by Guron (2005) that neonatal ACE inhibition in rats induces pronounced alterations in renal haemodynamics and function, characterized by reductions in ERPF and GFR, increased RVR and impaired tubular sodium and water reabsorption, which are evident at weaning.

Mice

Postnatal days 1-10

Inhibition of the RAS at different steps by postnatal administration of aliskiren as well as enalapril also caused a significant reduction in glomerular size in wild-type mice (Table 2.4-1).

Table 2.4-1 Effect of inhibition of various components of RAS on size of glomeruli [Frölich et al (2017)].

Treatment	Diameter of glomeruli (µm)
Vehicle	46.73 ± 0.51
Aliskiren (50 mg/kg/d)	40.85 ± 0.29[a]
Enalapril (0.1 mg/kg/d)	39.45 ± 0.25[a]
Telmisartan (0.5 mg/kg/d)	33.47 ± 1.00[a]

P1, postnatal day 1; RAS, renin-angiotensin system.
Wild-type mice C57BL6 were treated with the indicated substances from days P1 to P10. Kidneys were removed and processed for histomorphometric analysis. Data show means ± SEMs; $n = 6$ mice.
[a] $P < 0.05$ compared with vehicle.

Safety pharmacology studies in accordance with ICH S7A guideline are not available for enalapril, as some pharmacology studies were performed before the introduction of this battery of studies. Also based on its prolonged and widespread clinical use, the fact that specific safety studies are not available is not considered to be a limitation for this assessment.

2.5.3. Pharmacokinetics

Studies with enalapril in several species of animals revealed differences in the extent of the systemically available fraction after oral administration. The estimated systemically available fraction was 44% in rats, 64% in dogs, and 78% in rhesus monkeys following oral administration. Peak plasma levels of radioactivity were attained within 1 hour in rats, in 2 hours in dogs, and in 7 hours in monkeys. Excretions after an i.v. dose occurred mainly via the kidney, the 72-hour urinary excretions being 69%, 78%, and 71% of the administered dose in dogs, rats, and monkeys, respectively. Faecal excretions, apparently via the bile, were between 14-19% in the three species. After oral dosing, urinary excretions were 40% of the dose in dogs, 20% of the dose in rats, and 25% of the dose in monkeys and faecal excretions were 35%, 72%, and 36% of the dose in the three species, respectively. In rats, dogs and hamsters, radioactivity from 14C-enalapril was distributed primarily in the liver, kidneys, and lungs; radioactivity did not accumulate in any tissue upon repeated administration to rats. Neither enalapril nor enalaprilat effectively crossed the blood-brain barrier,

whereas radioactivity from 14C-enalapril was transferred via the placenta in hamsters and was incorporated into milk in rats [FDA (1985)].

The major metabolite of enalapril in dog and monkey urine was the active diacid enalaprilat. In vitro studies showed that hydrolysis of enalapril to enalaprilat occurred in the plasma of rat, mouse, gerbil and, to a lesser extent, guinea-pig. The plasma of man, dog, rabbit, monkey, cat, and hamster did not hydrolyze enalapril whereas liver homogenates from rat, dog, and man were capable of the bioactivation. Evidence for metabolism of enalapril to enalaprilat in addition to hydrolysis was found only in monkeys where approximately 16% of the urinary radioactivity was identified as des-propyl enalaprilat [FDA (1985)].

As there are interspecies differences in absorption, distribution, metabolism and excretion, human pharmacokinetics cannot reliably be predicted from animal studies. However, as bioactivation and pharmacological action such as effects on the RAAS are broadly similar, results derived from animal studies give a preliminary guidance with regard to safety and efficacy of enalapril in man [FDA (1985)].

2.5.4. Toxicology

Enalapril was assessed in a series of nonclinical studies and has been used in therapy for many years. Toxicokinetic investigations were not included in most of the toxicity studies. Despite this, the available results still allow a toxicological evaluation. Although the studies were not always performed to the current state of the art, this is more than compensated for by the many years of clinical experience with enalapril. Toxicity studies with enalapril have been performed in mice, rats, rabbits, and dogs and were conducted according to Good Laboratory Practice (GLP) regulations.

Acute toxicity of enalapril in mice and rats was investigated after oral, intravenous and subcutaneous administration; the LD50 values were 2 g/kg in both species (males and females) after oral administration. Signs of acute toxicity in both species were decreased activity, ptosis, bradypnoea, and loss of righting reflex. In female mice, pre-treatment with oral doses of HCT (900 mg/kg) did not significantly affect the acute toxicity of enalapril given orally one hour later whereas pretreatment with 27 mg/kg p.o. enalapril slightly increased the i.p. toxicity of HCT [FDA (1985)].

One-year toxicity studies were conducted with enalapril in rats at doses up to 90 mg/kg/day and in beagle dogs at doses up to 15 mg/kg/day. No drug-related histopathological lesions were reported in either study. With the exception of a slight reduction in body weight gain, rats tolerated a dose of 10 mg/kg/day. In addition to body weight loss, higher doses (30 and 90 mg/kg/day) caused serum biochemical changes (increased blood urea nitrogen, electrolyte changes) and a suspected increase in mortality. Dogs tolerated doses up to 15 mg/kg/day for one year without any important toxicity; the no-observed-adverse-effect level (NOAEL) in dogs could not be established but is at least 15 mg/kg/day. However, dogs given doses up to 90 mg/kg/day in subchronic studies exhibited renal functional changes (nephrosis, increases in serum urea nitrogen and glucose, electrolyte changes), increases in GOT, GPT and/or alkaline phosphatase in serum accompanied by liver lesions, and mortalities. Saline supplementation was shown to ameliorate the toxicity of 50 mg/kg/day enalapril in dogs [FDA (1985)].

Maternal and foetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and foetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day. Enalapril was not teratogenic in rabbits. There was no foetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril. Foetotoxicity expressed as a decrease in average foetal weight occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline [FDA (1985)].

Angiotensin converting enzyme inhibitors, as a class, have been shown to be foetotoxic (causing injury and/or death to the foetus) when given in the second or third trimester [FDA (1985)].

Enalapril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation, in the rec-assay, sister chromatid exchange with cultured Chinese hamster cells (up to 20 mg/ml), and the micro-nucleus test with mice. In the in vitro chromosomal aberration test, enalapril was clastogenic at 10 and 20 mg/ml but not at 5 mg/ml [FDA (1985)].

There was no evidence of a carcinogenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively (150 and 300 times the MRHDD for humans based on body weight; 13 times and MRHDD on a body surface area basis), and no evidence of carcinogenicity was noted [FDA (1985)].

A full regulatory toxicology program has already demonstrated an adequate safety profile of enalapril. Non-clinical data for enalapril reveal no special hazard for humans (adults and paediatric age groups) based on conventional studies of ancillary pharmacology, repeat-dose toxicity, genotoxicity and carcinogenic potential. Enalapril and its salt enalapril maleate have been adequately studied in extensive nonclinical toxicity studies reported in literature. There are no toxicological concerns.

2.5.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment has been performed to evaluate the potential environmental risk resulting from the use of enalapril 0.25 mg orodispersible tablet containing 0.25 mg (as maleate) per orodispersible tablet. No bioaccumulation of enalapril is expected since the logDow determined for enalapril according to OECD 107 under GLP conditions showed values below the threshold value of 4.5.

Results from Phase I studies were:

$$PEC_{Surfacewater} = \frac{20\ mg\ (Dose_{ai}) \times 0.01\ (F_{pen})}{200\ l\ (Wastew_{inhab}) \times 10\ (Dilution)} = 0.0001\ mg/l = 0.1\ \mu g/l$$

As the predicted concentration in surface water is above the limit value of 0.01 µg/l, the calculation was further refined by the applicant using the prevalence data of heart failure in children from birth to 17 years in Spain, since it is the only country where prevalence data of heart failure in the paediatric population was detected in the public domain. This data has been used as representative for other European countries. The refined calculated concentration of enalapril in surface water was well below the threshold of 0.01 µg/l. Since no other environmental concerns are apparent, it is agreed that the medicinal product is unlikely to represent a risk for the environment making further testing of environmental effects not necessary.

2.5.6. Discussion on non-clinical aspects

The legal basis of this submission falls under Article 10.3 of Directive 2001/83/EC as amended ("Hybrid application"). This hybrid application relies on the results of pre-clinical tests conducted for the reference product RENITEC® enalapril maleate tablets. No new animal or in vitro studies have been conducted. Considering that this is a Paediatric Use Marketing Authorisation (PUMA) Application, data from juvenile animal safety studies have been included in the Non-clinical Overview. The Overview was based on literature review and was considered appropriate.

Enalapril and its salt enalapril maleate have been adequately studied in extensive nonclinical toxicity studies reported in literature. There are no toxicological concerns identified. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and is considered acceptable.

2.5.7. Conclusion on the non-clinical aspects

The CHMP considered the application acceptable from non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

To address the unmet medical need for a licensed enalapril product for children with HF, a Framework 7 project ("Labeling of Enalapril from Neonates up to Adolescents", LENA) was conducted between November 2013 and April 2019. Within this time frame, the task was to perform a paediatric drug development program and collectively generate all necessary data to lay the groundwork for a paediatric-use marketing authorization (PUMA). The LENA project generated core scientific data from four clinical trials WP07, WP08, WP09 and WP10. For the clinical trials, WP02 had developed Enalapril Orodispersible Mini-Tablets (ODMTs) of 1 mg and 0.25 mg. WP07 generated clinical data for Enalapril ODMTs in healthy adult volunteers. WP08, WP09 and WP10 generated clinical data for Enalapril ODMTs in children with heart failure. WP06 developed case report forms and performed data management for the clinical studies.

The clinical program includes a relative bioavailability study (WP07) between the new enalapril ODMT administration and the already marketed immediate release tablets. This relative bioavailability study was conducted with the highest strength (1 mg ODMT) and demonstrated equivalent pharmacokinetics / bioequivalence to the reference product (Renitec® 5 mg tablets). A bioavailability study for the enalapril ODMT 0.25mg in adults was not required as part of the PIP as it was considered that a biowaiver would suffice. A BCS-based biowaiver for enalapril ODMT 0.25mg, is proposed according to the following grounds:

- Enalapril maleate is classified as BCS class III, which corresponds to its classification by the WHO [Verbeeck 2017]. Enalapril maleate, the active substance present in both enalapril ODMT and the reference product, is "highly soluble" as defined by the EMA, FDA and WHO BCS guidelines (solubility is at least 5 mg/ml over the pH range 1.2 to 6.8), whereas it is assumed not to be highly permeable, as supported by a negative log D estimation. Notably in this sense, pharmacokinetic data show that only 60-70% of an oral dose of enalapril maleate is absorbed from the intestinal tract into the enterocytes. Although estimates of enalapril's effective intestinal permeability are high and the lack of complete absorption may be due to hydrolysis of enalapril to enalaprilat within the gut lumen, it cannot be unequivocally ruled out that absorption (fa) is less than the cutoff value, especially in light of the low log D value. Thus, enalapril cannot conclusively be considered a highly absorbable drug substance [Verbeeck 2017].

- Enalapril is not considered to have a narrow therapeutic index [Verbeeck 2017].

- A similar bioavailability was found for 10 x 1 mg ODMT formulation when compared to 2 x 5 mg Renitec® tablets as shown in PK study WP07. This allows the conclusion that, when administered as an ODMT, enalapril is absorbed in the gastrointestinal tract, while absorption in the oral cavity can be

excluded. Therefore, extending the concept of BCS-based biowaiver, which applies to immediate-release solid oral dosage forms, to enalapril ODMT appears endorsed.

- Enalapril shows a linear pharmacokinetic in the dose range of 0.25 mg and 1 mg, as found in the PK studies WP08 and WP09 which were conducted using both the 0.25 mg and 1 mg ODMT depending on the required dose. Data extracted from the reports, for Cmax and AUC for enalapril for occasions where only the 0.25 mg or 1 mg strength was used, show that the rate and extent of absorption is proportional between strengths even if there is a wide variability.

- Neither of the ODMT formulations (0.25 mg and 1 mg) include excipients that might affect bioavailability. The qualitative compositions are very similar hence it is highly unlikely that these excipients at the quantities present would have a clinical impact on drug release or bioavailability.

Based on the above-mentioned grounds and following recommendations from the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), a BCS-based biowaiver was claimed by the applicant.

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

To support the application, the applicant has submitted three pharmacokinetic/pharmacodynamic studies and one bioavailability study.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	WP07	m.5.3.1.2	Relative BA and Safety in HV	An open label, randomized 3- way crossover, 3-treatment, 3- period study under fasting conditions	Treatment A: 2 x 5 mg of Renitec®, swallowed with 240ml of water (fasting). Treatment B: 10 x 1mg of ODMT, swallowed with 240ml of water (fasting). Treatment C: 10 x 1mg of ODMT,	24[a]	Healthy subjects	Single dose	Complete; Full

					dispersed on the tongue following wetting of the mouth with 20ml of water (fasting). Oral route				
PK	WP08	m.5.3.3.2	Paediatric PK in patients with DCM	A multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose PK bridging study with exploratory pharmacodyna mic assessments	Enalapril maleate ODMT 1.0 mg Enalapril maleate ODMT 0.25 mg Treatment was up to 8 weeks, with a minimum treatment duration of 3 days. Oral route	26[b]	Patients with DCM	Up to 8 weeks	Complete; Full
PK	WP09	m.5.3.3.2	Paediatric PK in patients with CDH	A multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose PK bridging study with exploratory pharmacodyna mic assessments	Enalapril maleate ODMT 1.0 mg Enalapril maleate ODMT 0.25 mg Treatment was up to 8 weeks, with a minimum treatment duration of 3 days. Oral route	63[b]	Patients with CDH	Up to 8 weeks	Complete; Full
Safety	WP10	m.5.3.5.2	Safety of enalapril ODMTs	A multi-centre, multi-national Phase II/III prospective, open-label, safety follow up	Enalapril maleate ODMT 1.0 mg Enalapril maleate ODMT 0.25 mg Oral route	86[b]	Patients with CDM or CDH	Up to 10 months	Complete; Full

				study in infants and children enrolled in the trials WP08, WP09.					

a) All subjects received treatments B and C and twenty-three subjects (23, 95.8%) received treatment A.
b) Evaluable patients

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

WP07

Study WP07: Study 602295, EudraCT number: 2014-000956-28: Relative Bioavailability of Enalapril Administered as orodispersible Minitablets (ODMT) in Healthy Adults

Methods

- Study design

This was an open label, single dose randomized 3-way crossover, 3-treatment, 3-period study. Twenty-four (24) healthy male and female subjects were planned to be enrolled and each administered a 10 mg enalapril dose on 3 occasions, at least one week apart, as follows:

- Treatment A: 2 x 5mg of Renitec®, swallowed with 240ml of water (fasting);
- Treatment B: 10 x 1mg of ODMT, swallowed with 240ml of water (fasting);
- Treatment C: 10 x 1mg of ODMT, dispersed on the tongue following wetting of the mouth with 20ml of water (fasting).

Blood samples (2.7 ml each) will be collected in serum tubes at predose and 10min, 20min, 30min, 45min and at 1h, 1.25h, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, 36 and 48 hrs postdose

This was an open study. No blinding procedures apply, but the bioanalysis was conducted blinded.

There will be a minimum of 7 days of wash-out between treatments.

Test and reference products

Product Characteristics	**Test product**	**Reference product**
Name	Enalapril 1 mg, orodispersible mini tablet	Renitec®
Strength	1 mg	5 mg
Dosage form	Orodispersible tablet	Tablet
Manufacturer/Supplier/MA holder	Proveca	MSD Belgium
Member State where the reference product was purchased from		Belgium
This product was used in the following trials	WP07	WP07

- Population(s) studied

No a-priori-sample size calculation was done. The sample size was 24 healthy subjects in groups of 4 subjects per treatment sequence.

Adult healthy non-smoking male and female subjects, 18-55 years old, with a BMI between 18.5 and 30 kg/m2 inclusive. Women of childbearing potential had to agree to practice a highly effective method of birth control from screening until at least to the end of study visit.

Overall, 24 (100%) subjects were enrolled in this study. All 24 subjects received treatments B and C. Twenty-three (23, 95.8%) subjects received treatment A and was excluded from analysis.

- Analytical methods

The same bioanalytical method is the same as in WP07 and has been used for both WP08 and WP 09.

Essential features:

For determination of the PK of enalapril and its active metabolite enalaprilat, liquid chromatography-triple quadrupole tandem mass spectrometry followed by solid-phase extraction of serum samples was applied (Shimadzu HPLC 10 coupled with AB Sciex API 2000 mass spectrometer). The ion transitions were mass-to-charge ratio (m/z) 377.2 to 234.2 m/z for enalapril, 349.1 to 206.1 m/z for enalaprilat and 425.3 m/z to 351.2 m/z for the internal standard benazepril. Moreover, the applied bioanalytical method was characterized by a small sample volume of 50 µL serum encompassing a calibration range from 0.195 – 200 ng/mL for enalapril and 0.180 – 180 ng/mL for enalaprilat.

The method was fully validated according to EMA and FDA bioanalytical method validation guidelines by using European Pharmacopoeia Reference Standard of enalapril and enalaprilat. Obtained mean accuracy values for enalapril ranged from 92.1% to 108.4% of the nominal concentration at the lower limit of quantification (LLOQ), from 91.6% to 100.2% at the low concentration level, from 94.3% to 100.4% at the medium level and from 92.6% to 98% at the upper limit of quantification (ULOQ). The time different intermediate precision varied between 5.0 to 9.5% across all concentration levels and was subsequently well within the guideline limits of ±15% (±20% at LLOQ). Regarding the active metabolite enalaprilat, the mean accuracy values ranged as follows: At the LLOQ the mean accuracy ranged from 88.0% to 105.5%, at the low concentration level the mean accuracy ranged from 90.2% to 98.8%, at the medium level from 94.0% to 100.9% and from 93.2% to 106.4% at the ULOQ. Study samples measured below the LLOQ were set to 0 while samples above the ULOQ were re-measured as dilution.

- Pharmacokinetic Variables
    - The primary and secondary pharmacokinetic parameters that are identified below were calculated from the individual serum concentrations vs. actual time profiles or from the individual urinary recovery data of both ENA and ENAAT by a non-compartmental analysis according to the following guidelines:
    - The area under the serum concentration-time curve from time zero to the last quantifiable observed concentration (AUC0-tz)
    - The maximum observed concentration (Cmax)
    - The time to Cmax (tmax)

- Statistical methods

- To compare and evaluate the relative bioavailability of enalapril and enalaprilat after the single oral administration of the previously mentioned treatments (A, B, and C), the geometric mean ratios of each pair and the 90% confidence intervals of these ratios will be calculated for AUC0-tz and Cmax.
- An analysis of variance (ANOVA) will be performed on the natural logarithmic transformed Cmax, AUC0-tz, and AUC0-∞ and will include treatment, period, and sequence as fixed effects, and subject nested within sequence as random effect. The obtained confidence interval limits will be backtransformed via antilog.
- Observed tmax times will be evaluated separately and independently for each of the group comparisons of interest based on the U-test of Mann Whitney.

- Safety data
  - All 24 subjects were included in the assessment of safety and tolerability. No SAE's occurred.
  - Sixteen (16) out of the 24 subjects reported a total of 32 post-dose adverse events of which 25 were considered drug related (9 following Renitec® , 8 following ODMT swallowed and 8 following ODMT dispersed).
  - All the adverse events were mild in intensity except for one moderate headache following Renitec® and all adverse events were resolved by the end of the study.
- Pharmacokinetic Conclusion

Table B vs A Statistical analysis for enalapril (ln-transformed values)

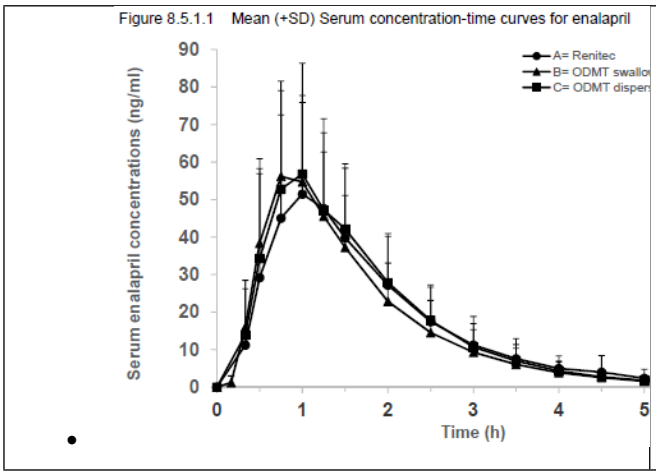
Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC(0-t)	99.19	92.32 – 106.58	
Cmax	102.78	91.28 – 115.72	
* estimated from the Residual Mean Squares			

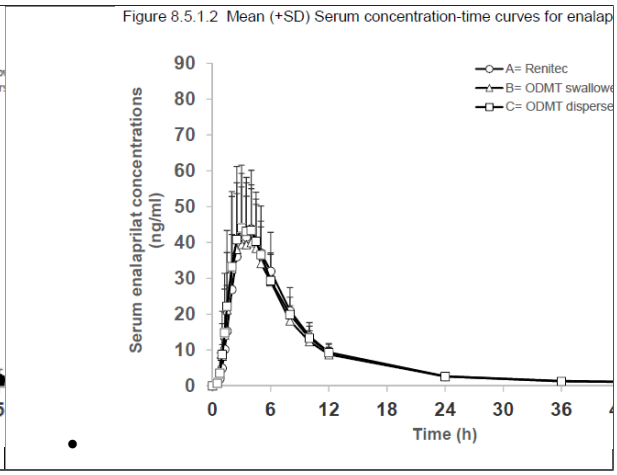
- Table C vs A Statistical analysis for enalapril (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC(0-t)	105.72	96.40 – 113.59	
Cmax	113.31	100.83 – 127.57	
* estimated from the Residual Mean Squares			

- Table C vs B Statistical analysis for enalapril (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC(0-t)	106.58	99.31 – 114.36	
Cmax	110.24	98.09 – 123.90	
* estimated from the Residual Mean Squares			





Study WP08 and WP09

The primary objective of Studies WP08 and WP09 was to obtain paediatric pharmacokinetic data of enalapril and its active metabolite enalaprilat in paediatric patients treated with enalapril ODMTs. This data described the dose exposure in the paediatric population with heart failure due to DCM and CHD. The primary endpoint, bioavailability of enalapril and enalaprilat in children (0 month - <12 years) (AUC from 0 to time of last sampling point, Cmax and tmax), was investigated using descriptive pharmacokinetics.

To explore the age dependency of the enalapril exposure, the bioavailability of enalapril and its active metabolite enalaprilat was furthermore descriptively described in the different age subsets (birth to less than 12 months, 12 months to less than 6 years, 6 years to less than 12 years) of the paediatric population (AUC from 0 to time of last sampling point, Cmax and tmax).

WP08: Protocol ID 2015-602295-01; EudraCT number 2015-002335-17: Orodispersible Minitablets of Enalapril in Children with Heart Failure due to Dilated Cardiomyopathy (DCM)

- Study design

This was a multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose PK bridging study with exploratory PD assessments in paediatric patients with DCM requiring ACE inhibitor treatment. The study was initiated in 8 sites in The Netherlands, Austria, Hungary, UK, Germany and Serbia. Two groups of children (ACEI pre-treated and treatment naïve children) with heart failure due to DCM were treated with enalapril ODMTs over a period of 8 weeks with the maximum tolerated dose following a defined dose titration scheme.

- Population(s) studied

A minimum of 50 patients was originally planned to be enrolled in this trial. According to a modification to the PIP agreed by the PDCO, this number was changed to 25 patients in Substantial Amendment No. 2. Eligible were all male and female children (1 month - <12 years) with the diagnosis of heart failure secondary to DCM. Inclusion of (amended) sub-sets of patients was envisaged as follows:

- A minimum of 10 infants (1 month to less than 12 months, increased from originally 8)
- A minimum of 8 patients aged 12 months to less than 6 years (decreased from originally 18 patients).

- A minimum of 6 patients aged 6 years to less than 12 years (decreased from originally 18 patients).

WP09: Protocol ID 2015-602295-02; EudraCT number 2015-002396-18: Orodispersible Minitablets of Enalapril in Children with Heart Failure due to Congenital Heart Disease (CHD)

Methods

Study design

This was a multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose pharmacokinetic bridging study with exploratory pharmacodynamic assessments in paediatric patients with CHD requiring ACE inhibitor treatment. The study was initiated in 8 sites in The Netherlands, Austria, Hungary, UK, Germany and Serbia. Two groups of children (ACEI pre-treated and treatment-naïve children) with heart failure due to CHD were treated with enalapril ODMTs over a period of 8 weeks with the maximum tolerated dose following a defined dose titration scheme.

- Population(s) studied

Number of patients (planned and analysed):

A minimum of 50 patients were originally planned to be enrolled. In accordance with an agreed Request for Modification of an approved PIP, this was increased to a minimum of 60 evaluable patients for the primary endpoint (full PK). Up to 15 additional patients were permitted to be enrolled to ensure sufficient evaluable patients.

Common features of studies WP08 and WP09

- Analytical methods

The same bioanalytical method is the same as in WP07 and has been used for both WP08 and WP 09.

- Pharmacokinetic Variables

The same pharmacokinetic data analysis was used for both WP08 and WP 09.

The bioavailability of enalapril and its active metabolite enalaprilat in young children (1 month to < 12 years) was determined using descriptive PK investigations of area under the curve (AUC) from 0 to time of last sampling point and maximal concentration (Cmax) as well as time to maximal concentrations (tmax). This primary endpoint was depicted to obtain paediatric PK data of enalapril and its active metabolite enalaprilat in patients treated with enalapril ODMTs to describe the dose exposure in the paediatric population with DCM.

Separate NCA analyses were conducted for naïve patients and those pre-treated with ACE inhibitors, where a full serum profile was performed at the initial dose visit and at steady-state respectively. steady state for pre-treated patients was defined as treatment with the ODMTs for more than 7 days after the patient had been switched from their ACE inhibitor pre-treatment to the study treatment. A full serum profile for naïve patients at the initial dose visit consisted of 6 serum samples taken at 0h (pre-dose) and at 1h, 2h, 4h, 6h, and 12h after the administration of the dose. A full sampling profile

for patients taken at steady state dosing consisted of 5 serum samples taken at 0h, 1h, 2h, 4h and 6h. With twice daily dosing, the sample taken before dosing (trough) could be used as the 12h sample.

PK parameters Cmax, tmax, and AUC were calculated by non-compartmental procedures where the following abbreviations were defined:

- Cmax maximum of observed concentration
- tmax time of maximum of observed concentration
- AUC0-12 area under the concentration-time-curve calculated by the so called trapezoidal rule within the dose interval of 12h (AUC0-12 = AUCtau)
- Cmax,ss maximum of concentration in a dosing interval at steady state
- tmax,ss time of Cmax,ss
- AUCtau,ss area under the concentration-time-curve calculated by the so called trapezoidal rule within a dose interval at steady-state.

Furthermore, parameters of non-compartmental PK were normalized by dose as well as body weight with abbreviations such as Cmax,ss,norm for Cmax,ss and AUCss,norm for AUCtau,ss. PK data analysis was conducted at the Institute of Clinical Pharmacy and Pharmacotherapy, Heinrich-Heine Universität Düsseldorf, Germany.

- Statistical methods

The same statistical methods were used for both WP08 and WP09, for the age groups as indicated below.

Primary endpoints

Pharmacokinetics: The bioavailability of enalapril and its active metabolite enalaprilat in children (1 month - < 12 years) (AUC from 0 to time of last sampling point, Cmax and tmax); descriptive pharmacokinetic investigation.

Secondary endpoint analysis of pharmacokinetics

To determine the secondary endpoint (bioavailability of enalapril and its active metabolite enalaprilat in the different age subsets) the dose and weight normalized AUCtau, Cmax,ss and tmax,ss of enalapril and enalaprilat were compared between the age subsets

- WP 08 (age group 1, 1 to <12 months, age group 2, 12 months to <6 years and age group 3, 6 years to >12 years);

- WP 09 (age group 1; 1 to <12 months, age group 2; 12 months to <6 years and age group 3; 6 years to >12 years).

Based on this, the relative bioavailability of the ODMTs as comparison drug exposure (AUC) and rate and extend of absorption (Cmax and tmax) within the given age cohorts of paediatric patients were calculated. In addition, weight and dose normalized AUCtau,ss, Cmax, ss and tmax, ss) were compared between the different age subsets using statistical testing for two group comparison (t-test(x~y) for two samples).

Population pharmacokinetic analysis

In addition to the non-compartmental analysis of the full PK profiles, population PK modelling was performed on collected PK and PD data from the start to the end of the study. A covariate analysis was

performed to investigate sources of variability of the resultant dose exposure relationship, and covariates were included from various patient characteristics collected in this study such as sex, age, weight, height, disease score, GFR, aetiology of disease and further relevant covariates, which are listed in the flow charts of the study.

To maximise the value of the PK/PD data, the analysis was performed on the complete paediatric HF data set from the PK/PD Study in CHD or DCM patients Protocol Nr. 2015-602295-02, EudraCT Nr. 2015- 002396-18 (WP09) and Safety Study Protocol Nr. 2015-602295-03, EudraCT Nr. 2015- 002397-21 (WP10) in addition to this study, using a non-linear mixed-effects modelling approach. The final model was then used to calculate PK parameters such as AUCtau,ss, and Cmax,ss to support the recommended doses of enalapril in patients by simulating dose recommendations for enalapril ODMTs.

Results

- *Safety data*

Adverse Events

WP08

The administered enalapril ODMT doses were well tolerated. Eleven (34.5%) patients did not experience any AEs during their study participation. Forty-two AEs occurred in 21 of the 32 (65.6%) patients enrolled into this study. Most frequently observed AEs were pyrexia in 4 patients (12.5%), nasopharyngitis and rash in 3 children each (9.4%). 1 SAE (syncope due to hypotension in the context of a gastro-intestinal infection and hospitalisation for observational purposes), unrelated to IMP intake, was reported.

No deaths occurred. No rehospitalisation due to heart failure including the need for heart transplantation or the institution of mechanical circulatory support occurred.

WP09

The administered enalapril ODMT doses were well tolerated. Eighteen (25.7%) patients did not experience any AE during their study participation. In 52 of the 70 (74.3%) patients enrolled into this study 118 AEs occurred. Only 7 AEs (5.9%), were assessed as possibly, probably or certainly related with IMP intake. Eight (6.8%) AEs were of severe intensity, 32 (27.1%) AEs were of moderate intensity and 78 AEs (66.1%) of mild intensity. Most frequently observed AEs were cardiac operation (15 AEs,12.7%), pyrexia (14 AEs, 11.9%), and rhinitis (9 AEs, 7.6%). All other AEs described below occurred less frequently. Five SAEs without causal relationship with the IMP occurred; all but one (paresis right hemidiaphragma after cardiac surgery) resolved without sequela. No deaths occurred.

Primary endpoint

WP08

The bioavailability of enalapril and its active metabolite enalaprilat in the paediatric population aged from one month to below 12 years were described by means of AUC, Cmax and tmax in paediatric patients with HF due to DCM following administration of enalapril ODMTs (see Tables 10 and 11).

Table 10: Parameters of non-compartmental analysis of enalapril under single dose or approximated multiple dose (mean, SD)

Patients (n)	AUCtau (ng/mL*h)	Cmax (ng/mL)	tmax (h)	AUCss,norm* (ng/mL*h/mg*kg)	Cmax,ss,norm* (ng/mL/mg*kg)
all (26) mean	53.974	22.552	1.757	495.636	203.054
all (26) SD	35.498	19.995	0.996	228.463	148.969
naive (3) mean	17.475	7.202	1.661	459.757	184.564
naive (3) SD	6.211	5.041	0.573	68.998	95.124
pretreated (23) mean	58.735	24.554	1.770	500.316	205.465
pretreated (23) SD	34.973	20.388	1.047	242.243	156.021

SD standard deviation

Table 11. Parameters of non-compartmental analysis of enalaprilat under single dose or approximated multiple dose (mean, SD)

Patients (n)	AUCtau (ng/mL*h)	Cmax (ng/mL)	t-max (h)	AUCss,norm* (ng/mL*h/mg*kg)	Cmax,ss,norm* (ng/mL/mg*kg)
all (26) mean	161.165	18.973	4.560	1326.830	154.520
all (26) SD	142.750	17.857	2298	823.046	95.043
naive (3) mean	11.442	1.822	6.006	400.377	64.443
naive (3) SD	11.987	1.656	6009	405.321	57.304
pretreated (23) mean	180.694	21.210	4.371	1447.671	166.269
pretreated (23) SD	140.313	17.798	1.548	789.008	93.358

SD standard deviation

WP09

AUC, Cmax and t-max values of the total patient cohort and separated according to pre-treatment status are listed in the tables below for enalapril and enalaprilat.

Table 15: Parameters of non-compartmental analysis of enalapril under single dose or approximated multiple dose (mean, SD)

Patients (n)	AUCtau (ng/mL*h)	Cmax (ng/mL)	t-max (h)	AUCss,norm* (ng/mL*h/mg*kg)	Cmax,ss,norm* (ng/mL/mg*kg)
All (63) mean	55.77	18.37	1.83	820.7	275.3
All (63) SD	39.04	11.85	1.05	521.5	158.6
Naive (29) mean	56.33	16.29	2.04	950.2	283.4
Naive (29) SD	39.76	7.62	1.25	602.9	138.1
Pretreated (34) mean	55.33	20.14	1.65	710.9	268.5
Pretreated (34) SD	39	14.4	0.82	418.8	175.8

SD Standard deviation, *normalized to dose and body weight

Table16: Parameters of non-compartmental analysis of enalaprilat under single dose or approximated multiple dose (mean, SD)

Patients (n)	AUCtau (ng/mL*h)	Cmax (ng/mL)	t-max (h)	AUCss,norm* (ng/mL*h/mg*kg)	Cmax,ss,norm* (ng/mL/mg*kg)
All (63) mean	84.63	10.19	6.26	1405	178
All (63) SD	64.51	7.52	3.57	1083.8	146.2
Naive (29) mean	55.7	8.07	8.41	1409.6	202.9
Naive (29) SD	60.1	8.4	3.84	1431.4	199.5
Pretreated (34) mean	109.31	12	4.42	1401.1	156.8
Pretreated (34) SD	58.24	6.24	1.95	684.4	73.4

SD Standard deviation; *normalized to dose and body weight

Secondary endpoint

WP08

For enalapril, the bioavailability concerning the rate and extent of exposure is shown below and this indicates a lower bioavailability of enalapril in infants compared to older age groups.

Table 14: Relative bioavalability (%) of enalapril (ENA) for AUCtau,ss,norm (ng/mL*h/mg*kg) and Cmax,ss,norm.

Age group	ENA AUCtau,ss,norm	AG3	AG2	AG1
	medians	514.6	470.7	375.6
AG3	514.6	100	109.3	137
AG2	470.7	91.5	100	125.3
AG1	375.6	73	79.8	100

Age group	ENA Cmax,ss,norm	AG3	AG2	AG1
	medians	241	225.3	97.1
AG3	241	100	107	248
AG2	225.3	93.5	100	231.9
AG1	97.1	40.3	43.1	100

For enalaprilat, the bioavailability concerning the rate and extent of exposure is shown below and this indicates a lower bioavailability of enalaprilat in infants compared to older age groups. The relative bioavailability of enalapril and enalaprilat according to age group is shown in Figure 8.

Table 15: Relative bioavailability (%) of enalaprilat (ENAAT) for AUCtau,ss,norm (ng/mL*h/mg*kg) and Cmax,ss,norm.

Age group	ENAAT AUCtau,ss,norm	AG3	AG2	AG1
	medians	1618.7	1285.4	929.5
AG3	1618.7	100	125.9	174.2
AG2	1285.4	79.4	100	138.3
AG1	929.5	57.4	72.3	100

Age group	ENAAT Cmax,ss,norm	AG3	AG2	AG1
	medians	187.8	148.8	109.6
AG3	187.8	100	126.2	171.4
AG2	148.8	79.2	100	135.8
AG1	109.6	58.3	73.6	100

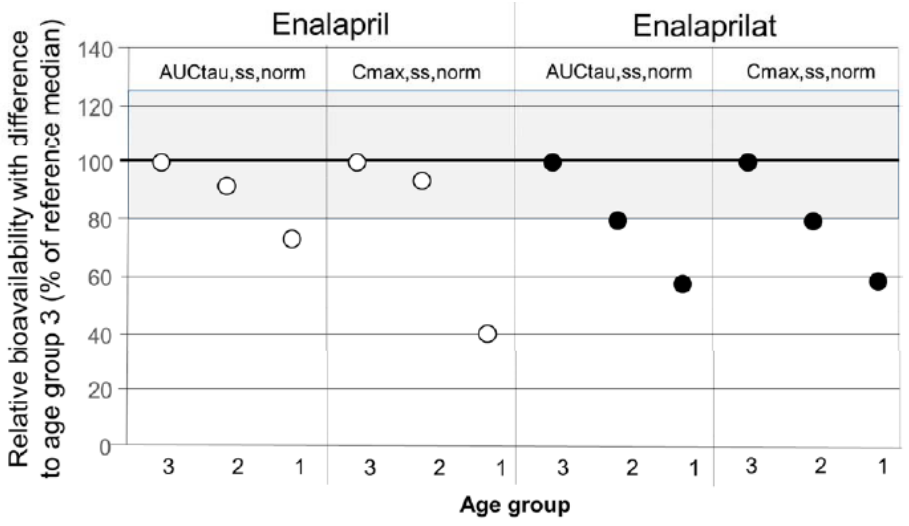


Figure 8: Relative bioavailability regarding rate and extent (Cmax,ss,norm; AUCtau,ss,norm) of absorption and exposure for enalapril and enalaprilat with difference compared to age group 3 calculated as % to the median of age group 3. The grey area depicts a relative bioavailability range between 80% to 125%.

The comparisons of the bioavailability for enalapril and enalaprilat between age groups indicate a lower rate and extent of exposure in infants compared to older children with DCM. It has to be noted that the

number of patients in the age subsets is small (n=6 to n=11). Therefore, a population PK analysis was performed with the combined patient cohort of paediatric heart failure patients due to DCM and CHD (WP09) (section 16) and will lead to dosing recommendations based on the PK exposition in combination with the PD results.

WP09

The bioavailability of enalapril and its active metabolite enalaprilat in the different age subsets (age group 1 (AG1) 0 to <12 months and age group 2 (AG2) 12 months to <6 years) of the paediatric study population (AUCtau, Cmax and t-max) were described. Based on the median of the age groups, the relative bioavailability of PK parameters AUCtau,ss,norm and Cmax, ss according to age groups of enalapril (ENA) and enalaprilat (ENAAT) were calculated and are provided in Tables below.

Table 19: Relative bioavailability (%) of enalapril (ENA) for AUCtau,ss,norm (ng/mL*h/mg*kg) and Cmax,ss,norm (ng/mL/mg*kg).

Age group	AUCtau,ss,norm	AG2	AG1
	medians	778.2	772.6
AG2	778.2	100	100.7
AG1	772.6	99.3	100

Age group	Cmax,ss,norm	AG2	AG1
	medians	471.9	257.1
AG2	471.9	100	183.6
AG1	257.1	54.5	100

The bioavailability of enalapril indicates a lower rate of exposure in the young age group compared to the older age group (54% in age group 2 compared to age group 1).

Table 20: Relative bioavailability (%) of enalaprilat (ENAAT) for AUCtau,ss,norm (ng/mL*h/mg*kg) and Cmax,ss,norm (ng/mL/mg*kg).

Age group	AUCtau,ss,norm	AG2	AG1
	medians	1258.9	1156.6
AG2	1258.9	100	108.8
AG1	1156.6	91.9	100

Age group	Cmax,ss,norm	AG2	AG1
	medians	130.5	142.7
AG2	130.5	100	91.4
AG1	142.7	109.4	100

It should be noted that the number of patients in age group 2 is small (n=7) compared to age group 1 (n=56). Furthermore, by combining all patients below one year together, age dependent differences between neonates and young and older infants can be masked.

Therefore, a population PK analysis was performed with the combined patient cohort of paediatric HF patients due to DCM and CHD and will lead based on the PK exposition in combination with the PD results.

2.6.2.2. Pharmacodynamics

Mechanism of action

After oral administration in adults, enalapril is hydrolysed via hepatic carboxylesterase (CES) 1 to the

active metabolite enalaprilat, which acts as an ACE inhibitor. ACE is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the vasoconstrictor substance angiotensin II and hence inhibition of ACE results in decreased plasma angiotensin II. This also leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion. The mechanism of action of enalapril is therefore primarily via the suppression of the RAAS. However, ACE is identical to kininase II, and so enalapril may also exert its effects by blocking the degradation of bradykinin, a potent vasodepressor peptide.

Primary and secondary pharmacology

Exploratory pharmacodynamics for brain natriuretic peptides (Nt-proBNP), shortening fraction and RAAS associated with enalapril orodispersible tablets in children with heart failure were studied in two clinical studies; 32 children aged 1 month to <12 years with heart failure due to dilated cardiomyopathy (DCM) (WP08) and 70 children aged birth to 6 years with heart failure due to congenital heart disease (CHD) (WP09): mean age 555 days, mean weight 8.92 kg and height 74.01 cm; 46% were females and 54% were males. The data are presented below.

In children with DCM, Nt-proBNP median values (range) did not change from 32 (5 to 1 777) pmol/L at the start to 35 (3 to 1 302) pmol/L (p=ns) at the end of the study. Only 10% of patients in this cohort were ACEi naïve. In children with CHD, Nt-proBNP levels were lower at the end of the study compared to the beginning. The median Nt-proBNP value at the start of the study were 171 (1 to 2 789) pmol/L and 73 (5 to 2 165) pmol/L (p=ns) at the end. In this cohort 44% of patients were naïve to ACEi treatment.

In patients with DCM, echocardiography (shortening fraction) mean values (±SD)) slightly, but significantly increased in all patients from 22.3% (SD 7.3) to 25.1% (SD 7.8) ($p < 0.05$, t-test) reflecting an improvement of the cardiac conditions of the patients in all age groups. In patients with CHD, shortening fraction remained almost the same during the study period. Mean values (±SD) at the screening and end of study visits were 38.7% (SD 8.6) and 38.5% (SD 6.2), respectively.

In terms of effects on the RAAS, renin, plasma renin activity and angiotensin I, all increased at the end of the two studies compared to pre-dose values. Aldosterone concentrations decreased at 4 hours after administration of enalapril orodispersible tablets as well as at the end of the study. The observed changes were unlikely to be a consequence of the natural course of disease or maturation-dependent changes of the RAAS system. A comparable trend for the four parameters of the RAAS system was observed in ACEi naïve and ACEi pre-treated cohorts, with the main difference being in the baseline pre-dose values. The observed changes in markers of the RAAS during the course of enalapril orodispersible tablets treatment lie within the expected pattern of ACE inhibition.

2.6.3. Discussion on clinical pharmacology

To support the application, the applicant has submitted one bioequivalence study, two pharmacodynamic/pharmacokinetic studies, no therapeutic equivalence studies.

In congenital heart diseases (CHD) the child's heart is subject to volume overload that is accompanied by the initial signs of congestion such as increased ventricle thickness as a compensatory response. Enalapril is used to treat these patients prior to closure of the left-right shunts since the clinical picture correlates with the cardiac situation in dilated cardiomyopathy (DCM). After surgery, enalapril treatment may still be used in a small proportion of patients in whom the shunt may not be adequately closed, prior to repeat surgery. This patient group has been neglected until now. However, since the LENA trials addressed this situation, therapeutic options available to this group have opened up. This

group included mainly young infants and neonates, expanding the age range in which enalapril ODMTs were studied.

The design of the enalapril ODMT study in children with CHD and HF (WP09) had the same goals and design as that described for the enalapril ODMT study in children with DCM and HF (WP08). The studies were performed as part of an agreed Paediatric Investigation Plan (PIP) and hence all criteria were discussed and agreed upon by the EMA Paediatric Committee (PDCO) in addition to local regulatory agencies and Ethics Committees.

All paediatric clinical trials were performed between January 2016 and July 2018 in 7 investigational sites in The Netherlands, Austria, Hungary, Germany and Serbia. It is of note, that the PDCO recommendation had an impact on the age range investigated. The investigation for the paediatric cohort with heart failure from aged 1 month to below 12 years of age consisted of patients with dilated cardiomyopathy (DCM; WP08) and patients from birth to below 6 years of age in patients with congenital heart diseases (CHD; WP09). In the agreed PIP the PDCO agreed not to include adolescents into the WP8 and WP9 studies but rather to substitute the age range from 12 to 17 years with a modelling and simulation exercise to delineate dosing. With this approach the whole patient age range was covered.

Pharmacokinetics

The report on population pharmacokinetics was provided on request during the procedure. The Report supported the data and conclusions of the PK study WP07. The main PK analysis performed was based on a non-compartmental (NCA) evaluation of the PK data from the clinical trials (Laeer, 2022). This approach allowed comparison of relevant PK metrics across age groups as well as with adults. The population PK analysis was used to complement the NCA. This was endorsed by the CHMP.

A major objection regarding a biowaiver for the 0.25 mg strength was raised during the assessment. A biowaiver for the 0.25mg strength, based on the bioequivalence established for the 1.0 mg strength, could be viewed from two perspectives: (1) as an additional strength biowaiver, meaning that the application contains enough information to meet the requirements in the BE guideline, except for the proportionality of the ratio of the amount of excipients to the active, and pharmacokinetic linearity not yet being demonstrated and different manufacturing processes for the two strengths, which needed a thorough justification; and (2) it is stated that enalapril is a BCS class III drug substance; however, in order to accept a BCS based biowaiver, there was a lack of an appropriate reference comparator. Even if the CHMP would accept Renitec 1.0 mg as a comparator, the BCS class III based biowaiver requires same qualitative composition and that no critical excipients (eg, mannitol) are present. This requirement was not met and the applicant was requested to provide an appropriate justification. Alternatively, the applicant was asked to justify that further data are not needed for the 0.25 mg strength, in particular taking into account the data with this strength from the clinical studies in children (W08 and 09). In the response provided the applicant stated that the pharmacokinetic evaluation of enalapril and its active metabolite enalaprilat in paediatric patients treated with enalapril ODMTs (either 0.25 mg or 1 mg) was the primary objective of the clinical studies WP08 and WP09. Dose was titrated to the effect by the clinicians using both strengths. In addition, the pharmacokinetic studies WP08 and WP09 showed that the dose corrected AUC and Cmax (in paediatric patients receiving, as a first dose, 0.25 mg or 1 mg ODMTs) are proportional for both strengths of enalapril ODMTs within the acceptable limit of ±25% described in the *Guideline on the Investigation of Bioequivalence for immediate release drug products (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**)*. Therefore, it was agreed that further data was not needed for the 0.25 mg strength.

Pharmacodynamics

The applicant presented data regarding the effect of enalapril in secondary pharmacodynamics (PD) endpoints on studies WP08, WP09 and WP10. Some of the PD endpoints studied were related to the mechanism of action of enalapril and aimed to support the effect of enalapril on the renin-angiotensin-aldosterone axis (RAA). The endpoints studied were: renin levels, plasma renin activity, angiontensin 1 levels and aldosterone levels.

In studies WP08 and WP09 the study population included both ACEI-naïve subjects and subjects already on ACEI willing to switch to enalapril ODMTs.

The number of ACE-inhibitor naïve patients, however, was low (n=3) with one patient below 12 months of age and two patients between 1 year and 6 years of age. The applicant stated that it can be expected that renin levels are higher in ACEI-treated subjects, related to the inhibition of ACE and of a positive feedback upstream of the RAA axis, which is clearly supported by the literature. However, when analysing the ACEI-group of WP08 (excluding the 3 ACEI-naïve subjects), and also the ACEI-group (non-naïve) of study WP09, the renin levels were lower at the End of Study Visit (mean 662.5 pg/mL vs 1992 pg/mL) although plasma renin activity was higher. The applicant has discussed these results. Apart from the expected effect of enalapril on the RAAS system, it has been reported that age dependent changes and the natural course of the disease can interact with the RAAS system and renin and plasma renin activity are decreased with increasing age. The small sample size in some age groups and the absence of a control group can also have an impact on the interpretation of the generated exploratory efficacy/PD data presented in the applicant's response. Although, qualitatively, the PD results in RAA markers general can be expected mechanistically and are supported by evidence, there was a lack of rational regarding the translation of its clinical significance in terms of dose/exposure of enalapril and magnitude of aldosterone reduction (and elevation of renin, angiotensin I) when compared to what is described in adults. Additionally, the PK/PD relationship results presented by the applicant were not satisfactory in providing a PK/PD bridging. The applicant was asked to present data would allow for translation of the magnitude of effect on the RAA markers. The applicant presented the requested data, but also stated that generating more data to allow translation of the magnitude of effect on the RAA markers is not considered feasible due to both constraints in paediatric research and the difficulties in defining and justifying the inclusion of a control arm in children which are in clear need of treatment.

Given the observed high values of angiotensin I as well as renin and plasma renin activity after enalapril treatment, a question was posed regarding the quantification of angiotensin II. Knowing that high angiotensin I levels can lead to angiotensin II conversion by non-ACE pathways, the applicant was asked why angiotensin II was not considered as RAA marker along with aldosterone given the more relevant role of angiotensin II in cardiac remodelling mechanisms. The applicant responded, that considering the role of angiotensin II in cardiac remodelling mechanisms, data related to the effect of enalapril on angiotensin II could have provided some additional information on the pharmacodynamic effects of enalapril in the paediatric population with heart failure. However, this endpoint was not included in the WP08 and WP09 studies. The goal of the clinical development was to confirm the initial dose exposure equivalence to the adult starting doses, with the new paediatric ODMT.

The PD results from studies WP08, WP09 and WP10 were upon request from the CHMP included in section 5.1, under "Pharmacodynamic effects".

The applicant has presented data regarding two PD markers (other than the mechanistic PD markers related to RAA inhibition): effect on Nt-proBNP levels and on the Shortening Fraction by Echocardiography.

The absence of a control group prevented the observation of a relation between enalapril administration and a positive effect on the pharmacodynamic biomarkers chosen, limiting the establishment of a primary pharmacodynamic effect.

Echocardiography

On study WP08, the echocardiographic analysis shows a slight increase in the shortening fraction (SF) in the “End of Study Visit” although a relation to ACEI cannot be performed due to possible bias with the natural disease progression. Additionally, analysis by age groups show (Initial Dose Visit vs End of Study Visit): an absence of effect for the lowest age group (under 1 y.o.), represented by 20.3% (15.9 – 26%) vs 21.1% (15.6 – 26%); a significant effect for the medium age group (1-6 y.o.), represented by 22.8% (17.8 – 26.9%) vs 28.6% (24 – 31.8); and a decrease on SF on the top age group (6 -12 y.o.), represented by 24.9% (18.3 – 29.8%) vs 22.3% (15 – 29%). Although the third age group is associated with a lower subject number when compared to the lowest age group for example (5-6 vs 9-12 subjects), the standard deviation for both groups is not as different (7-8 for the lowest age group vs 8.3-8.9 for the highest age group).

This is line what was observed in study WP09, where none of the age groups were found to have statistical differences.

In study WP08, the evaluation of PD outcomes Nt-proBNP and echocardiography showed that the differences between the results of the Initial Visit and End of Study Visit are clearer in the 1-6 age groups, with an absence of statistical significance on the other age groups. On study WP09 no statistical difference was observed in any age group when comparing echocardiography results. Although Nt-proBNP results from study WP09 were statistically significant in the two age groups evaluated, clinical guidelines and scientific literature have devalued Nt-proBNP as biomarkers for treatment efficacy, recommending instead their use for the diagnosis stage and as heart failure exclusion criteria. Given the scarcity of pharmacodynamic evidence generated in these studies, the applicant was asked to justify the extrapolation amongst the different age groups. In response the applicant stated that the definition of paediatric doses per age group is based on PK data targeting a similar intial exposure in paediatric patients as in adults because the expected effect of ACEi is similar in adults and children. Extrapolation between age groups is based on pharmacokinetic considerations. The PD data collection was intended for exploratory purposes. The highly heterogenous population of cardiovascular paediatric patients and the limited sample size for which PD data is available do not allow to draw conclusions based on the generated pharmacodynamic evidence. The high variability of the PD observations does not allow to conclude if differences between age groups are related to differences in growth and maturation on the PD endpoint or just related to variability in the age groups associated to sample size limitations.

Although some literature exists regarding the beneficial effect of ACEI in paediatric heart failure, many questions remain regarding the magnitude of the beneficial effect regarding different age groups. The applicant was asked to discuss the effect of enalapril on heart failure biomarkers according to different age groups and also according to disease severity in paediatrics. In the response provided the applicant argued that in adults enalapril has a positive effect on heart-failure parameters beyond its BP-lowering effect. This effect is less apparent in the paediatric population, in which studies show conflicting results. The studies in the LENA work packages were designed to determine the PK profiles of enalapril ODMT and any PD endpoints were exploratory in nature. As such, no specific determinants can be made regarding the effect of enalapril on heart failure biomarkers according to different age groups and also according to disease severity in paediatrics.

The applicant has not initially provided clinical data related to hyperkalemia incidence nor addressed the relevance of hyperkalemia in the paediatric population although the available literature points out renal impairment, hypotension and hyperkalemia as common adverse reactions in children. The applicant was asked to discuss the potential for hyperkalemia in the paediatric population and any variability in the several age groups. The applicant provided a discussion on hyperkalaemia based on literature data and this point is adequately addressed in the agreed SmPC.

The applicant addressed the known information specific to enalapril PD interactions in the paediatric age range, highlighting the relevant role of potassium supplements, with the data that interaction of enalapril with potassium chloride is within the top five drug-drug interactions that are most frequently observed in a paediatric hospital. Additionally, the applicant indicated that coadministration of furosemide is an independent risk factor for developing acute kidney injury (AKI) in patients.

Taking into consideration the variability of the RAA axis activation throughout the paediatric age range and the known variability in the plasma levels of renin and aldosterone in individuals of African ancestry, the applicant presented as well the pharmacodynamic effect of enalapril in this specific paediatric population.

The applicant has initially failed to present a clear relationship between the pharmacokinetic and pharmacodynamic profiles. Although the applicant has cited some publications that give some PK/PD support, they are generally limited to studies with a small population and of limited age span, not allowing for a complete extrapolation to all of the paediatric age range. There are however other studies that point out the existence of conflicting results, mainly related to the variability of the RAA axis activation throughout the paediatric age range.

The applicant was asked to elaborate, discuss and provide stronger support on the extrapolation of results to all age sub-groups within the paediatric range. Several publications have shown that activation of RAA axis varies significantly along the paediatric age range and issues remain controversial in the PK/PD relationship depending on the paediatric age, not only on pure pharmacodynamic markers, but also on more clinically PD/efficacy biomarkers. In response provided the applicant admitted that taking into account the heterogeneity of paediatric heart failure and the diversity of the study population (age, naïve vs. non naïve patients, etc.) and considering the exploratory nature of the pharmacodynamic and efficacy endpoints used in the applicant's WP08 and WP09 studies, a clear conclusion on the extrapolation of results to all age sub-groups within the paediatric age range could not be drawn. However, enalapril is considered to be a first-line treatment for chronic heart failure in children and has been extensively used off-label for decades in this patient population.

2.6.4. Conclusions on clinical pharmacology

The CHMP considered application approvable from clinical pharmacology point of view.

2.6.5. Clinical efficacy

This application relies in part on the results of pre-clinical tests and clinical trials for the reference product (Renitec®) enalapril maleate tablets and in part on new clinical data.

New clinical studies were done in the frame of LENA project. The LENA project generated core scientific data out of the four clinical trials WP07, WP08, WP09 and WP10. WP07 generated clinical data for enalapril orodispersible mini-tablets (ODMTs) in healthy volunteers. WP08, WP09 and WP10 generated clinical data for enalapril ODMTs in children with heart failure.

Study WP07

Study WP07 - Relative Bioavailability of Enalapril Administered as orodispersible Minitablets (ODMT) in Healthy Adults

Report location	Module 5.3.1
Study period clinical	18th Aug 2014 – 15th September 2014
Study period bioanalytical	27th Aug 2014 – 21st September 2014
Design - Dose - Single/Multiple dose - Number of periods - Two-stage design - Fasting / fed - Number of subjects - dosed - completed the study - included in the final statistical analysis of AUC - included in the final statistical analysis of C_{max}	 10 mg Single dose 3-period No Fasting 24 B and C, 23 A 24 24 B and C, 23 A 24 B and C, 23 A

This was an open-label, single centre, randomised, three-way crossover, three-treatment, three-period study conducted in 24 healthy non-smokers, consisting of 11 non-pregnant, non- breastfeeding female and 13 male volunteers between 18 and 55 years old and a BMI between 18.5 and 30 kg/m2.

A total of 24 subjects from 22.1 to 47.2 years of age were enrolled (mean age 27.7 years; female 45.8%, male 54.2%; all subjects were white (100%)). All subjects received treatments B and C and twenty-three subjects (23, 95.8%) received treatment A.

Study WP08

Orodispersible Minitablets of Enalapril in Children with Heart Failure due to Dilated Cardiomyopathy (DCM) (32 paediatric patients)

Protocol Number 2015-602295-01

Clinical Phase 2/3

EudraCT Number 2015-002335-17

This was a multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose PK bridging study with exploratory PD assessments in paediatric patients with Dilated Cardiomyopathy (DCM) requiring ACE inhibitor treatment. The study was initiated in 8 sites in The Netherlands, Austria, Hungary, UK, Germany and Serbia. Two groups of children (ACEI pre-treated and treatment-naïve children) with heart failure due to DCM were treated with enalapril Orodispersible Minitablets (ODMTs) over a period of 8 weeks with the maximum tolerated dose following a defined dose titration scheme.

Primary endpoints WP08

Pharmacokinetic: The bioavailability of enalapril and its active metabolite enalaprilat in children (1 month - < 12 years) (AUC from 0 to time of last sampling point, Cmax and tmax); descriptive pharmacokinetic investigation (– this section is discussed under PK part).

Secondary endpoints WP08

Bioavailability by age group – this study is discussed under PK and safety part of AR only a short summary is given here.

Markers of the RAAS

The investigated 4 parameters of the RAAS system (Renin, Angiotensin I, Aldosterone, Plasma Renin Activity) showed a trend that the RAAS markers changed in the patient cohort during the course of enalapril ODMT administration in the expected pattern of ACE inhibition. Statistical testing, however, was precluded as only three ACEI pre-treatment naïve patients were entered into this trial.

Brain Natriuretic Peptides (BNP)

In the whole paediatric patient cohort Nt-proBNP values did not change in median values from 32 pmol/L before to 35 pmol/L at the end of the study. Patients demonstrated a high variability in Nt- proBNP values with minimum and maximum values of 5 to 1777 pmol/L before enalapril ODMT treatment compared to 3 to 1302 pmol/L at the end of the study.

Shortening Fraction

Shortening fraction slightly, but significantly increased in all patients from 22.3±7.3% to 25.1±7.8% ($p<0.05$) reflecting an improvement of the cardiac conditions of the patients in all age groups. Although an effect of ACEI could not be excluded, this could also be explained by the natural course of the disease.

Acceptability, Palatability

Acceptability of the 1 mg and the 0.25 mg enalapril ODMTs administered as single or multiple ODMTs up to 10 per dose, was 100% in all age groups. The same was true for swallowability with the exception of the 6 months to 5 years age group where swallowability was still high at 84.7%. Palatability was rated either as “positive” or “neutral” in patients of 1 month to 5 years of age. Older patient palatability ratings for taste, size of ODMT and ease of swallowing were rated more variably but in nearly all cases as “very good”, “good or “not sure”.

Safety parameters (see safety section of AR)

- Ross score
- Blood pressure and heart rate
- Renal safety parameters
- Haematology parameters
- Adverse events

Study WP09

Orodispersible Minitablets of Enalapril in young children with Heart Failure due to Congenital Heart Disease (CHD) (70 paediatric patients)

Protocol Number 2015-602295-02

Clinical Phase 2/3

EudraCT Number 2015-002396-18

This was a multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose pharmacokinetic bridging study with exploratory pharmacodynamic assessments in paediatric patients aged from birth to less than 6 years with CHD requiring ACE inhibitor (ACEI) treatment.

Primary objective

To obtain paediatric pharmacokinetic data of enalapril and its active metabolite enalaprilat in patients treated with enalapril ODMTs to describe the dose exposure in the paediatric population with CHD.

Secondary Objectives:

- To demonstrate safety, in particular renal safety, of enalapril ODMTs in children with CHD.

- To characterise the dose/safety relationship from a starting dose to an optimal maintenance dose.
- To explore the dose exposure/response relationship with pharmacodynamic parameters in the paediatric population with CHD.
- To investigate the Shortening Fraction (SF) in echocardiography.
- To investigate the acceptability and palatability of enalapril ODMTs in the paediatric population with CHD.

A minimum of 50 patients were originally planned to be enrolled. In accordance with an agreed Request for Modification of an approved PIP, this was increased to a minimum of 60 evaluable patients for the primary endpoint (full PK). Up to 15 additional patients were permitted to be enrolled to ensure sufficient evaluable patients.

Table : Study WP09 - Patient enrolled and evaluable for PK in accordance with the updated PIP

Age sub-set	Minimum planned	Enrolled	Evaluable
0 - <12 months	37	61	56
12 months - <6 years	Not specified	9	7

Main inclusion criteria

Male and female children (0 - <6 years; weight greater than 2.5 kg) with the diagnosis of heart failure due to congenital heart disease (CHD) requiring after load reduction by drug therapy. Patients naïve to ACEIs and those already on ACEI but willing to switch to the IMP could participate.

Exclusion criteria

- Neonates if born < 37 weeks of gestation.
- Severe HF and/or end stage heart failure precluding introduction or continuation of ACEI.
- Too low blood pressure, e.g. <P5.
- Uncorrected primary obstructive valvular disease, or significant systemic ventricular
- outflow obstruction, dilated restrictive or hypertrophic cardiomyopathy.
- Uncorrected severe peripheral stenosis of large arteries including severe coarctation of the aorta.
- Severe renal impairment with serum creatinine >2x Upper Limit of Normal (ULN) according to the hospital's test methodology).
- History of angioedema.
- Hypersensitivity to ACEI.
- Concomitant medication (dual ACEI therapy, renin inhibitors, angiotensin II antagonists, NSAIDs except for salicylic acid in antiplatelet therapy)
- Already enrolled in another trial

Duration of treatment – up to 8 weeks, with a minimum duration therapy of 3 days

Statistical methods

For the safety endpoints (vital parameters, renal function, adverse events, rehospitalisation and death) and the other secondary endpoints (RAA-markers, echocardiography, acceptability and palatability) descriptive statistics for the intention to treat (ITT) and the per protocol (PP) population have been done. These included the number of observations (N), mean, standard deviation (SD), median, min, max, 1st quartile and 3rd quartile (where indicated). In addition, exploratory pharmacodynamic and pharmacokinetic analyses have been done for hypothesis generating purposes using Wilcoxon test and t-Test. Although these studies were not designed and powered to provide confirmation of efficacy, these

analyses helped to interpret the gathered data particularly regarding the PK/PD model and the planning of future studies.

Study WP10

Follow-up Safety trial in children with chronic Heart Failure therapy receiving Orodispersible Minitablets of Enalapril (86 paediatric patients)

Protocol Number 2015-602295-03

Clinical Phase 2/3

EudraCT Number 2015-002397-21

The Primary Objective of this study was the assessment of safety.

The Secondary Objectives:

- To describe the acceptability and palatability of enalapril ODMTs.
- To collect additional information about pharmacokinetics and pharmacodynamics of enalapril ODMTs during long term treatment
- NT-proBNP values

WP10 contained a Phase II/III prospective, open-label, safety follow-up study in infants and children enrolled in the trials 2015-602295-01 (WP08) and 2015-602295-02 (WP09) under stable optimal dose or no longer under enalapril ODMT treatment, with exploratory pharmacodynamic and pharmacokinetic assessments in children under IMP treatment.

Patients in the previous WP8 and WP9 trials were up-titrated under close clinical observation to an optimal dose and maintained this dose for the remaining duration of 2 months in these LENA trials. Patients who had completed this treatment period under enalapril ODMT treatment those who had received enalapril ODMTs for at least 3 days but had stopped, were invited to join the open long-term observation safety study “WP10” for an additional 10 months. Of the 102 patients enrolled in WP08 and WP09 trials 86 continued into the WP10 trial.

Number of patients

All patients from the previous LENA trials (WP08 and WP09) trials who received at least three days treatment with enalapril ODMT, were asked to participate in the study conducted in WP10 (originally it was planned to enroll at least 100 patients however this was reduced to at least 85 patients following an agreed Request for Modification of an approved PIP). A minimum of 40 patients recruited as neonates or infants in WP08 and WP09 were planned to be enrolled, with at least 10 patients in each of the following age subsets at time of enrolment into WP08 or WP09; 0-<3 months, 3-<6 months and 6-<12 month (see Table below).

Age sub-set (at WP08/09 enrolment)	Minimum Planned	Enrolled
0 to less than 12 months, of which	40	64
0-< 3 months	10	23
3-< 6 months	10	25
6-< 12 months	10	15
12 months to less than 6 years	Not specified	19

6 -< 12 years	Not specified	4
Total		86

Inclusion Criteria

- Patients from trial trials 2015-602295-01 (WP08) and 2015-602295-02 (WP09) who have been treated with enalapril Orodispersible Minitablets and are still under ODMT treatment.
- Patients from the WP08 and WP09 trials who have been treated for at least 3 days with enalapril Orodispersible Minitablets and are no longer under ODMT treatment.
- Patient and/or parent(s)/legal representative provided written informed consent for participation in this Follow-up Safety Trial and assent was received from the legal representative(s) of the patient according to national legislation and as far as achievable from the child.

Exclusion criteria

Patients who had been enrolled and treated in the 2015-602295-01 (WP08) and 2015-602295- 02 (WP09) trials had fulfilled the respective in- and exclusion criteria of those protocols. As it was the aim of this Follow-up Study to observe the safety of all patients exposed to enalapril ODMT treatment, no additional exclusion criteria were defined in this protocol. However, adapted to the health situation of the patient, the investigator was requested to decide whether planned study activities could be performed

Primary endpoints

- Adverse events.

Secondary endpoints

- Blood pressure in paediatric patients under and after enalapril ODMT treatment.
- Renal function in paediatric patients under and after enalapril ODMT treatment.
- Exploratory pharmacokinetics and pharmacodynamics in paediatric patients under enalapril ODMT treatment.
- Acceptability and palatability of the novel formulation in paediatric patients under enalapril ODMT treatment.
- Echocardiography (Shortening Fraction).
- Rehospitalisation due to heart failure including the need for heart transplantation or the institution of mechanical circulatory support.
- Death due to worsening of the underlying disease.

Results

In the cohort of children that were included in WP08 and WP09, half were already on ACEI and in most of them the enalapril-ODMTs were not up-titrated after inclusion. Thus, the effects of increasing doses of ACEI on pharmacodynamic parameters could not be reliably estimated. Pharmacodynamic and safety parameters were analysed in a descriptive fashion as secondary endpoints. For the following parameters, statistical comparisons before and after the end of the study or between age groups were performed (t-test or Wilcoxon test).

Echocardiography (Shortening Fraction)

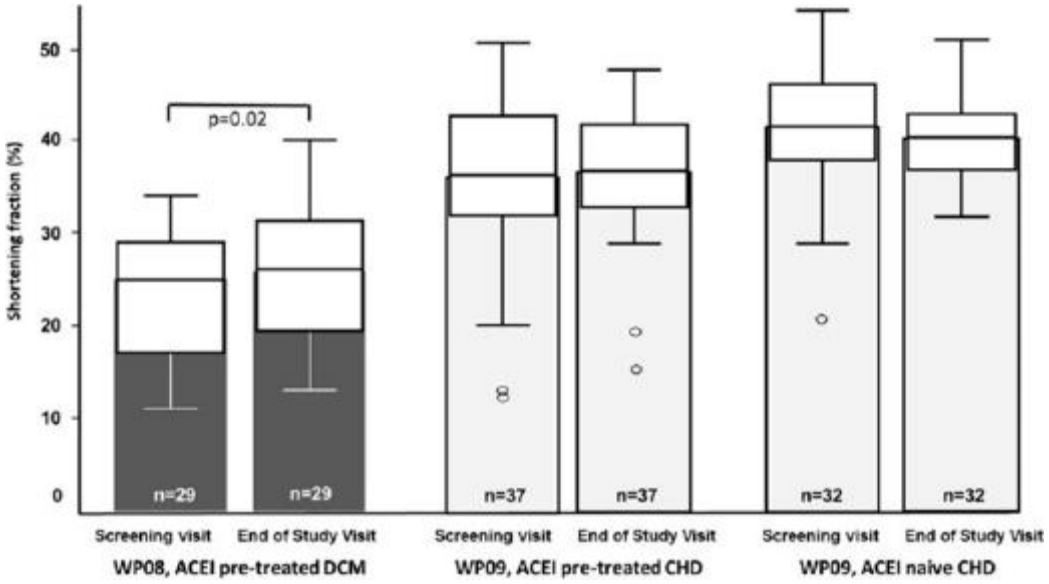
In patients with dilated cardiomyopathy (WP08), shortening fraction (SF) slightly, but significantly increased in all patients from 22.3±7.3% to 25.1±7.8% ($p<0.05$, t-test) reflecting an improvement of the cardiac conditions of the patients in all age groups (see figure below). Although an effect of ACEI could not be excluded, this could also be explained by the natural course of the disease.

In patients with congenital heart disease (WP09), SF remained almost the same during the trial period, which was expected from the aetiology of the disease. Mean value at the Screening Visit was 38.7% and mean value at the End of Study Visit was 38.5%.

RAAS

The investigated 4 parameters of the RAAS system (renin, angiotensin I, aldosterone, plasma renin activity) supported the probability that the administration of the enalapril ODMT was related to the changes seen in the RAAS parameters. A comparable trend for the 4 parameters of the RAAS system was observed in ACEI naïve and ACEI pre-treated cohorts, with the main difference residing in the baseline pre-dose values.

Figure : Shortening fraction in WP08 (black boxplots and bars) and WP09 patients (grey boxplots and bars) in patients pre-treated or naive to ACEI. T-test with $p<0.05$ indicate significant improvement in shortening fraction of pre-treated WP08 patients



These observations are in line with expected changes in the RAAS system related to ACE inhibition. Enalaprilat as the active metabolite of enalapril inhibits the angiotensin converting enzyme (ACE) and reduces the formation of angiotensin II as well as aldosterone. Lower angiotensin II concentrations reduce the negative feedback for renin and increases renin concentrations. Hence, plasma renin activity increases as well as angiotensin I concentrations. In summary, due to ACE inhibition, lower concentrations of aldosterone and higher concentrations of renin, plasma renin activity and angiotensin I would be expected.

All markers of the RAAS were measured in this patient cohort. The observed changes in markers of the RAAS during the course of enalapril ODMT treatment lies within the expected pattern of ACE inhibition.

The statement that RAAS parameter changes are related to enalapril ODMTs is strongly supported by the data. Even if no control group was included for comparison, and despite the natural course of disease can lead to a stimulation of the RAAS system, these factors are unable to explain the decrease in the aldosterone concentrations seen 4 hours after ODMT administration and that aldosterone concentrations remained decreased until the end of the study, both in ACEI naïve and ACEI pre-treated cohorts. Age

dependent changes can also interact with the RAAS system and decreasing aldosterone concentrations had been reported with increasing age. Renin, angiotensin I and plasma renin activity have also been reported to be decreased with increasing age. Instead, in this patient cohort, renin, angiotensin I and plasma renin activity were increased during the course of studies WP08 and WP09. Thus, the investigation of 4 parameters in parallel and at the same time strongly supports the probability that it is more likely that the administration of the enalapril ODMTs is associated with the changes in the RAAS parameters seen and that the changes were not due to the course of disease or maturation dependent changes of the RAAS system.

Published studies in paediatric heart failure with enalapril

A summary of off-label study data on paediatric enalapril trials in heart failure available from literature is shown in the following table:

Table: Summary of paediatric trials in heart failure available from the literature

Study ID	Number of patients	Age of population	Exact indication	Dosage and type of formulation (duration)	Type of trial	Level of evidence [a]	Effects	Tolerability and adverse effects
Hsu et al (2010)	230	20.1 (SD 8.9) days	Single ventricle physiology	0.1 – 0.4 mg/kg/day; exact formulation not described (14 months)	Double blind RCT with placebo	1b	No improvement in somatic growth, ventricular function or heart failure severity	Serious adverse events occurred in 88 patients in the enalapril group. The results of this randomized trial do not support the routine use of enalapril in this population.
Kouatli et al (1997)	18	14.5 (SD 6.2) years	After Fontan procedure	0.2–0.3 mg/kg/day once daily (10 weeks)	Double blind placebo-controlled crossover trial	1b	Enalapril administration for 10 weeks did not alter abnormal systemic vascular resistance, resting cardiac index, diastolic function or exercise capacity	The proportion of subjects who reported side effects was no higher when they were taking enalapril than when they were taking the placebo.

Mori et al (2000)	24 (3 enalapril)	0.3 – 16 years	Aortic or mitral regurgitation	0.15–0.4 mg/kg/day [mean 3.4 (SD 2.0) years]	Prospective cohort (randomised)	2b	Mean change in Z-value for LV end diastolic dimensions –0.25 (SD 0.33) for ACEi group versus –0.42 (SD 0.48) for control group (p = 0.0007) Mean change in mass normalized to growth: –72% (SD 89) of normal for the ACEi group vs. –37% (SD 35) of normal for control group (p = 0.0007)	There were no patients who had side effects or withdrew from the therapy in the ACE inhibitor group.
Leversha et al (1994)	63	4 years (SD 5.4 months)	Congenital and acquired heart disease	0.04–0.94 mg/kg/day, once, twice or three times daily (1 day–3 years)	Prospective cohort	2b	58% of all patients had improved signs of CHF. The dose received by those who improved was significantly greater (p = 0.04) than that received by those who showed no change.	Enalapril was clinically safe and effective for children with cardiac failure secondary to ventricular impairment, valvar regurgitation, or after cardiac surgery.
Webster et al (1992)	26	6 months – 15 years	Intracardiac shunts	Enalaprilat IV 0.06 mg/kg (30 min)	Prospective cohort	2b	Mean pulmonary-systemic flow ratio decreased from 2.9 (SD 0.3) to 2.4 (SD 0.3) (p < 0.05) and the mean left-to-right shunt from 7.4 (SD 0.8) to	There were no adverse effects.

							5.9 (SD 0.7) l/min/m2 (p < 0.02) after enalapril treatment	
Sluysmans et al (1992)	8	<10 months	Isolated large ventricular septal defect	Enalaprilat IV 0.02 mg/kg (15 min) and enalapril 0.16 mg/kg orally once daily (7 days)	Prospective cohort	2b	IV administration: absolute left-to- right shunt decreased 27% [7.5 (SD 6.3) to 5 (SD 3.7) l/min/m2, p < 0.05]. Systemic blood flow did not change. Pulmonary blood flow decreased 15.5% (p < 0.1). Mean decrease of aortic mean pressure was 9% (66 (SD 9) to 61 (SD 9) mm Hg, p < 0.0001). Oral administration: six patients had increased weight gain [82 (SD 59) to 166 (SD 94) g/week] and bottle feeding [milk, 139 (SD 16) to 158 (SD 13) ml/kg/day; p < 0.05]	The enalapril trial was well tolerated. This study suggests a beneficial effect of ACE inhibitors in the management of infants with a left-to-right ventricular shunt and CHF. Careful monitoring of the clinical response is needed before initiating long-term therapy.
Seguchi et al (1992)	35	1 month – 17 years	CHF	0.11–0.8 mg/kg/day orally, twice a day (7-44 days)	Prospective cohort2b	2b	Significant decrease in left ventricular end-diastolic dimension, hepatomegaly and cardiothoracic ratio (p < 0.05)	Acute renal failure developed in a 3 month old infant one day after enalapril administration. Renal function

								returned to normal one day after discontinuation of enalapril. Four patients developed hyperkalaemia. Discontinuation of spironolactone normalized this in the 3 patients taking this.
Study ID	Number of patients	Age of population	Exact indication	Dosage and type of formulation (duration)	Type of trial	Level of evidence a	Effect	Tolerability and adverse effects
Rheuban et al (1990)	11	1 – 13 months	CHF secondary to left-to-right shunt lesions	IV enalaprilat 0.01 mg/kg, single dose (20 min)	Prospective cohort	2b	Significant reduction in systemic vascular resistance [18.1 (SD 4.7) to 14.2 (SD 3.5) Wood units*m2; p<0.001]. Reduction in pulmonary/systemic blood flow ratio (p = non-significant).	Results indicated a beneficial acute hemodynamic response to the intravenous administration of enalaprilat when given to infants with large left-to-right shunts and congestive heart failure.
Lewis et al (1993)	81 (of which 27 AEC inhibitor and two enalapril)	3.6 (SD 0.6) years	Dilated cardiomyopathy	Dose not mentioned (2 years)	Retrospective cohort	2b	Significantly better survival during the first year (p < 0.05) with continuation of this trend throughout the second year (p = 0.06). Beyond 2 years, this difference was no	Results suggests that cardiac failure in patients treated with ACE inhibitors may have been on average somewhat more severe.

							longer significant.	
Robinson et al (2002)	9	13.8 (SD 3) years	Transposition of the great arteries s/p intra-arterial switch after intra-arterial baffle	0.1-0.5 mg/kg/day, rounded to the nearest 2.5 mg (12 months)	Case study (prospective)	4	No improvement in exercise performance in patients with transposition of the great arteries in whom the intra-atrial baffle procedure had been performed.	No adverse events described.
Eronen et al (1991)	8	1.5 – 11.2 years	CHF and dilated cardiomyopathy	0.5 mg/kg/day, orally once daily (5 days)	Case study (prospective)	4	Diminished afterload, reflected by a decrease in mean SBP from 104 to 96 mm Hg (p = 0.054), and a decrease in heart size from 582 to 523 ml/m2 (p = 0.09)	The medication was well tolerated, and no subjective side-effects were reported. The fall in blood pressure was well tolerated, and none of the patients showed symptoms due to hypotension.
Lipschultz et al (2002)	18	1 – 18.1 years	Ventricular dysfunction due to doxorubicin treatment	5-40 mg/day; exact formulation not described (10 years)	Case study (retrospective)	4	Progressive improvement towards normal values of LV dimension, afterload, fractional shortening and mass in the first 6 years of enalapril treatment.	No adverse enalapril reactions were noted.

Study ID	Number of patients	Age of population	Exact indication	Dosage and type of formulation (duration)	Type of trial	Level of evidence a	Effect	Tolerability and adverse effects
Frenneaux et al (1989)	8	4 days – 12 weeks	Severe heart failure	Suspension of crushed tablet, 0.12–0.43 mg/kg/day once daily (2 weeks)	Case study	4	Mean (SEM) liver size had decreased from 2.3 (0.36) cm to 1.2 (0.24) cm below the costal margin, mean respiratory. Rate had fallen from 63 (3.2) to 53 (2.8) breaths per minute. The mean heart rate increased from 136 (6.4) to 143 (4.2). beats per minute and the mean SBP fell from 88 (4.0) mm Hg to 82 (6.5) mm. No p-values were reported.	One infant with severe myocarditis did not tolerate enalapril because of hypotension and later died of intractable heart failure.

[a] Level of evidence according to Johansen et al.: systematic reviews and meta-analyses of RCTs (1a), RCT (1b), non-randomised controlled trials (2a), cohort studies (2b), case- control studies (3), case studies, expert opinion.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CHF, congestive heart failure; IV, intravenous; LV, left ventricle; RCT, randomised controlled trial; SBP, systolic blood pressure; SEM, standard error of the mean.

2.6.6. Discussion on clinical efficacy

Enalapril is an ACE inhibitor used in the treatment of hypertension and heart failure. It may also be given prophylactically to patients with asymptomatic left ventricular dysfunction to delay the onset of symptomatic heart failure, and has been used in patients with left ventricular dysfunction to reduce the incidence of coronary ischaemic events, including myocardial infarction.

Enalapril owes its activity to enalaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 4 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Enalapril is given orally as the maleate.

Enalaprilat is not absorbed orally but is given by intravenous injection; its haemodynamic effects

develop within 15 minutes of injection and reach a peak in 1 to 4 hours. The action lasts for about 6 hours at recommended doses. Enalaprilat is given as the dihydrate, but doses are expressed in terms of the anhydrous substance. Enalaprilat 1.38 mg as the dihydrate is equivalent to about 1.25 mg of anhydrous enalaprilat.

In the management of heart failure, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus, treatment should begin with a low dose under close medical supervision. In patients with heart failure or asymptomatic left ventricular dysfunction enalapril maleate is given orally in an initial dose of 2.5 mg daily. The usual maintenance dose is 20 mg daily as a single dose or in 2 divided doses although up to 40 mg daily in 2 divided doses has been given.

Enalapril has been subject to both dose-finding and efficacy studies in children with hypertension or heart failure and is licensed for use in hypertension in both the EU and the USA.

In the UK, recommended oral doses of enalapril maleate for hypertension are given according to weight as follows:

- 20 kg to < 50 kg: initial dose of 2.5 mg once daily, increased if necessary to a maximum of 20 mg once daily
- ⩾ 50 kg: initial dose of 5 mg once daily, increased if necessary to a maximum of 40 mg once daily

In the USA, an initial dose of 80 micrograms/kg (maximum of 5 mg) once daily is recommended.

The BNFC suggests the following doses, which may be given to neonates and children in the treatment of hypertension, heart failure, or proteinuria in nephritis:

- neonate: initial dose of 10 micrograms/kg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased if necessary to a maximum of 500 micrograms/kg daily in 1 to 3 divided doses
- 1 month to 11 years: initial dose of 100 micrograms/kg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased if necessary to a maximum of 1 mg/kg daily in 1 or 2 divided doses
- 12 to 17 years: initial dose of 2.5 mg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased to a usual maintenance dose of 10 to 20 mg daily in 1 or 2 divided doses. Those weighing 50 kg and over may be given up to 40 mg daily in 1 or 2 divided doses

The bioavailability of enalapril is approximately 60%. Tmax for enalapril is 1 hour after oral administration for enalaprilat metabolite (active), 3 to 4.8 hours in adults, whereas in children and infants it is 3 – 6 hours. When food is taken with orally administered tablets no effect on PK parameters were demonstrated, whereas with enalapril suspension, the effect of food was following: Cmax decreased by 46%, Tmax delayed by 20 minutes with a high-fat meal; Enalaprilat metabolite (active), Cmax decreased by 36%, Tmax delayed by 62 minutes, AUC reduced by 23% with a high-fat meal.

In the report from the Expert Group Meeting on Paediatric Heart Failure organised by the European Medicines Agency in 2010 enalapril was considered a first-line treatment for chronic heart failure in children.

As the pathophysiology of heart failure in children is believed to be similar to that in adults with chronic heart failure caused by DCM, the applicant conducted a PK bridging study (WP08) in paediatric patients with DCM aged 1 month to less than 18 years. The primary objective of this study was to obtain

paediatric PK data of enalapril ODMTs to describe the dose exposure in paediatric DCM patients in order to identify the doses that lead to an equivalent systemic exposure to that achieved during the treatment of adults. Neonates were not included in the study WP08 since DCM generally does not occur in newborns' but develops in infancy.

The younger population was therefore investigated in a study of children with congenital heart disease (CHD) (WP09). This study recruited paediatric patients aged from birth to less than 6 years, excluding neonates born at less than 35 weeks of gestational age to obtain paediatric PK data of enalapril ODMTs to describe the dose exposure in young children with CHD.

In response to the major objection raised at D120 LoQs regarding the proposed indication including neonates from birth, the applicant submitted a step by step presentation of the popPK model documentation.

The applicant agreed initially to restrict the indication to treatment of heart failure in children from one month, to less than 18 years. Consequently the major objection was considered resolved.

However, due to unmet medical need and the split opinion of clinical experts regarding the off-label use of enalapril in neonates the applicant was invited to reconsider the exclusion of neonates <1 month. The applicant presented a PK/PD justification on the extrapolation approach that considered data available from neonates demonstrating acceptable exposure margins. Pop. PK analysis was done with model simulations, fixed exponents for allometric scaling, maturation functions, simulation of exposure parameters provided and compared with older age groups can be used/provided. The applicant demonstrated that the available PK data are sufficient to establish the bridge between adults and the youngest children. This reassurance also took into account not only the target/maintenance dose but the initial dose that an go as low as 0.01 mg/kg/day. The applicant provided the full popPK analysis report, including diagnostic plots and updated the maturation function for clearance. The adequacy of extrapolating efficacy and safety from adults/older children to neonates was justified, including the discussion related to publication by Ku et al. (Pediatr Cardiol. 2017 Jan; 38(1): 155–161), which demonstrated severe adverse effects of enalapril particularly in infants <30 days of age. Also, the scarcity of subjects <30 days in clinical studies (n=4) is now reflected in SmPC section 4.4 and section 5.1.

The applicant in their response provided data that allowed to state that final covariate model described in the LENA project ("run051") has been used to perform population modelling of the PK of enalaprilat. It was shown that administration of enalapril ODMT to children from birth to adolescents provides overall exposures matching those expected in adults taking into account both the target/maintenance dose and the initial dose (as low as 0.01 mg/kg/day).

It can be agreed that the pathophysiological process leading to heart failure in DCM in children is considered to be similar to that in adults. Hence, based on PK and safety data, extrapolation from adults to neonates can be justified.

The applicant has presented a PK/PD justification on the extrapolation approach from birth to indicate the administration of the drug product should not be excluded in neonates <1 month. The extrapolated exposure, along with the limited data generated in the population <1 month on PD endpoints and safety, demonstrated acceptable exposure margins and support the use of the Aqumeldi from birth. As far as the PK aspects of this response are concerned, the methods employed are adequate and the results consistent with the original data.

Enalapril is used to treat hypertension and congestive heart failure in infants and is approved in USA for patients from 1 month of age. Ku et al, 2017 identified all infants exposed to enalapril in the first 120 days of life and discharged from 348 NICUs from 1997 to 2012. This author demonstrated in this study that from a cohort of 887,910 infants, there were 662 (0.07%) infants identified who were

exposed to enalapril during their initial hospitalization. Enalapril was used in 0.03% to 0.09% infants from 1997 to 2002 and in 0.07% to 0.10% infants from 2003 to 2012 – thus the use remained relatively constant. A total of 142 infants (21%) experienced the composite outcome of death (3), hypotension requiring pressors (25), hyperkalaemia (83), or elevated serum creatinine during exposure to enalapril (34). Infants <30 days postnatal age at first exposure were more likely to experience hyperkalaemia, elevated serum creatinine, and hypotension. Longer durations of exposure to enalapril were associated with increased odds of hyperkalaemia and death, but not elevated creatinine or hypotension. Approximately one in five infants exposed to enalapril experienced at least one AE during treatment, with hyperkalaemia being the most common AE. Among infants without congenital anomalies such as congenital heart disease, death during enalapril therapy was extremely rare (Ku et al 2017).

Elimination of enalapril and its active metabolite enalaprilat is primarily renal with reduced kidney function leading to increased exposures. This could potentially explain why infants age <30 days are at increased risk for other AEs (of which hypotension is the earliest and most often reported AE). In a study of enalapril and enalaprilat pharmacokinetics in 12 subjects age 10 days to 6.5 years with congestive heart failure, mean area under the curve values of active metabolite per enalapril dose normalized for body weight and body surface area were five-fold greater in the three subjects age <20 days compared to subjects >20 days old (Nakamura et al 1994). This suggests that infants <20 days old would require a significantly lower dose than their older counterparts. Hypotension, acute renal failure, decreased urine output, and azotaemia associated with use of enalapril have been reported in preterm and term infants (Ku et al 2017).

The applicant in their response stated that it is agreed that lack of data alone should not lead to a contraindication in accordance with the EMA SmPC Guideline. In line with the recommendations, sections 4.2 and 4.4 have been amended in the Product Information to state that: No data is available for treatment of paediatric subjects with liver impairment. Dose adjustment is not considered necessary however such children should only be treated with enalapril under strict monitoring. Treatment of children below the age of 1 month with hepatic impairment is not recommended. For children less than 30 days of age it is stated that treatment of infants < 30 days of age should only be conducted with rigorous monitoring, including blood pressure, serum potassium levels and renal function.

applicant has also agreed with the following indication: AQUMELDI is indicated for the treatment of heart failure in children from birth to less than 18 years.

2.6.7. Conclusions on the clinical efficacy

The CHMP considered all issues related to the assessment of efficacy of enalapril orodispersible tablets to be solved and that the product is approvable from the clinical efficacy point of view.

2.6.8. Clinical safety

Safety data were analysed from studies: WP07, WP08, WP09 and WP10.

Study WP07 safety results

Enalapril Orodispersible Minitablets (ODMTs) have been administered in a bioequivalence study in a total of 24 healthy adult male and female volunteers. The drug was well tolerated and no clinically

relevant differences in safety and tolerability were seen compared with currently approved solid oral dosage forms of enalapril.

Study WP08 safety results

This was a multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose PK bridging study with exploratory PD assessments in paediatric patients with Dilated Cardiomyopathy (DCM) requiring ACE inhibitor treatment. The study was initiated in 8 sites in The Netherlands, Austria, Hungary, UK, Germany and Serbia. Two groups of children (ACEI pre-treated and treatment-naïve children) with heart failure due to DCM were treated with enalapril Orodispersible Minitablets (ODMTs) over a period of 8 weeks with the maximum tolerated dose following a defined dose titration scheme.

Ross Score

Clinical symptoms measured using the Ross scoring system were low with 0 points with a range of 0 to 2 points at the entry into the study and did not change over time during the trial with 0 points and a range of 0 to 2 points at the end of the study.

Blood Pressure and Heart Rate

During the 8 weeks of therapy the mean values of blood pressure did not change over time. The same trend was observed for heart rate. Also, during the 8-h blood pressure and heart rate observation after ingestion of the first enalapril ODMTs at the Initial Dose Visit no changes were reported in blood pressure or heart rate in naïve or ACEI pre-treated patients.

Renal Safety Parameters

At various time points the numbers of creatinine values that were out of range varied from 6-19%. Higher than normal creatinine levels expected for patient age was found in only one patient. At inclusion, creatinine was less than 2xULN in all patients and remained stable throughout time although the level did not fall to normal values. Some patients had lower than expected creatinine levels, but this decrease was not consistently detected in the majority of patients at all study time points.

GFR was estimated by calculation of the CrCl out of serum creatinine levels according to the modified Schwartz formula. However, GFR was constant over time in the study.

Potassium levels were generally within normal range, although in 10 children potassium levels were increased above ULN at single time points. There were no cases where potassium was systematically increased at the majority of visits. In all but one case potassium levels were ≤ 5.5 mmol/L. In one case a potassium level of 5.8 mmol/L was found, and this resolved spontaneously. This child was on enalapril and carvedilol, but without diuretics (spironolactone). Kidney function in this child was normal as measured by serum creatinine and BUN.

In 7/32 children BUN levels were increased above the ULN at single time points. In three children BUN was increased in the majority of tests and ranged between 6-10 mmol/L. In all other cases the increase in BUN was incidental, while all other values were within normal range. In 12/32 cases BUN levels were low at one or more visits.

Microalbuminuria was reported as percentage (%) of children above the ULN. It was consistently reported in only one patient as of the first visit. As this patient prematurely left the study and was lost to follow-up, only limited data are available. Microalbuminuria was incidentally reported in three other cases, but at other visits microalbumin was within normal range.

Haematology Parameters

Haematology results (number of leucocytes, platelets, haematocrit and haemoglobin values), showed no systematic changes between the Screening and the End-of-Study Visits. In the majority of cases the deviation from normal was only mild without the need for any therapeutic intervention.

However, in one child haemoglobin dropped from 111 g/L at the Initial Dose Visit to 72 g/L at the End-of-Study Visit. Notably this child also suffered from recurrent airway infection.

Platelets were mildly increased in a number of patients, which is common in young children at times of mild (viral) infection. In one patient platelets were 64 at the first visit but had increased to the normal range at the last visit.

Finally, white blood cell count was slightly increased at the Initial Dose Visit in 3 cases and slightly decreased in one patient at the End-of-Study Visit. No relationship with the underlying disease or the use of drugs was suspected.

Adverse Events

The administered enalapril ODMT doses were well tolerated. Eleven (34.5%) patients did not experience any AEs during their study participation. Forty-two AEs occurred in 21 of the 32 (65.6%) patients enrolled into this study. Most frequently observed AEs were pyrexia in 4 patients (12.5%), nasopharyngitis and rash in 3 children each (9.4%).

Serious Adverse Events

One SAE (syncope due to hypotension in the context of a gastro-intestinal infection and hospitalisation for observational purposes), unrelated to IMP intake, was reported.

Deaths

No deaths occurred.

Rehospitalization

No rehospitalisation due to heart failure including the need for heart transplantation or the institution of mechanical circulatory support occurred.

Applicant's conclusion regarding safety issues in Study WP08

Blood pressure to renal safety, Ross Score, markers of the RAAS and Nt-proBNP did not show IMP related alterations in the studied patient population over the 8 week treatment period.

With only 2 (4.9%) IMP-related adverse events and 1 unrelated SAE that occurred in 21 of the 32 (65.5%) enrolled patients assessed in possible relationship with IMP administration, the individually adapted dosing of 0.25 mg and 1 mg enalapril ODMTs showed a very satisfactory safety profile.

Acceptability of administration of 1 to 10 ODMTs (0.25 mg and 1 mg) in patients aged between 1 month and 12 years was 100%. All assessments (100%) in children below 6 months and above 6 years revealed complete swallowability. In the age group of 6 months to 5 years complete swallowability was achieved in 84.7% of the assessments. Palatability of both dose strengths of enalapril ODMT was also rated positive or neutral in 97% of cases.

Study WP09 safety results

This study was a multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose pharmacokinetic bridging study with exploratory pharmacodynamic assessments in paediatric patients with congenital heart disease (CHD) requiring ACE inhibitor treatment. The study was initiated in 8 sites in The Netherlands, Austria, Hungary, UK, Germany and Serbia. Two groups of children (ACEI

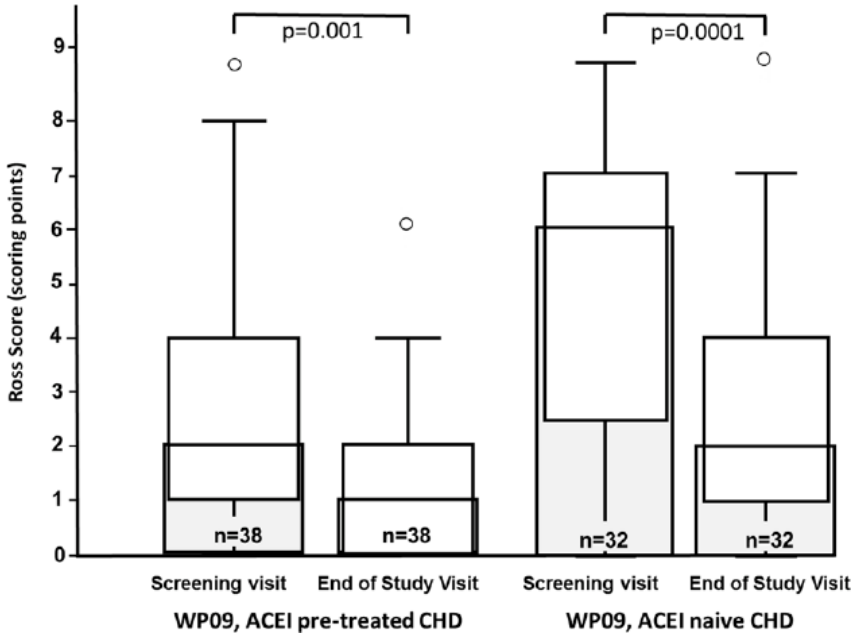
pre-treated and treatment-naïve children) with heart failure due to CHD were treated with enalapril ODMTs over a period of 8 weeks with the maximum tolerated dose following a defined dose titration scheme.

Safety Parameters

Ross Score

In 61 patients younger than 12 months of age the mean Ross Score value significantly decreased ($p<0.0001$) from 4.1 at the Screening Visit to 2.0, at the End-of-Study Visit. More than half of the patients (N= 32) aged up to 12 months were treated with enalapril ODMTs for the first time in addition to standard decongestive therapy. Eight patients out of 61 were successfully and safely up-titrated to the target dose defined by the protocol. All other patients (N= 38) were successfully and safely switched to an equivalent dose of enalapril ODMT. The Ross Score mean value significantly decreased in both, naïve and ACEI pre-treated children at the End-of- Study Visit, from 5.1 to 2,5, ($p<0.0001$); and from 2.7 to 1.2 ($p<0.001$) respectively (Figure).

Figure : Ross score in WP09 (grey boxplots and bars) patients naïve or pretreated with ACEI. Wilcoxon test $p<0.05$ indicate significant improvement in the Ross clinical symptom score of naïve and pretreated patients with heart failure due to congenital heart disease.



Blood Pressure and Heart Rate

During the 8 weeks of therapy the mean values of blood pressure did not change over time. The same trend was observed for heart rate. After ingestion of enalapril ODMTs no obvious changes were reported in blood pressure in naïve or ACEI pre-treated patients. The lowest blood pressure values, both systolic and diastolic, were noted three hours after enalapril ODMT intake. However, hypotension, an AE related to enalapril ODMT was recorded twice in one patient.

Renal Safety Parameters

The mean value for the renal safety parameter potassium did not change over the 8 weeks of therapy at any time points. However, hyperkalaemia was observed in two patients as an AE related to enalapril ODMT. Median values of urea/BUN did not vary between Screening and End-of-Study Visits and remained within reference range values. All serum creatinine values were lower than 2x ULN at any timepoint in the study. In four or less children per visit, microalbumin values were not within normal limits and belonged to the upper limit of normal (ULN).

Haematology Parameters

Haematology results (number of leucocytes, platelets, haematocrit and haemoglobin values), showed no systematic changes between the Screening and the End-of-Study Visit. In the majority of cases the deviation from normal was only mild without the need for any therapeutic intervention.

Lower haemoglobin values were noted in 16 cases at the Screening Visit, and in slightly larger number at the End-of-Study Visit; in 18 cases. The mean value of haemoglobin at the Screening Visit was 118.76 g/l, and a bit lower at the End-of-Study Visit, namely 114.73 g/l. No relationship with the the use of IMP was suspected.

Adverse events

The administered enalapril ODMT doses were well tolerated. Eighteen (25.7%) patients did not experience any AE during their study participation. In 52 of the 70 (74.3%) patients enrolled into this study 118 AEs occurred. Only 7 AEs (5.9%), were assessed as possibly, probably or certainly related with IMP intake. Eight (6.8%) AEs were of severe intensity, 32 (27.1%) AEs were of moderate intensity and 78 AEs (66.1%) of mild intensity. Most frequently observed AEs were cardiac operation (15 AEs,12.7%), pyrexia (14 AEs, 11.9%), and rhinitis (9 AEs, 7.6%). All other AEs described below occurred less frequently.

Serous adverse events (SAE)

Five SAEs without causal relationship with the IMP occurred; all but one (paresis right hemidiaphragma after cardiac surgery) resolved without sequela.

Deaths

No deaths occurred.

Applicant's conclusions regarding safety in WP9:

With 118 AEs (average 2.3 AEs/patient) in 52 of the 70 patients (74.3%) and the fact that only 6.5% of the AEs and none of the 5 SAEs had causal relationship with IMP administration, enalapril ODMTs of 0.25 mg and 1 mg administered in individually adapted doses between 0.125 mg and 4 mg demonstrated a satisfactory safety profile.

Acceptability of one to four enalapril ODMTs with a content of 0.25 mg and 1 mg enalapril reached a level of 100% in all age groups. Palatability of both dose strengths of enalapril ODMTs was also rated positive or neutral in 96.9% of cases.

Study WP10 - open long-term observation safety study

This was a Phase II/III prospective, open-label, safety follow-up study in infants and children enrolled in the trials 2015-602295-01 (WP08) and 2015-602295-02 (WP09) under stable optimal dose or no longer under enalapril ODMT treatment, with exploratory pharmacodynamic and pharmacokinetic assessments in children under IMP treatment.

Patients in the previous WP8 and WP9 trials were up-titrated under close clinical observation to an optimal dose and maintained this dose for the remaining duration of 2 months in these LENA trials. Patients who had completed this treatment period under enalapril ODMT treatment those who had received enalapril ODMTs for at least 3 days but had stopped, were invited to join the open long-term observation safety study “WP10” for an additional 10 months. Of the 102 patients enrolled in WP08 and WP09 trials 86 continued into the WP10 trial.

Primary endpoint

To demonstrate the safety of enalapril ODMTs.

The administered enalapril ODMT doses were well tolerated. Thirty-seven (43.02%) patients did not experience any adverse event during their study participation. In 49 of the 86 (56.98%) patients enrolled into this study 137 AEs occurred. Six of these events were classified as medical events as they occurred in 3 patients that were not or no longer under IMP (tonsillopharyngitis, 2 x prolonged mechanical ventilation in the same patient, vomiting and diarrhoea, running nose and neutropenia). Only 1 adverse event (0.76%) (intermittent dizziness and blurred vision when sitting or standing up) was rated possibly related with IMP intake by the investigator. All other 130 adverse events had no causal relationship with the intake of study medication. Eleven adverse events (8.40%) were of severe intensity, 57 AEs (43.51%) were of moderate intensity, but also 2 of the 6 medical events (33.33%) were of moderate intensity. 63 AEs (48.09%) were of mild intensity and 4 (66.66%) medical events were also classified as mild. Most frequently observed AEs were epistaxis (8 AEs in 1 patient), rhinitis (7 AEs in 5 patients), upper respiratory tract infections (7 AEs in 7 patients), and cardiac failure (7 AEs in 2 patients).

Eighty eight (67.18%) AEs occurred in patients who were below one year of age when they joined the previous WP08 or WP09 study.

Serious adverse events

Seven SAEs occurred in 7 patients and were assessed as being without causal relationship with IMP administration. Four Serious Medical Events occurred in 2 patients who were not or no longer under IMP when the Serious Medical Event occurred.

Deaths

No deaths occurred, and no rehospitalisation due to heart failure including the need for heart transplantation was reported.

Secondary Outcomes WP10 devoted to safety and tolerance of study drug

Acceptability and palatability of enalapril ODMTs.

Acceptability:

In total, 256 acceptability tests were performed: A total of 74 (28.9%) acceptability assessments were performed at the 1st Follow-up Visit, 136 (53.1%) assessments during the 2nd., 3rd., or 4th. Follow-up Visit and 46 (18.0%) assessments during the Close-out Visit. In total, 95 (37.1%) assessments were performed with the 1 mg enalapril ODMT, 148 (57.8%) assessments with the 0.25 mg enalapril ODMT. In 13 assessments both dose strengths were administered simultaneously. In 203 (79.3%) assessments complete swallowability was observed. In 53 (20.7%) observations children aged 2 months to 12 years only partially swallowed the ODMT or chewed on it. No other levels of acceptability were observed. As acceptability is a composite of the two observed criteria level, acceptability of administration of 1 to 10 ODMTs in patients between 2 months and 12 years was 100%.

Palatability

The percentage of children showing pleasant reactions at the 1st Follow-up Visit appeared to be higher in children older than 5 months with exception of “Taste” in the 6 to 12 years Age Group. All other patients showed “Neutral” reactions or rated the palatability as “good”. Only one older patient rated the size of the ODMTs as “Not sure”. In the course of the further Follow- up Visits and the Close-out Visit the rating of “pleasant” and “very good” dominated. The patients in Age Group 3 (6 to 12 years) were somewhat more critical than the observing investigators but overall, their assessment of the palatability of the enalapril ODMTs was also very satisfactory. There was no difference between the 1 mg and the 0.25 mg enalapril ODMTs because the percentage of their overall rating of “Pleasant”/“Neutral” and “Really good”/”Good”/”Not sure” versus “Unpleasant” and ”Bad” was comparable. The two ratings of “unpleasant reactions” occurred after administration of four and six 0.25 mg ODMTs respectively, the one rating “bad taste” after administration of four 1 mg enalapril ODMTs. Overall, a favourable or neutral palatability rating could be observed in more than 90% of the assessments and thus could be considered satisfactory in all age groups.

The applicant concluded that by reviewing the acceptability and palatability of enalapril minitablets, it was found that the majority of patients had a positive experience when taking the both the 0.25 mg and 1 mg enalapril ODMT.

Clinical Laboratory Evaluations

Renal function in paediatric patients under and after enalapril ODMT treatment

Renal function was assessed based on the measurements of several variables:

- Potassium levels: No significant difference in mean serum potassium levels between 1st Follow-up Visit and Close-out Visit were observed in any of the age groups.
- Blood urea nitrogen levels: blood urea nitrogen levels were significantly higher at the Close-out visit in the youngest age group compared to the start of the study. For all other age groups, no significant difference in mean blood urea nitrogen level existed between 1st Follow-up Visit and Close-out Visit.
- Creatinine levels: mean serum creatinine levels were similar at time of 1st Follow-up Visit and the Close-out Visit in all age groups.
- Microalbuminuria: no surprising results were seen in the presence of microalbuminuria as values were similar in all age groups at the time of 1st Follow-up Visit and the Close-out Visit.
- GFR values: mean and median GFR levels were comparable to reference GFR values corrected for age, indicating proper renal function in patients.

A similar percentage of patients had laboratory values below or above normal ranges at start compared to the end of the study, thus demonstrating excellent safety.

Clinical laboratory values were evaluated, including leucocyte levels, haematocrit, haemoglobin and thrombocyte levels. Both haematocrit as well as thrombocyte levels changed statistically significantly over the course of the study in the youngest age group. However, these changes are not clinically relevant and, in the case of haematocrit, can be partly explained by the effect of age on these parameters.

Vital Signs, Physical Findings, and Other Observations Related to Safety

- Blood pressure in paediatric patients under and after enalapril ODMT treatment.

Mean arterial pressure (MAP) was calculated based on measure systolic and diastolic blood pressure. MAP increased in every Age Group throughout the duration of the study except for children aged 6-12 months where it showed a minor decrease.

- General safety

General safety was assessed based on several variables:

  - ECG: No changes other than disease-related changes were detected, and no changes in clinical management resulted from the ECG analyses.
  - Shortening fraction (ECHO): mean and median values increased over the course of the study, an effect that can be attributed to age-related changes.
  - Ross score: mean and median Ross scores were slightly higher at the 1st Follow-up Visit compared to the Close-out Visit in Age Group 1a, 1b and 2, whereas in Age Group 1c and 3, mean and median Ross scores were somewhat higher at the end of study. However, these changes were very minor.

The following data has been submitted by the applicant regarding the use of enalapril maleate tablets:

System organ class	Very common **(≥1/10)**	Common **(≥1/100** to <1/10)	Uncommon **(≥1/1,000** to <1/100)	Rare **(≥1/10,000** to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Anaemia (including aplastic and haemolytic)	Neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytope-nia, agranulocytosis, bone marrow depression, pancytopenia, lymphadeno-pathy, autoimmune diseases		
Endocrine disorders						Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders			Hypogly-caemia			
Psychiatric disorders		Depression	Confusion, nervousness, insomnia	Dream abnormality, sleep disorders		
Nervous system disorders	Dizziness	Headache, syncope, taste alteration	Somnolence, paresthesia, vertigo			
Eye disorders	Blurred vision					
Ear and labyrinth disorders			Tinnitus			
Cardiac disorders		Chest pain, rhythm disturbances, angina pectoris, tachycardia	Palpitations, myocardial infarction or cerebro-vascular accident*, possibly secondary to excessive hypotension in high risk patients			
Vascular disorders		Hypotension (including orthostatic hypotension)	Flushing, orthostatic hypotension	Raynaud's phenomenon		
Respiratory, thoracic, and mediastinal disorders	Cough	Dyspnoea	Rhinorrhoea, sore throat and hoarseness, bronchospasm / asthma	Pulmonary infiltrates, rhinitis, allergic alveolitis/ eosinophilia pneumonia		
Gastrointestinal disorders	Nausea	Diarrhoea, abdominal pain	Ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia,	Stomatitis/ aphthous ulcerations, glossitis	Intestinal angioede-ma	

			gastric irritations, dry mouth, peptic ulcer			
Hepatobiliary disorders				Hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice)		
Skin and subcutaneous tissue disorders		Rash, hypersensitivity/ angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported	Diaphoresis, pruritus, urticaria, alopecia	Erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma		A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/ myositis, arthralgia/ arthritis, a positive ANA, elevated ESR, eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.
Musculoskeletal, connective tissue, and bone disorders			Muscle cramps			
Renal and urinary disorders			Renal dysfunction,	Oliguria		

			renal failure, proteinuria			
Reproductive system and breast disorders			Impotence	Gynaecomastia		
General disorders and administration site conditions	Asthenia	Fatigue	Malaise, fever			
Investigations		Hyperkalaemia, increases in serum creatinine	Increases in blood urea, hyponatraemia	Elevations of liver enzymes, elevations of serum bilirubin		

2.6.8.1. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.6.9. Discussion on clinical safety

This application relies in part on the results of pre-clinical tests and clinical trials for the reference product (Renitec®) enalapril maleate tablets which have been marketed for more than 20 years and in part on new clinical data. The reference product is indicated for use in heart failure in adults only. Safety data available from the reference product are summarized below:

Contraindications:

- Hypersensitivity to the active substance or to any of the excipients or any other ACE inhibitor
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy
- The concomitant use of enalapril maleate tablets with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)
- Combination with sacubitril/valsartan due to the increased risk of angioedema. Do not administer enalapril maleate tablets within 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor [SPC Renitec]

All four trials provided within IMA (WP07, WP08, WP09, WP10) were performed as part of an agreed Paediatric Investigation Plan (PIP) and hence all criteria were discussed and agreed upon by the EMA Paediatric Committee (PDCO).

Patients in the previous WP08 and WP09 trials that were included in study WP10 were up-titrated under close clinical observation to an optimal dose and maintained this dose for the remaining duration

of 2 months in these LENA trials. Patients who had completed this treatment period under enalapril ODMT treatment and those who had received enalapril ODMTs for at least 3 days but had stopped, were invited to join the open long-term observation safety study “WP10” for an additional 10 months. Of the 102 patients enrolled in WP08 and WP09 trials 86 continued into the WP10 trial. The primary objective of this trial was to demonstrate the safety of enalapril ODMTs. Safety observations made in the reporting period showed that the IMPs were very well tolerated. The one adverse event that was considered as having a possible causality was mild (hypotensive reaction to enalapril). No drug-related SAEs and thus no SUSARs occurred. Also, no death occurred. Other safety parameters comprised blood pressure, renal monitoring, Ross score, Echocardiography, ECG and safety laboratory tests. Mean arterial pressure slightly increased in every Age Group throughout the duration of the study except for children between the ages of 6 and 12 months where a minor decrease was seen. Statistically significant differences between start and end of the study were observed in serum levels of BUN and creatinine in the youngest age group. However, these were minor and considered as not clinically relevant. Other secondary safety parameters did not show a statistically significant difference in mean levels at the start compared to the end of study visit in any age group and thus, this did not lead to concerns regarding the safety of enalapril ODMTs.

Also, the analysis of general safety parameters, including shortening fraction, Ross score and physical examination did not reveal any alarming or surprising results. Lastly, clinical laboratory values were evaluated, including leucocyte levels, haematocrit, haemoglobin and thrombocyte levels. Both haematocrit as well as thrombocyte levels changed statistically significantly over the course of the study in the youngest age group. However, these changes are not clinically relevant and, in the case of haematocrit, can be partly explained by the effect of age on these parameters.

The secondary objectives of this trial were to describe the acceptability and palatability of enalapril ODMTs, as well as to collect additional information about pharmacokinetics and pharmacodynamics of enalapril ODMTs during long term treatment.

Enalapril and enalaprilat were measured at each of the five study visits under IMP administration. The number of samples decreased from initially 80 to 31 until the end of the study as patients with congenital heart disease stopped IMP administration after surgery during the trial, or improved and therefore stopped medication. The mean weight and dose normalized concentrations were between 13.0 and 48.0 [ng/mL/mg*kg] for enalapril and 81.2 and 105.7 [ng/mL/mg*kg] for enalaprilat. Several concentrations for enalapril had “0” values. Enalapril has a short half-life of 2 to 4 hours. Since the samples were taken at the end of the dosing interval before the next dose was taken, enalapril concentrations could have been below the limit of quantification in several samples. Enalaprilat, however, has a longer half-life of 8 to 12 hours. The measured concentrations of “0” for enalaprilat indicate potential adherence problems to their medication during the follow up study.

Since children had already been treated with enalapril ODMT before the beginning of the trial, IMP related changes could not be investigated in WP10. Renin, plasma renin activity, angiotensin I and aldosterone concentrations decreased over time. At the beginning of the trial, renin, plasma renin activity, angiotensin I and aldosterone values were to 1095 pg/mL, 60.4 ng/mL/h , 3.2 ng/mL and 363.9 pg/mL respectively, and at the end of the trial values were 285.9 pg/mL, 20.6 ng/mL/h 1.4 ng/mL and 184.5 pg/mL respectively. As it is known that the investigated RAAS parameters decrease in concentrations throughout the first years of life, this might explain the observed decrease in concentrations in the investigated patient population and thus has demonstrated the likely maturation of the RAAS system.

By reviewing the acceptability and palatability of enalapril minitablets, it was found that the majority of patients had a positive experience when taking the both the 0.25 mg and 1 mg enalapril ODMT.

The proposed earlier contraindication for “Paediatric patients with pre-existing liver abnormalities” or “Children < 1 month of age with liver abnormalities” was not considered appropriate since lack of data alone should not lead to a contraindication. Taking also into consideration both that “liver abnormalities” represent a very broad array of clinical conditions, it was agreed to introduce a warning statement in sections 4.2 and 4.4 that no data are available for children with pre-existing liver conditions, that children (any age) with hepatic impairment should only be treated with enalapril under very strict monitoring and that treatment of children below the age of 1 month is not recommended.

The very low initial dose used did not produce in the submitted trials any hepatobiliary disorders, which could be also due to the very low number of neonates with AE reported in the trials. Despite this, the applicant has introduced a contraindication that lowers the risk of developing hepatobiliary disorders (group of patients excluded “Paediatric patients with pre-existing liver abnormalities”) in neonates with circulatory failure. This is important since structured recommendations on the management of liver dysfunction in patients with congenital heart disease (CHD) are scarce. Several factors can contribute to causing liver dysfunction in patients with CHD. The cause for liver impairment can be the result from a wide spectrum of various different causes, including liver congestion, hypoxemia or low cardiac output. Liver congestion from backward failure of the heart is a frequent phenomenon that can result in the development of cardiac fibrosis and cirrhosis. Not only venous congestion itself is responsible for hemodynamic related liver dysfunction in CHD, as oxygen supply can be affected by multiple factors in CHD such as low cardiac output, cyanosis or impaired oxygenation because of lung problems related to CHD. Impaired lung function is observed frequently as non-cardiac problem in CHD. The impaired oxygen supply becomes particularly relevant when sinusoidal pressure is already elevated due to venous congestion. This in turn reduces portal inflow and makes the liver more susceptible to ischemic alterations due to a reduced flow of the hepatic artery such as in ischemic hepatitis. Chronic hepatic ischemia (resulting from cardiac insufficiency) is a known factor for the development of liver fibrosis. Hemodynamic pathophysiology of CHD related liver disease should be seen in the context of both forward and backward cardiac failure. Liver diseases in CHD do not only occur in the context of hemodynamic alterations (this is especially true in the adult population).

Pathophysiologically, liver changes occur in a wide variety of CHDs, and the mechanisms are different, but reported in literature.

Concluding, no important risks were associated with enalapril ODMT administration in paediatric patients from one month to 12 years of age. The scarcity of subjects <30 days in clinical studies (n=4) is reflected in SmPC sections 4.4 and 5.1.

2.6.10. Conclusions on the clinical safety

Based on the presented bioequivalence study(ies)against the reference product, Renitec®, which demonstrated bioequivalence between the 1 mg strength, and taking in to account the availability of in vivo data for the 0.25 mg strength from paediatric clinical studies WP08 and WP09, these in vivo data were considered to be sufficient to support the approval of the 0.25 mg strength without the need for further data.

In addition, the proposed indication, i.e. treatment of heart failure in children from birth to 18 years, is based on an extrapolation approach with PK bridging, targeting the equivalent systemic exposure to that achieved during the treatment of adults.

However, considering that the indication also covers pre-term and term neonates the applicant was asked and adequately justified during the procedure, that the extrapolation approach is adequate also for this age group (neonates) considering potential differences in PK/PD relationship and safety compared to adults. In addition, the applicant demonstrated that the available PK data are sufficient to

establish the bridge between adults and the youngest children. The reassurance was provided also taking into account not only the target/maintenance dose but the initial dose that can go as low as 0.01 mg/kg/day.

The applicant was asked to consider the use of enalapril in the treatment of neonates further justifying (presenting efficacy/safety data and adequacy of extrapolation of all data to neonates) in particular based on the findings published by Ku et al. (Pediatr Cardiol. 2017 Jan; 38(1): 155–161), which demonstrated severe adverse effects of enalapril particularly in infants <30 days of age.

This is mainly due to the fact that many cases of nephrotoxic effects of RAAS inhibitors (acute renal failure, renal tubular dysplasia) have been reported in foetuses and newborns exposed to RAAS inhibitors during the second and third trimesters of pregnancy in humans. Ku et al. (2017) examined the safety of enalapril in young infants and found that treatment in the first 30 days of life led to severe adverse effects (death, hyperkalaemia, elevated serum creatinine and hypotension) in up to 20 % of infants. The mechanisms involved in ACE inhibitor-induced acute renal failure are reduced renal blood flow and increased renal vascular resistance with decreased glomerular filtration rate at birth in combination with hypotension and decreased renal elimination of enalapril rendering young infants particularly sensitive to ACE inhibitor-induced renal failure.

The European Medicines Agency Expert Group Meeting on Paediatric Heart Failure considered enalapril a first-line treatment for chronic heart failure in children. The literature regarding this is heterogenous in outcome and studied population. However, it can be agreed that the expected effect of ACEi is similar in adults and children and therefore, extrapolation from adults to children of all ages based on PK data targeting a similar exposure in paediatric patients as in adults could be acceptable.

The applicant has performed a Population PK (popPK) model including allometric exponents and maturation functions for the relevant PK parameters of enalaprilat. Predictions were made covering all paediatric age groups from neonates to adolescents and compared with adult exposure margins at the starting dose as well as the maintenance dose of enalapril. The PK data from studies WP08 and WP09 has been used in this analysis to establish a bridge between adults and the youngest children focusing on exposure. Population modelling of the PK of enalaprilat was performed based on the final covariate model described in the LENA project (“run051”) and using the NONMEM® datastream as reported. The paediatric PK parameters for a 1st order absorption 1-compartment PK model were estimated by applying allometric scales on the clearance (CL) and volume of distribution (V).

Throughout the simulation process, the full compounded population variability was extracted from both the parameter and weight distributions at each age group. The allometric scales were applied for the proposed age, but weights for allometric scaling were extracted from the corresponding age dependent distributions from typical Age-Weight listings (CDC 2000). Weight distributions were constructed using the reported 95th quantile and these distributions were sampled together with the random effects for CL and V2.

In order to increase resolution, a dense simulation grid was built with 69 time points for each of the age – dose levels. The full PK cycles, Day 1 and Day 11, had 19 time points each.

The PK exposures were evaluated across fourteen age levels at 1 day, 28 days then 4-year-old (yo), 12 yo and adult (20 yo). Additionally, the dose of 0.01 mg/kg/day was simulated as adjusted only by the paediatric weight (3.5 kg) for the 1-day-old neonate.

As far as the PK aspects of this response are concerned, the methods employed are adequate and the results consistent with the original data.

The applicant in their response provided data that allowed to state that final covariate model described in the LENA project (“run051”) has been used to perform population modelling of the PK of enalaprilat.

It was shown that administration of enalapril ODMT to children from birth to adolescents provides overall exposures matching those expected in adults taking into account both the target/maintenance dose and the initial dose (as low as 0.01 mg/kg/day).

It was agreed that the pathophysiological process leading to heart failure in DCM in children is considered to be similar to that in adults. Hence, based on PK and safety data, extrapolation from adults to neonates can be justified.

The applicant has presented a PK/PD justification on the extrapolation approach from birth to indicate the administration of the drug product should not be excluded in neonates <1 month. The extrapolated exposure, along with the limited data generated in the population <1 month on PD endpoints and safety, demonstrate acceptable exposure margins and support the use of the Aqumeldi from birth.

As far as the PK aspects of this response are concerned, the methods employed are adequate and the results consistent with the original data.

The referred to study (Ku et al 2017) has shown that from a cohort of 887,910 infants, we identified 662 (0.07%) infants who were exposed to enalapril during their initial hospitalization. Enalapril was used in 0.03% to 0.09% infants from 1997 to 2002 and in 0.07% to 0.10% infants from 2003 to 2012 – thus the use remained relatively constant. A total of 142 infants (21%) experienced the composite outcome of death (3), hypotension requiring pressors (25), hyperkalaemia (83), or elevated serum creatinine during exposure to enalapril (34). Infants <30 days postnatal age at first exposure were more likely to experience hyperkalaemia, elevated serum creatinine, and hypotension. Longer durations of exposure to enalapril were associated with increased odds of hyperkalaemia and death, but not elevated creatinine or hypotension. Approximately one in five infants exposed to enalapril experienced at least one AE during treatment, with hyperkalaemia being the most common AE. Among infants without congenital anomalies such as congenital heart disease, death during enalapril therapy was extremely rare (Ku et al 2017).

Elimination of enalapril and its active metabolite enalaprilat is primarily renal, reduced kidney function leading to increased exposure could potentially explain why infants age <30 days are at increased risk for other AEs (of which hypotension is the earliest and most often reported AE). In a study of enalapril and enalaprilat pharmacokinetics in 12 subjects aged 10 days to 6.5 years with congestive heart failure, mean area under the curve values of active metabolite per enalapril dose normalized for body weight and body surface area were five-fold greater in the three subjects age <20 days compared to subjects >20 days old (Nakamura et al 1994). This suggests that infants <20 days old would require a significantly lower dose than their older counterparts. Hypotension, acute renal failure, decreased urine output, and azotaemia associated with use of enalapril have been reported in preterm and term infants (Ku et al 2017).

The CHMP considered that the initially applied therapeutic indication: “AQUMELDI is indicated for the treatment of heart failure in children from birth to less than 18 years.’’ is approvable from the clinical safety perspective.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant identified the following safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns (version 1.0, sign-off date 13-Sep-2023)

Summary of safety concerns	
a) Important identified risks	• Hyperkalaemia • Symptomatic hypotension, particularly following the first dose
b) Important potential risks	• None
c) Missing information	• Children with hepatic impairment • Safety in paediatric patients < 1 month of age

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities are proposed.

2.7.3. Risk minimisation measures

None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

Currently, the PSUR frequency for enalapril is five years with DLP for the next PSUR 23-03-31. A five-year PSUR cycle for Aqumeldi, being the first ACE inhibitor indicated from birth, is considered too long. On the other hand, enalapril is a very well established and common substance used in large number of medical products. To increase the PSUR frequency for all enalapril containing products would therefore be unnecessary.

Based on this reasoning, a separate entry in the EURD list for enalapril (centrally authorised product for use in children below the age of 18) is needed, as it cannot follow the already existing entry for enalapril maleate.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

To facilitate a potential alignment in the future of the “paediatric” enalapril PSUR with the overall enalapril PSUR, it is proposed that the same DLP (i.e., XX-03-31) should be used in the EURD.

The new EURD entry to be created will be named “Enalapril (centrally authorised product for use in children below the age of 18)”.

The applicant for Aqumeldi agrees to align their DLP for DD/MM with the one existing for the enalapril 5 PSUR frequency. The new EURD entry for Enalapril (centrally authorised product for use in children below the age of 18) will therefore have a DLP of 31/03/XX and a 1 year PSUR frequency while the existing enalapril entry will remain with the DLP of 31/03/23, next DLP of 31/03/2028 and a 5 y PSUR frequency.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This is a Paediatric Use Marketing Authorisation (PUMA) Application for Aqumeldi 0.25 mg oro-dispersible tablets. The agreed therapeutic indication is: Aqumeldi is indicated for the treatment of heart failure in children from birth to less than 18 years.

Paediatric heart failure (PHF) represents an important cause of morbidity and mortality in childhood. Etiology and pathogenesis are different between adults and children: the first mainly relates to ischemia, the latter is a consequence of congenital heart diseases (CHDs) or cardiomyopathies in most cases.

More than 50% of paediatric patients have heart failure due to CHD, with this aetiology being disproportionately high in the first year of life. It is associated with ventricular dysfunction, volume or pressure overload. Heart failure in paediatric patients with CHD has various aetiologies and the risk of ventricular dysfunction depends on the specific type of malformation.

3.1.2. Available therapies and unmet medical need

Currently, there are well-established guidelines for the management of heart failure in the adult population. Due to the lack of research trials in children, the clinical guidelines for the treatment of PHF

have historically been reliant on expert consensus, and the extrapolation of data from trials performed in adults.

In the clinical setting, diuretics and angiotensin-converting enzyme inhibitors (ACE-I) are used, with beta-blockers and devices for electric therapy as other options. In the end-stage disease, heart transplantation is the best choice of treatment, while a left ventricular assist device can be used as a bridge to transplantation (due to the difficulties in finding organ donors), recovery (in the case of myocarditis), or destination therapy (for patients with systemic disease). In adults, enalapril is licensed for the treatment of hypertension and heart failure (HF), as well as for reducing proteinuria in chronic kidney disease (CKD). The SmPC for Renitec reference medicinal product states that there is only limited experience of the use of enalapril in hypertensive paediatric patients older than 6 years of age. The mechanism of action of enalapril and its potential pharmacodynamic interactions are believed to be similar in adults and paediatric patients.

The importance of pharmacological treatment in PHF, especially dilated cardiomyopathies (DCM), is emphasized by the low availability of donor hearts. Owing to this scarcity, mortality within the first year of presentation remains extremely high, highlighting the need for optimal treatment in children to prevent or postpone transplantation. In children, whilst in clinical practice enalapril is used for similar indications as adults, in the European Union (EU) it is only recommended for use in children with hypertension and a body weight over 20 kg. In children with HF the doses of enalapril used off-label are based on empirical evidence combined with data extrapolated from adult studies. A further challenge regarding dosing of ACE-I in paediatrics is the lack of authorised age-appropriate formulations licensed for use in PHF throughout EU.

Therefore, there is an unmet medical need for a licensed medicinal product for children with HF that could be administered with age-appropriate formulations.

This application concerns a hybrid version of Aqumeldi 0.25 mg oro-dispersible tablets.

3.1.3. Main clinical studies

This application relies in part on the results of pre-clinical tests and clinical trials for the reference product (RENITEC®) enalapril maleate tablets and in part on new clinical data.

The new clinical data were generated within a EU 7th Framework Program where the LENA project was conducted (“Labeling of Enalapril from Neonates up to Adolescents”, LENA).

The LENA project generated core scientific data from four clinical trials WP07, WP08, WP09 and WP10. With respect to clinical trials, WP02 developed the Enalapril Orodispersible Mini-Tablets (ODMTs) of 1 mg and 0.25 mg strengths. WP07 generated clinical data for Enalapril ODMTs in healthy adult volunteers. WP08, WP09 and WP10 generated clinical data for Enalapril ODMTs in children with HF.

WP07: Relative Bioavailability of Enalapril Administered as Orodispersible Mini-Tablets in 24 healthy adult volunteers. This was an open label, single dose randomized 3-way crossover, 3-treatment, 3-period study in 24 healthy male and female subjects, each administered a 10 mg enalapril dose on 3 occasions, at least one week apart. The primary objective of this study was to assess the relative bioavailability of a single 10 mg dose of enalapril administered as ten (10) times 1.0 mg ODMTs taken with water and dispersed in the oral cavity versus an authorized standard enalapril tablet formulation (reference product: Renitec® 2 x 5 mg tablets, MSD Belgium) taken with water. Secondary endpoints were general safety and tolerability including local tolerability and palatability of enalapril administered as ODMT.

WP08: This was a multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose pharmacokinetic (PK) bridging study with exploratory pharmacodynamic (PD) assessments in paediatric patients with dilated cardiomyopathy (DCM) requiring ACE inhibitor treatment. Two groups of children (ACEI pre-treated and treatment naïve children) with HF due to DCM were treated with enalapril ODMTs over a period of 8 weeks with the maximum tolerated dose following a defined dose titration scheme.

WP09: This was a multi-centre, multi-national Phase II/III prospective, open-label, single and multiple dose PK bridging study with exploratory PD assessments in paediatric patients with Congenital Heart Disease (CHD) requiring ACE inhibitor treatment. Two groups of children (ACEI pre-treated and treatment-naïve children) with HF due to CHD were treated with enalapril ODMTs over a period of 8 weeks with the maximum tolerated dose following a defined dose titration scheme.

The primary objective of Studies WP08 and WP09 was to obtain paediatric PK data of enalapril and its active metabolite enalaprilat in paediatric patients treated with enalapril ODMTs. This data described the dose exposure in the paediatric population with HF due to DCM and CHD. The studies were conducted using both strengths (1mg and 0.25mg) of the ODMTs. The primary endpoint, bioavailability of enalapril and enalaprilat in children (0 month - <12 years) (AUC from 0 to time of last sampling point, Cmax and tmax), was investigated using descriptive pharmacokinetics.

The secondary endpoint was the bioavailability of enalapril and its active metabolite enalaprilat in the different age subsets. To determine it the dose and weight normalized AUCtau, Cmax,ss and tmax,ss of enalapril and enalaprilat were compared between the age subsets:

- WP08 (age group 1, 1 to <12 months, age group 2, 12 months to <6 years and age group 3, 6 years to >12 years);

- WP09 (age group 1; 0 to <12 months, age group 2; 12 months to <6 years).

Based on this, the relative bioavailability of the ODMTs as comparison drug exposure (AUC) and rate and extend of absorption (Cmax and tmax) within the given age cohorts of paediatric patients were calculated. In addition, weight and dose normalized AUCtau,ss, Cmax, ss and tmax, ss) were compared between the different age subsets using statistical testing for two group comparison (t-test(x~y) for two samples).

In addition to the non-compartmental analysis of the full PK profiles, population PK modelling was performed on collected PK and PD data from the start to the end of the studies.

WP10: This was a multi-centre, multi-national Phase II/III prospective, open-label, safety follow up study in infants and children enrolled in the trials WP08 and WP09. The duration of treatment was up to 10 months. The primary objective of this study were safety issues. The secondary objectives were to describe the acceptability and palatability of enalapril ODMTs and to collect additional information about pharmacokinetics and pharmacodynamics of enalapril ODMTs during long term treatment.

3.2. Favourable effects

Enalapril owes its activity to enalaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 4 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Enalapril is given orally as the maleate.

Enalaprilat is not absorbed orally but is given by intravenous injection; its haemodynamic effects develop within 15 minutes of injection and reach a peak in 1 to 4 hours. The action lasts for about 6

hours at recommended doses. Enalaprilat is given as the dihydrate, but doses are expressed in terms of the anhydrous substance. Enalaprilat 1.38 mg as the dihydrate is equivalent to about 1.25 mg of anhydrous enalaprilat.

In the management of HF, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus, treatment should begin with a low dose under close medical supervision. In patients with HF or asymptomatic left ventricular dysfunction enalapril maleate is given orally in an initial dose of 2.5 mg daily. The usual maintenance dose is 20 mg daily as a single dose or in 2 divided doses although up to 40 mg daily in 2 divided doses has been given.

In the UK, recommended oral doses of enalapril maleate for hypertension are given according to weight as follows:

- 20 kg to < 50 kg: initial dose of 2.5 mg once daily, increased if necessary to a maximum of 20 mg once daily
- ≥ 50 kg: initial dose of 5 mg once daily, increased if necessary to a maximum of 40 mg once daily

In the USA, an initial dose of 80 micrograms/kg (maximum of 5 mg) once daily is recommended.

The British National Formulary for Children (BNFC) suggests the following doses, which may be given to neonates and children in the treatment of hypertension, heart failure, or proteinuria in nephritis:

- neonate: initial dose of 10 micrograms/kg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased if necessary to a maximum of 500 micrograms/kg daily in 1 to 3 divided doses
- 1 month to 11 years: initial dose of 100 micrograms/kg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased if necessary to a maximum of 1 mg/kg daily in 1 or 2 divided doses
- 12 to 17 years: initial dose of 2.5 mg once daily with careful monitoring of blood pressure for 1 to 2 hours after the first dose, increased to a usual maintenance dose of 10 to 20 mg daily in 1 or 2 divided doses. Those weighing 50 kg and over may be given up to 40 mg daily in 1 or 2 divided doses

The bioavailability of enalapril is approximately 60%. T_{max} for enalapril is 1 hour after oral administration and for enalaprilat metabolite (active) it is 3 to 4.8 hours in adults, whereas in children and infants it is 3 – 6 hours. With regards to the impact of food with orally administered tablets, no effect on PK parameters were demonstrated, whereas on enalapril suspension, the effect of food C_{max} decreased by 46%, T_{max} delayed by 20 minutes with a high-fat meal; Enalaprilat metabolite (active), C_{max} decreased by 36%, T_{max} delayed by 62 minutes, AUC reduced by 23% with a high-fat meal.

In adults, enalapril is a drug with well-established medical use and proven efficacy for the treatment of CHF and hypertension as well as for prevention of symptomatic HF in patients with EF below 35%.

Scientific literature, submitted by the applicant in support of this hybrid application, shows that enalapril is considered a standard pharmacological therapy for PHF which is based on studies in adults with HF. Fourteen studies in the public domain report on the efficacy of enalapril in children with HF; two of these studies were double-blind placebo-controlled randomised trials (RCT's). These two RCTs comparing enalapril to placebo were conducted in PHF patients with single ventricle physiology [Hsu et al (2010) and Smeets et al (2020)]. These children have a special haemodynamic situation, and the clinical effects of enalapril might not be comparable to other forms of HF.

To date studies reporting paediatric PK data are: 1) study in 40 hypertensive children aged 2 months to 16 years [Wells 2001] and 2) study in 22 patients with CHF [Lloyd 1989; Nakamura 1994]. Only 3 patients were neonates, 17 were infants below 1 year of age, and 2 were children between 2.8 and 6.5 years. Therefore, reliable PK data of enalapril to delineate a dosing regimen for paediatric patients with HF are not available from current literature data.

A clinical program (LENA project) was therefore undertaken to generate appropriate PK data in the paediatric population to allow bridging to adult data to demonstrate efficacy of enalapril in congestive heart failure.

The newly developed mini-tablets disintegrate immediately upon contact with water or saliva. The objectives of the paediatric trials were achieved. Where paediatric pharmacokinetic data of enalapril and its active metabolite enalaprilat were obtained for the enalapril ODMT and a dose exposure in the paediatric population with HF due to DCM and CHD. The comparisons of the bioavailability for enalapril and enalaprilat between age groups indicated a lower rate and extent of exposure of the enalapril ODMT in infants compared to older children when assessed globally.

WP07: The results indicated that the 10 x 1 mg ODMT formulation when swallowed fell within the bioequivalence criteria limits when compared to 2 x 5 mg Renitec® tablets. Following dispersion in the mouth, a slightly higher Cmax for enalapril was observed as compared to the reference formulation. However, the rate and extent of exposure of the active metabolite enalaprilat were within the criteria limits for bioequivalence. Finally, it was demonstrated that the method of administration of the ODMT, swallowed or dispersed, did not significantly affect the bioavailability of enalapril.

WP08:

Primary endpoint: paediatric PK data of enalapril and its active metabolite enalaprilat in patients treated with enalapril ODMTs were obtained and a dose exposure in the paediatric population with DCM was described.

Dose and weight normalized exposure for enalapril was 496 ng/mL*h/mg*kg and that for enalaprilat was 1327 ng/mL*h/mg*kg with a high coefficient of variation of 46% and 62% respectively. Dose and weight normalised maximum plasma concentrations were 203 ng/mL/mg*kg for enalapril and 155 ng/mL/mg*kg for enalaprilat. They also had high coefficients of variation of 73% for enalapril and 61% respectively. Maximum plasma concentrations were achieved expectedly about 3 hours earlier for enalapril with 1.7 hours after dosing compared to the active metabolite enalaprilat with 4.6 hours after ODMT dosing.

The non-compartmental descriptive PK results presented are in line with the objectives of the study. Extent and rate of absorption for the comparison between ACEI pre-treated and naïve patients are quite similar in the case of enalapril but not in the case of enalaprilat.

Secondary endpoint: A comparison between age groups with respect to rate and extent of exposure show lower values in infants with CHD. This result have implications on the dose recommendations according to age groups which are ascertained on the basis of the population pharmacokinetics analysis.

Exploratory pharmacodynamics for brain natriuretic peptides (Nt-proBNP), shortening fraction and RAAS associated with enalapril ODMTs in children with HF were also studied. In children with DCM, Nt-proBNP median values (range) did not change from 32 (5 to 1 777) pmol/L at the start to 35 (3 to 1 302) pmol/L (p=ns) at the end of the study. Only 10% of patients in this cohort were ACEi naïve.

In patients with DCM, echocardiography (shortening fraction) mean values (±SD) slightly, but significantly increased in all patients from 22.3% (SD 7.3)% to 25.1% ±(SD 7.8)% ($p < 0.05$, t-test) reflecting an improvement of the cardiac conditions of the patients in all age groups.

WP09:

Primary endpoint: paediatric PK data of enalapril and its active metabolite enalaprilat in patients treated with enalapril ODMTs were obtained and a dose exposure in the paediatric population with CHD was described.

AUCss,norm and Cmax,ss,norm point estimates were similar for enalapril for the pre-treated and the naïve patient group (950 and 711 ng/mL*h/mg*kg; 283 versus 269 ng/mL/mg*kg). The point estimates were similar and in the same range for enalaprilat (1409 versus 1401 ng/mL*h/mg*kg; 203 versus 157 ng/mL/mg*kg). This indicates that enalapril PK in this patient cohort is dose proportional and that naïve and pre-treated patients can be jointly analysed.

The non-compartmental descriptive PK results presented are in line with the objectives of the study. Extent and rate of absorption for the comparison between ACEI pre-treated and naïve patients are quite similar in the case of enalapril but not in the case of enalaprilat for Cmax.

Secondary endpoint: The bioavailability of enalaprilat between both age groups for children with CHD did not show substantial differences in the rate and extent of exposure between them. No difference could be found for the active metabolite enalaprilat.

In children with CHD, Nt-proBNP levels were lower at the end of the study compared to the beginning. The median Nt-proBNP value at the start of the study were 171 (1 to 2 789) pmol/L and 73 (5 to 2 165) pmol/l (p=ns) at the end. In this cohort 44% of patients were naïve to ACEi treatment.

In patients with CHD, shortening fraction remained almost the same during the study period. Mean values (±SD) at the screening and end of study visits were 38.7% (SD 8.6) and 38.5% (SD 6.2) respectively.

3.3. Uncertainties and limitations about favourable effects

- Biowaiver: The clinical program includes a bioequivalence study (WP07) between the enalapril ODMT administration and the marketed immediate release tablets. This bioequivalence study was conducted with the highest strength (1 mg ODMT) and confirmed equivalent pharmacokinetics to the reference product (Renitec® 5 mg tablets). A bioavailability study for the enalapril ODMT 0.25mg in adults was not required as part of the PIP as it was considered that a biowaiver would suffice. The applicant proposed a BCS-based biowaiver that would cover the enalapril ODMT 0.25mg strength since a biowaiver for additional strength (the 0.25mg strength), based on the bioequivalence established for the 1.0 mg strength, was not agreed upon. For an additional strength biowaiver, the application contained information that did not meet the requirements of the *Guideline on the investigation of bioequivalence (BE) (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)*, with respect to the proportionality of the ratio of excipients amounts to the active, different manufacturing processes for the two strengths, and pharmacokinetic linearity not being demonstrated. In their BCS-based biowaiver request, the applicant stated that enalapril is a BCS class III drug substance. However, according to ICH M9 Guideline, for BCS Class III drugs, all of the excipients should be qualitatively the same and quantitatively similar. Therefore, the completely different excipient composition between the applicant's formulation and the reference precludes a BCS-based approach to be successful. Also, BCS biowaiver requires the same strength for test and reference products which was not met. However, the CHMP considered the results of both clinical studies, W08 and W09, were conducted using both the 1 mg and the 0.25 mg strengths, where the availability of *in vivo* data for the 0.25 mg strength was considered to be sufficient to support the approval of the 0.25 mg strength without the need for further *in vivo* data.

• Proposed therapeutic indication (paediatric patients from birth). There were uncertainties with respect to posology (and safety) in children < 30 days of age. The full popPK analysis report, including diagnostic plots was provided as well as additional scientific justifications regarding PK/PD for the extrapolation approach to indicate the administration of the drug product to children from birth. In the submitted responses the applicant produced data that allowed to state that the final covariate model described in the LENA project ("run051") has been used to perform population modelling of the PK of enalaprilat. It was shown that administration of enalapril ODMT to children from birth to adolescents provides overall exposures matching those expected in adults taking into account both the target/maintenance dose and the initial dose (as low as 0.01 mg/kg/day).

Thus, uncertainties and limitations that initially appeared were considered resolved.

3.4. Unfavourable effects

In total 86 children with HF received enalapril ODMT for up to 1 year in clinical studies with Aqumeldi. As such the data are considered limited. Data on the use of Aqumeldi in children below 1 month of age in the clinical studies is scarce (n=4) and this information was included in the product information.

WP08:

In study WP08 no adverse events (AE) were reported in 11 patients (34,5%). Altogether 42 AE were reported in 21 of the 32 children included in the study (65,5%). Most frequently observed AEs were pyrexia in 4 patients (12.5%), nasopharyngitis and rash in 3 children each (9.4%).

WP09:

In study WP09 no AE were reported in 18 (25,7%) patients. In 52 of the 70 (74.3%) patients enrolled into this study 118 AEs occurred. Only 7 AEs (5.9%), were assessed as possibly, probably or certainly related with investigational medicinal product (IMP) intake. Eight (6.8%) AEs were of severe intensity, 32 (27.1%) AEs were of moderate intensity and 78 AEs (66.1%) of mild intensity. Most frequently observed AEs were cardiac operation (15 AEs,12.7%), pyrexia (14 AEs, 11.9%), and rhinitis (9 AEs, 7.6%).

WP10:

Of the 102 patients enrolled in WP08 and WP09 trials 86 continued into the WP10 trial. The primary objective of WP10 trial was to demonstrate the safety of enalapril ODMTs.

The administered enalapril ODMT doses were well tolerated. Thirty-seven (43.02%) patients did not experience any adverse event during their study participation. In 49 of the 86 (56.98%) patients enrolled into this study 137 AEs occurred. Six of these events were classified as medical events as they occurred in 3 patients that were not or no longer under IMP (tonsillopharyngitis, 2 x prolonged mechanical ventilation in the same patient, vomiting and diarrhoea, running nose and neutropenia). Only 1 adverse event (0.76%) (intermittent dizziness and blurred vision when sitting or standing up) was rated possibly related with IMP intake by the investigator. All other 130 adverse events had no causal relationship with the intake of study medication. Eleven adverse events (8.40%) were of severe intensity, 57 AEs (43.51%) were of moderate intensity, but also 2 of the 6 medical events (33.33%) were of moderate intensity. 63 AEs (48.09%) were of mild intensity and 4 (66.66%) medical events were also classified as mild. Most frequently observed AEs were epistaxis (8 AEs in 1 patient), rhinitis (7 AEs in 5 patients), upper respiratory tract infections (7 AEs in 7 patients), and cardiac failure (7 AEs in 2 patients). Eighty eight (67.18%) AEs occurred in patients who were below one year of age when they joined the previous WP08 or WP09 study.

By reviewing the acceptability and palatability of enalapril minitablets, it was found that the majority of patients had a positive experience when taking both the 0.25 mg and 1 mg enalapril ODMT.

Serious Adverse Events (SAE)

A small number of SAE was recorded in clinical studies with Aqumeldi.

No deaths occurred in the assessed studies.

In study WP08 – One SAE was reported (syncope due to hypotension in the context of a gastro-intestinal infection and hospitalisation for observational purposes) that was considered unrelated to IMP intake.

In study WP09 - five SAEs without causal relationship with the IMP occurred; all but one (paresis right hemidiaphragm after cardiac surgery) resolved without sequela.

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In Study WP10 – 7 safety adverse events were recorded were assessed as being without causal relationship with IMP administration. Four Serious Medical Events occurred in 2 patients who were not or no longer under IMP when the Serious Medical Event occurred.

No rehospitalisation due to HF including the need for heart transplantation was reported.

3.5. Uncertainties and limitations about unfavourable effects

- Neonates were not included in the study WP08 since DCM generally does not occur in newborns but develops in infancy. The younger population was therefore investigated in a study of children with CHD in WP09. This study recruited paediatric patients aged from birth to less than 6 years, excluding neonates born at less than 35 weeks to obtain paediatric PK data of enalapril ODMTs, to describe the dose exposure in young children with CHD.
- In the cohort of children that were included in WP08 and WP09, half were already on ACEI and in most of them the enalapril-ODMTs were not up-titrated after inclusion. Thus, the effects of increasing doses of ACEI on pharmacodynamic parameters could not be reliably estimated in all the proposed population.
- Pharmacodynamic and safety parameters were analysed in a descriptive fashion as secondary endpoints.
- Based on the presented bioequivalence study(ies) against the reference product, Renitec®, which demonstrated bioequivalence between the 1 mg strength, and taking in to account the availability of in vivo data for the 0.25 mg strength from paediatric clinical studies WP08 and WP09, these in vivo data were considered to be sufficient to support the approval of the 0.25 mg strength without the need for further data. The bioequivalence study was conducted with the 1 mg ODMT strength (higher strength) and confirmed equivalent pharmacokinetics to the reference product (Renitec® 2 x 5 mg tablets). A biowaiver for lower, 0.25 mg strength, based on the bioequivalence established for the 1.0 mg strength, was not agreed upon since the requirements of the *Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)*, with respect to the proportionality of the ratio of excipients amounts to the active, different manufacturing processes for the two strengths, and pharmacokinetic linearity were not fulfilled. Also BCS-based biowaiver considering enalapril is a BCS class III drug substance was not agreed as according to ICH M9 Guideline, for BCS Class III drugs, all of the excipients should be qualitatively the same and quantitatively similar and the BCS biowaiver requires the same strength for test and reference products which was not met. However, the

CHMP considered the results of both clinical studies, W08 and W09, were conducted using both the 1 mg and the 0.25 mg strengths, where the availability of in vivo data for the 0.25 mg strength was considered to be sufficient to support the approval of the 0.25 mg strength without the need for further data.

- The proposed indication, i.e. treatment of heart failure in children from birth to 18 years, is based on an extrapolation approach based on PK bridging, targeting the equivalent systemic exposure to that achieved during the treatment of adults. However, there are uncertainties with respect to the safety (and posology) in children < 30 days of age. The popPK model documentation was not considered to be sufficiently detailed and it was unclear if the current model is relevant for simulating exposure in patients younger than 28 days. In particular, the equation describing clearance adjusted for the maturation appears unphysiological with the value of CL drastically approaching the value 0 L/h with decreasing age. An alternative model accounting for a basal ability to eliminate enalapril in new-borns (such as a slope-intercept model) would be more physiological for the maturation function. It is not only the median, but also the 5-95th of AUC and Cmax in patients 1-30 days of age that would need to reasonably overlap with observed data in older age groups for an extrapolation based on PK to be acceptable. If the exposure is simulated to be higher in 1 day old patients, the safety consequences should be discussed. The applicant provided the full popPK analysis report, including diagnostic plots (goodness of fit, virtual predictive checks), and updated the maturation function for clearance. The applicant provided analysis of potential safety issues in children< 30 days of age. The findings published by Ku et al. [Pediatr Cardiol. 2017 Jan; 38(1): 155-161], which demonstrated severe adverse effects of enalapril particularly in infants <30 days of age were discussed and a comprehensive literature search for ACEi/ARB exposure in infants <30 days of age was performed. The scarcity of subjects <30 days in clinical studies (n=4) was reflected in the SmPC sections 4.4 and 5.1. This is mainly due to the fact that many cases of nephrotoxic effects of RAAS inhibitors (acute renal failure, renal tubular dysplasia) have been reported in foetuses and newborns exposed to RAAS inhibitors during the second and third trimesters of pregnancy in humans. Ku et al. (2017) examined the safety of enalapril in young infants and found that treatment in the first 30 days of life led to severe adverse effects (death, hyperkalaemia, elevated serum creatinine and hypotension) in up to 20 % of infants. The mechanisms involved in ACE inhibitor-induced acute renal failure are reduced renal blood flow and increased renal vascular resistance with decreased glomerular filtration rate at birth in combination with hypotension and decreased renal elimination of enalapril rendering young infants particularly sensitive to ACE inhibitor-induced renal failure. In the submitted responses the applicant has produced data that allowed to state that the final covariate model described in the LENA project (“run051”) has been used to perform population modelling of the PK of enalaprilat. It was shown that administration of enalapril ODMT to children from birth to adolescents provides overall exposures matching those expected in adults taking into account both the target/maintenance dose and the initial dose (as low as 0.01 mg/kg/day). Thus, uncertainties and limitations that initially appeared have been resolved.
- Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information currently at this stage of the procedure.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The mechanism of action of enalapril and its potential pharmacodynamic interactions are believed to be similar in adults and paediatric patients. The mechanism of action of enalapril is therefore primarily via the suppression of the RAAS. Enalapril has been subject to both dose-finding and efficacy studies in children with hypertension or HF and is licensed for use in hypertension.

This application for the treatment of heart failure in children from birth to less than 18 years relies in part on the results of pre-clinical tests and clinical trials for the reference product (RENITEC®) enalapril maleate tablets and in part on new clinical data. The new data were generated within the EU LENA project that was aiming at developing the age appropriate formulation for the use in children and at extrapolation from adults to children of all ages based on new PK data targeting a similar exposure in paediatric patients as in adults. The generated PD/efficacy data in the current program were supplemented by the published data on the (off-label) use of enalapril in children.

The LENA project generated core scientific data from four clinical trials WP07, WP08, WP09 and WP10. WP07 generated clinical data for enalapril orodispersible mini-tablets (ODMTs) in healthy volunteers.

WP08, WP09 and WP10 generated clinical data for enalapril ODMTs in children with HF. As the pathophysiology of heart failure in children is considered to be similar to that in adults with chronic heart failure caused by DCM, the applicant conducted a PK bridging study (WP08) in paediatric patients with DCM aged 1 month to less than 18 years. The primary objective of this study was to obtain paediatric PK data of enalapril ODMTs to describe the dose exposure in paediatric DCM patients in order to identify the doses that lead to an equivalent systemic exposure to that achieved during the treatment of adults.

Neonates were not included in the study WP08 since DCM generally does not occur in newborns but develops in infancy. The younger population was therefore investigated in a study of children with congenital heart disease (CHD) (WP09). This recruited paediatric patients aged from birth to less than 6 years, excluding neonates born at less than 35 weeks to obtain paediatric PK data of enalapril ODMTs, to describe the dose exposure in young children with CHD.

The primary objectives of these studies were achieved.

In the cohort of children that were included in WP08 and WP09, half were already on ACEI and in most of them the enalapril-ODMTs were not up-titrated after inclusion. Thus, the effects of increasing doses of ACEI on pharmacodynamic parameters could not be reliably estimated in all the proposed population.

Pharmacodynamic and safety parameters were analysed in a descriptive fashion as secondary endpoints. Based on the presented bioequivalence study(ies) against the reference product, Renitec®, which demonstrated bioequivalence between the 1 mg strength, and taking in to account the availability of in vivo data for the 0.25 mg strength from paediatric clinical studies WP08 and WP09, these in vivo data were considered to be sufficient to support the approval of the 0.25 mg strength without the need for further data. The CHMP considered the results of both clinical studies, W08 and W09, were conducted using both the 1 mg and the 0.25 mg strengths, where the availability of *in vivo* data for the 0.25 mg strength was considered to be sufficient to support the approval of the 0.25 mg strength without the need for further data.

In addition, the proposed indication, i.e. treatment of heart failure in children from birth to 18 years, is supported by an extrapolation approach based on PK bridging, targeting the equivalent systemic

exposure to that achieved during the treatment of adults. However, there were uncertainties with respect to the posology and safety in children < 30 days of age: the popPK model documentation was not considered to be sufficiently detailed and it was unclear if the current model was relevant for simulating exposure in patients younger than 28 days. The findings published by Ku et al. [Pediatr Cardiol. 2017 Jan; 38(1): 155-161], which demonstrated severe adverse effects of enalapril particularly in infants <30 days of age were analised and discussed as well as a comprehensive literature search for ACEi/ARB exposure in infants <30 days of age was performed. This is mainly due to the fact that many cases of nephrotoxic effects of RAAS inhibitors (acute renal failure, renal tubular dysplasia) have been reported in foetuses and newborns exposed to RAAS inhibitors during the second and third trimesters of pregnancy in humans. Ku et al. (2017) examined the safety of enalapril in young infants and found that treatment in the first 30 days of life led to severe adverse effects (death, hyperkalaemia, elevated serum creatinine and hypotension) in up to 20 % of infants. The mechanisms involved in ACE inhibitor-induced acute renal failure are reduced renal blood flow and increased renal vascular resistance with decreased glomerular filtration rate at birth in combination with hypotension and decreased renal elimination of enalapril rendering young infants particularly sensitive to ACE inhibitor-induced renal failure.

The applicant produced data that allowed to state that the final covariate model described in the LENA project (“run051”) has been used to perform population modelling of the PK of enalaprilat. It was shown that administration of enalapril ODMT to children from birth to adolescents provides overall exposures matching those expected in adults taking into account both the target/maintenance dose and the initial dose (as low as 0.01 mg/kg/day). Thus, uncertainties and limitations that initially appeared have been resolved.

The proposed earlier contraindications for “Paediatric patients with pre-existing liver abnormalities” or “Children < 1 month of age” were not considered appropriate considering that the lack of data alone should not lead to a contraindication. Taking also into consideration that “liver abnormalities” represents a very broad array of clinical conditions, the applicant introduced a warning statement in sections 4.2 and 4.4 that no data is available for children with pre-existing liver conditions, that children (any age) with hepatic impairment should only be treated with enalapril under very strict monitoring and that treatment of children below the age of 1 month is not recommended should justify which safety issues with treatment of patients with liver abnormalities in the entire paediatric population are justifying a contraindication, taking into consideration both that “liver abnormalities” represents a very broad array of clinical conditions. Also, the scarcity of subjects <30 days in clinical studies (n=4) should be reflected in SmPC section 4.4 and section 5.1.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information currently at this stage of the procedure.

Safety of enalapril ODMTs was studied in WP08, WP09 and for a period of up to 10 months in WP10. Safety observations made in the reporting period of WP10 showed that enalapril ODMTs was well tolerated. The adverse event considered as having a possible causality was mild (hypotensive reaction to enalapril). No SAEs and SUSARs occurred. No deaths occurred.

Other safety parameters studied in WP10 comprised blood pressure, renal monitoring, Ross score, echocardiography, ECG and safety laboratory tests. Mean arterial pressure slightly increased in every age group throughout the duration of the study except for children between the ages of 6 and 12 months where a minor decrease was seen. Statistically significant differences between start and end of the study were observed in serum levels of BUN and creatinine in the youngest age group. However, these were minor and considered as not clinically relevant, furthermore the potential risks with long-

term treatment of small children have been discussed by the applicant and no new risk has been identified.

3.6.2. Balance of benefits and risks

There is an unmet medical need for a licensed medicinal product for children with HF that would be possible to be administered with age-appropriate formulations. The Expert Group Meeting on Paediatric Heart Failure organised at the European Medicines Agency in 2010 considered enalapril a first-line treatment for CHF in children. It was concluded in the report from this meeting that PK studies should be conducted in children to achieve systemic exposures similar to those in adults.

Enalapril is licenced in adults for the treatment of HF and the mechanism of action of enalapril and its potential PD interactions are believed to be similar in adults and paediatric patients. This application for the treatment of heart failure in children from birth to less than 18 years relies in part on the results of pre-clinical tests and clinical trials for the reference product and in part on new clinical data. Extrapolation from adults to children of all ages is based on new PK data (generated within LENA project) targeting a similar exposure in paediatric patients as in adults. Considering that the indication also covers pre-term neonates and term neonates a justification was analysed and accepted that the extrapolation approach is relevant also for this age group considering potential differences in PK/PD relationship and safety compared to adults. The applicant demonstrated clearly that the available PK data is sufficient to establish the bridge between adults and the youngest children. The age appropriate formulation for the use in children were developed within the LENA project (ODMTs). The generated PD/efficacy data in the current program were supplemented by the published data on the (off-label) use of enalapril in PHF.

In the submitted responses the applicant has produced data that allowed to state that the final covariate model described in the LENA project ("run051") has been used to perform population modelling of the PK of enalaprilat. It was shown that administration of enalapril ODMT to children from birth to adolescents provides overall exposures matching those expected in adults taking into account both the target/maintenance dose and the initial dose (as low as 0.01 mg/kg/day).

Safety of enalapril ODMTs was studied in PHF within LENA project WP08, WP09 and up to 10 months in WP10. Safety observations made in the reporting period showed that the enalapril ODMTs was well tolerated with only one adverse event that was considered as having a possible causality that was mild. There were no deaths reported. No drug-related SAEs and thus no SUSARs occurred.

New clinical data in children were obtained within WP08, WP09 and WP10 and support the extrapolation of efficacy and safety of the product for use in children. Additional justification was requested, taking into account the unmet medical need for this product as well as enalapril's off-label use in children. If enalapril ODMT are suitable for neonates was initially not clear. The applicant demonstrated that the available PK data are sufficient to establish the bridge between adults and the youngest children. In particular there were uncertainties with respect to the posology and safety in children < 30 days of age: the popPK model documentation was not considered to be sufficiently detailed and it was unclear if the current model is relevant for simulating exposure in patients younger than 28 days and the findings published by Ku et al. [Pediatr Cardiol. 2017 Jan; 38(1): 155-161], which demonstrated severe adverse effects of enalapril particularly in infants <30 days of age were discussed.

The proposed earlier contraindication for "Paediatric patients with pre-existing liver abnormalities" or: "Children < 1 month of age with liver abnormalities" were not considered appropriate considering that lack of data alone should not lead to a contraindication. Taking also into consideration that "liver abnormalities" represents a very broad array of clinical conditions, the applicant introduced a warning

statements in sections 4.2 and 4.4 that that no data is available for children with pre-existing liver conditions, that children (any age) with hepatic impairment should only be treated with enalapril under very strict monitoring and that treatment of children below the age of 1 month is not recommended.

The safety of enalapril in neonates was of particular concern during the assessment. Enalapril is used to treat hypertension and congestive heart failure in infants (approved in USA from 1 month of age). The study by Ku et al 2017 has shown that from a cohort of 887,910 infants, 662 (0.07%) infants were identified who were exposed to enalapril during their initial hospitalization. Enalapril was used in 0.03% to 0.09% infants from 1997 to 2002 and in 0.07% to 0.10% infants from 2003 to 2012 – thus the use remained relatively constant. A total of 142 infants (21%) experienced the composite outcome of death (3), hypotension requiring pressors (25), hyperkalaemia (83), or elevated serum creatinine during exposure to enalapril (34). Infants <30 days postnatal age at first exposure were more likely to experience hyperkalaemia, elevated serum creatinine, and hypotension. Longer durations of exposure to enalapril were associated with increased odds of hyperkalaemia and death, but not elevated creatinine or hypotension. Approximately one in five infants exposed to enalapril experienced at least one AE during treatment, with hyperkalaemia being the most common AE. Among infants without congenital anomalies such as congenital heart disease, death during enalapril therapy was extremely rare. Elimination of enalapril and its active metabolite enalaprilat is primarily renal, reduced kidney function leading to increased exposures could potentially explain why infants age <30 days are at increased risk for other AEs (of which hypotension is the earliest and most often reported AE). In a study of enalapril and enalaprilat pharmacokinetics in 12 subjects age 10 days to 6.5 years with congestive heart failure, mean area under the curve values of active metabolite per enalapril dose normalized for body weight and body surface area were fivefold greater in the three subjects age <20 days compared to subjects >20 days old (Nakamura et al 1994). This suggests that infants <20 days old would require a significantly lower dose than their older counterparts. Hypotension, acute renal failure, decreased urine output, and azotaemia associated with use of enalapril have been reported in preterm and term infants (Ku et al 2017). Therefore a warning was introduced in section 4.4 of the SmPC that AQUMELDI is not recommended in children in indications other than heart failure, that caution is advised in children below 1 month of age as they may be very sensitive to the medical product and that data on the use of Aqumeldi in children below 1 month of age in the clinical studies is scarce (n=4). Any signs of adverse events and electrolytes should be closely monitored.

The applicant applied initially for registration of both enalapril ODMT strengths: 0.25mg and 1 mg. The 1 mg strength was withdrawn during the procedure. In conclusion, the CHMP concluded that the benefit-risk balance of enalapril 0.25 mg ODMTs is considered positive.

3.7. Conclusions

The overall benefit/risk balance of Aqumeldi is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Aqumeldi is favourable in the following indication(s):

Aqumeldi is indicated for the treatment of heart failure in children from birth to less than 18 years.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0093/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.