# PROJECT FINAL REPORT

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| **Grant agreement no.:** | FP7 - 602295 |
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| **Project full title:** | **L**abeling of **E**nalapril from **N**eonates up to **A**dolescents |
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# Table of Contents

# Glossary

| Abbreviation / acronym | Description |
|---|---|
| ACE | Angiotensin converting enzyme |
| ACE-I | Angiotensin-converting enzyme inhibitors |
| CA | Consortium Agreement |
| CDA | Confidential Disclosure Agreement |
| CHD | Congenital Heart Disease |
| CSR | Clinical Study Report |
| DCM | Dilated Cardiomyopathy |
| DKP | Diketopiperazine, derivative of Enalapril |
| ECHDO | European Congenital Heard Disease Organisation (see here) |
| EMA | European Medicines Agency (see here) |
| EU | European Union |
| GA | General Assembly |
| HF | Heart failure |
| ICH | International Council on Harmonisation (see here) |
| IMPD | Investigational Medicinal Product Dossier |
| ODMTs | Orodispersible minitablets |
| PDCO | Paediatric Committee at the EMA (see here) |
| PIP | Paediatric Investigation Plan |
| PIP | Paediatric Investigation Plan |
| PM | Person Month |
| PO | Project Officer |
| PUMA | Paediatric-use marketing authorization |
| WP | Work package |

# 1. Final Publishable Summary Report

**Labeling of Enalapril from Neonates up to Adolescents**

## 1.1 Executive Summary

The aim of the LENA (Labeling of Enalapril from Neonates to Adolescents) project, which was a collaborative project funded by the European Commission through its 7th Framework Programme (EU Grant Agreement 6022950), was to develop and clinically evaluate a new paediatric dosage form of the off-patent drug enalapril, for the treatment of heart failure in children. Although few clinical studies have been conducted in paediatrics, enalapril is considered a first-line treatment for chronic heart failure in children. However, reliable paediatric pharmacokinetic data on enalapril are not available and dose estimates are often based on adult patients. There is currently no licensed formulation of enalapril available in Europe suitable for use in children, resulting in the administration of extemporaneous oral preparations, for example crushed tablets in water. This can lead to inaccurate dosing/dosing errors, lack of chemical and physical stability and poor patient compliance.

The work conducted in this project was in accordance with an agreed Paediatric Investigation Plan (PIP) (EMEA-001706-PIP01-14-M02). The LENA consortium partners used their expertise and experience in paediatric enalapril formulation development, bioanalytical assay development, pharmacokinetic/ pharmacodynamic (PK/PD) modelling, care for children with heart failure, recruitment of paediatric populations for clinical studies, and management of complex as well as challenging conditions in clinical trials. The partners collaborated with selected small- and medium-sized enterprises (SMEs) with proven expertise in the field. The LENA project was overseen and advised by an independent **Ethical and Scientific Advisory Board (ESAB)** and patient data were evaluated by an independent **Data and Safety Monitoring Board (DSMB).**

A novel **age-appropriate solid oral drug formulation** of enalapril (0.25 mg and 1.0 mg strengths) containing paediatric-acceptable excipients, with a practical shelf life, was successfully developed for use in neonates and children. The rate and extent of enalapril absorption from the novel formulation were shown to be equivalent to that from conventional enalapril tablets, and paediatric patients of all age groups demonstrated high acceptability of the new formulation. The LENA project demonstrated via **three investigator driven bridging studies** that this novel drug formulation is clinically safe, reduces neuro-humoral stimulation and can be used to effectively stabilize and improve the health of the paediatric heart failure population. Furthermore, the clinical studies generated bioavailability data in different paediatric age sub-sets to delineate a dosing regimen in these patients. Hence all necessary data for the submission of a **paediatric use marketing authorisation (PUMA)** were generated that will enable the transformation of enalapril in paediatrics from off-lable to fully licensed use.

The LENA partners disseminated information and provided outreach to clinicians, parents and patients about the disease, modern drug treatment in children and the value of benefiting from participation in well organised clinical trials which adhered to the highest ethical standards. The LENA team together with European experts gathered epidemiological data to highlight current gaps in the care of paediatric patients with heart failure but also to facilitate the optimal distribution, marketing and pricing of the novel treatment options with enalapril ODMTs in the European Union member countries.

Overall, the LENA project has achieved its goals by providing a completely tested enalapril paediatric heart failure product ready for **broad dissemination to the paediatric population in the European Union Member States.**

## 1.2 Context and Objectives

LENA project is all about one simple question: **How can we provide a safe, effective and age-appropriate formulation of enalapril for children in Europe?** Acknowledging current shortcomings of paediatric drug development and aiming to develop an orally administered **age-appropriate formulation** of enalapril for use in neonates and infants, LENA's. Innovation process includes **investigator-driven trials** that collectively generated all necessary data for devising a paediatric-use marketing authorization (PUMA). LENA is therefore concluding its EU-funded activities with a completely tested product ready for **broad dissemination to the pediatric population in the European Union**.

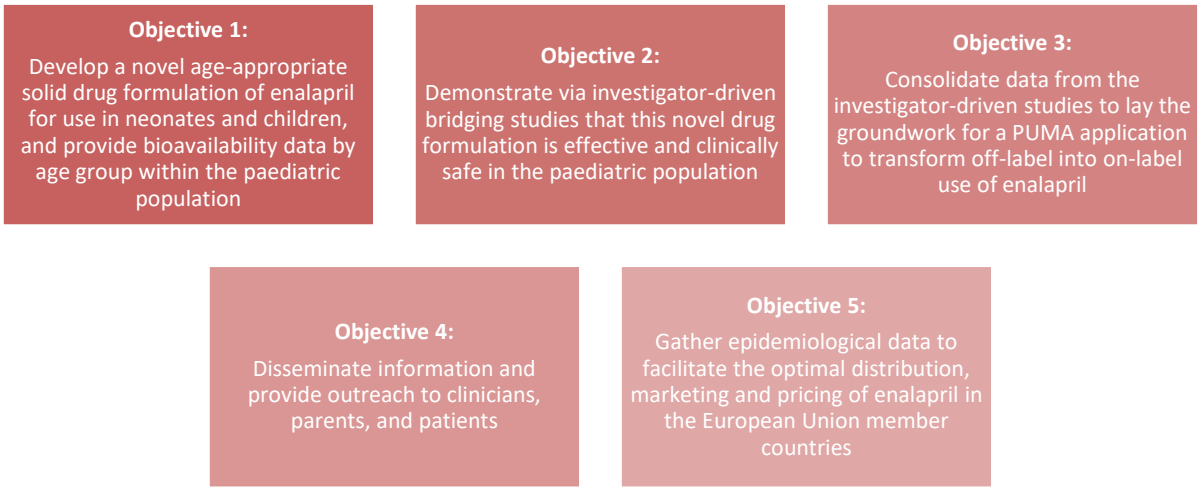


*Figure 1: The five "LENA" project objectives in a nutshell*

## 1.3 Main Results / Foreground

To achieve all targeted objectives, "LENA" project tasks were well structured and organized in fifteen work packages (WP). Figure 2 shows an overview of interactions and dependencies among the different work packages clustered in four clinical trials (orange colour coding), analytical and methodological, trial management and statistical frameworks (yellow colour coding) completed by scientific overall management and joint data analysis (white colour coding), pharmaceutical development of the LENA ODMTs and related non-clinical safety aspects (green colour coding) and – addressing a broad range of audiences – ethical considerations, education activities and dissemination and commercialisation (brown colour coding) as well as scientific coordination, project management, regulatory interactions and paediatric development (blue colour coding).

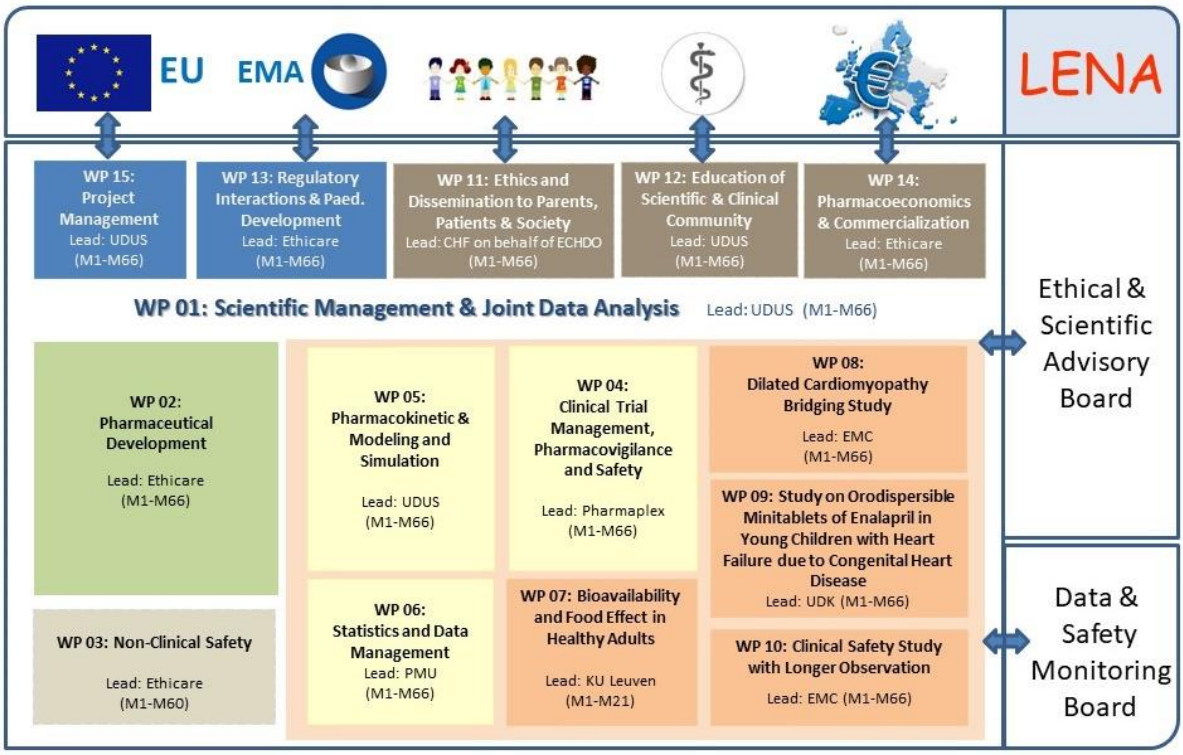


*Figure 2: "LENA" work package structure, dependencies and workflow*

The following pages summarize the main project results and the advancement of knowledge and technological progress achieved throughout the project.

### Scientific Management & Joint Data Analyis (WP1)

Scientific management was performed sucesfully. In the first phase of the LENA project, a process was organized to build up the LENA data base as a prerequisite to prepare the documents for regulatory authorities and ethics committee.

In the second and third phase of the LENA project UDUS together with Pharmaplex and Ethicare built the LENA Quality team and set up the LENA GxP infrastructure. It encounters the concept of good practice (GxP) where 'x' stands for the field of manufacturing (GMP), distribution (GDP), laboratory (GLP), and clinical (GCP). With this, the work performed in the LENA project met strict quality standards throughout the entire process of the LENA project. The LENA Quality Policy and assurance system harmonized the different levels of quality expertise of the LENA partners.

The scientific data management conceptualized the clinical trials such as the scientific content, study protocols, and also the practical aspects of trial performance. To cope with the highest ethical

standards for paediatric clinical trials, a pharmacokinetic/pharmacodynamic and communication training was developed and conducted with study nurses, technincians, scientists and physicians in addition to pre-site visits, site initiation visit. Also, the scientific data management supported approval processes of competent authorities', critically reviewed sponsor related documents.

The scientific data management initiated and conducted weekly telefone conferences from December 2015 up to June 2019. All LENA members were invited to participate. With this, a central communication platform was installed and served well throughout the project. It was used to discuss scientific topics during the study protocol development, patient related issues during the recruitment and study period, issues about study equipment, organization of sampling logistics to the clinical sites, monitoring, and organizational questions concerning tasks or meetings. The telefone conferences were relevant for identifying and discussing any challenges throughout the project such as the initiation of the two new recruitment sites, the new IMP batches to be manufactured and financed, new consumables, equipment and shipments, additional site visits, new trainings, regulatory approvals for new sites. Thus, the scientific management ensured that the expected scientific impacts listed in the work programme and agreed upon with all participants were addressed and targeted throughout the whole project and finally achieved.

The scientific management interacted with the Data and Safety Monitoring Board (DSMB) and the Ethical & Scientific Advisory Board (ESAB). The ESAB attended three of the General Assembly meetings and provided relevant ethical and scientific support to the LENA partners. The DSMB interacted through telephone conferences and received the development safety update report (DSUR).

All 4 LENA clinical trials (WP07, WP08, WP09, and WP10) were successfully developed and performed according to GCP and PDCO requirements.

In the LENA project, the workload even exceeded the work programme: 9 instead of 6 clinical sites for the paediatric trials were installed, 1 paediatric investigation plan (PIP) plus 2 requests for modification instead of only 1 PIP had been approved by the PDCO, extra batches of medication were manufactured, 7 General Assembly (GA) meetings instead of 6 and 7 Steering Committee (SC) meetings instead of 5 were held. It is of note, that members of the LENA teams performed 56 meetings on top of the GA and SC meetings. Furthermore, the LENA team performed more than 110 telephone conferences and requested 7 amendments to the LENA Grant Agreement.

Finally, the scientific data management organized successful a joint analysis of all data generated in the individual work packages and organized an adequate structuring, collaboration and contribution of the LENA partners to finalize the paediatric clinical study reports.

## Pharmaceutical Development (WP2)

Orodispersible minitablets (ODMTs, 2 mm in diameter and height, approx. 6.5 mg total mass, dose strengths: 0.25 mg and 1.00 mg enalapril maleate) were successfully developed from technical batches at lab- and pilot-scale to clinical batches under GMP. ODMTs are packaged in multi-dose containers with a child-proof closure system, including a desiccant in the cap to prevent water uptake from air moisture. The performed stability program at three different climate conditions (25°C/60% r.h., 30°C/65% r.h., 40°C/70% r.h.) with four to five batches per dose strength show good stability at ambient conditions. Enalapril degrades and forms the known Impurity D (acc. to Ph.Eur.) which is a diketopiperazine (DKP) derivative of Enalapril. The higher the temperature and the relative humidity, the higher is the decomposition rate. ODMTs were supplied for all four clinical trials of the LENA project (see work packages WP7, WP8, WP9, WP10) continuously and without delay in a package size of 200 ODMTs. A method for preparing individualized doses was developed and the required materials and medical devices were provided to the clinical centers. On request of the Paediatric Committee (PDCO) at the EMA, a method for preparing a dispersion of an ODMT for administering even smaller doses than the 0.25 mg ODMT (dispersion: 0.025 mg) was successfully developed. Additionally, the compatibility with beverages and nasogastric tubes was shown, as requested by PDCO.

## Non-clinical safety (WP3)

Enalapril maleate is a potent and specific inhibitor of angiotensin converting enzyme (ACE) *in vitro* and *in vivo*. Following oral administration, enalapril is bioactivated by hydrolysis of the ethyl ester to enalaprilat. A full regulatory toxicology programme has demonstrated an adequate safety profile of enalapril. A local buccal toxicity study in animal models was evaluated as not needed within the LENA project. Enalapril and the used excipients show good tolerability for the buccal epithelium. Ethicare's opinion has been fully confirmed by the PDCO during the Paediatric Investigation Plan (PIP) evaluation procedure. Regulatory documents were enriched with data and opinions on non-clinical safety and were accepted by the authorities, the PDCO, the national competent authorities evaluating the submitted IMPDs and the ethical commissions of the clinical centres.

## Clinical Trial Management, Pharmacovigilance and Safety (WP4)

The design and implementation of a risk-based quality management system from scratch in a publicly funded paediatric project of an academic consortium without common quality infrastructure as well as the ongoing quality oversight have been successfully completed with compilation of the Trial Master Files and two independent site audits which confirmed that the LENA QMS enabled the performance of studies with reliable patient protection and generation of quality data.

Design and implementation of a Clinical Trial Management Plan including provision and management of cost-efficient, experienced monitoring and regulatory affairs resources in all involved countries for the time of need enabled the performance of the clinical trials and with only few months recruitment delay despite the lack of an existing clinical trial infrastructure in a newly created consortium and a micro SME sponsor.

## Pharmacokinetic & Modeling and Simulation (WP5)

The modelling and simulation work package was responsible for providing the scientific background about the pharmacokinetics (PK) and the renin-angiotensin-aldosterone pharmacodynamics (PD) of enalapril in the paediatric population, also the statistical analysis plan for PK and PD in the healthy volunteer trial and the paediatric trials. The work package contained the workload of the central laboratory for the equipment and shipment logistics, the bioanalytics, and the pharmacokinetic and pharmacodynamic analysis for the primary endpoints and the pharmacodynamic RAAS system investigations.

Within this work package a GCLP structure for the LENA studies at the Institute of Clinical Pharmacy and Pharmacotherapy, with sampling, optimal storage and implementation of an effective operating shipment procedure was established. An information technology infrastructure was developed and established that enabled proper monitoring of all relevant steps via computerized tools for shipment of laboratory equipment, documents, consumables, empty bottles and sampling pouches to all clinical sites in time during the 29 months duration of the paediatric study conduct and also for enabeling opening of the two new clinical sites in the shortest time. During the paediatric trials, continuously five teams of two people have registered, arranged, prepared, analyzed and evaluated all LENA sample runs conducted according to GCLP requirements. The laboratory had been successfully upgraded for the analysis of HCV infected material from LENA children with hepatitis infections during operation without any delay in sample analysis.

Work package 5 together work package 6 develped and conducted a simulation training to familiarize all team members with the complex PK/PD sampling and communication tasks of the studies. Also, intensive on-site support to improve patient recruitment and blood sampling according to the specific needs of the clinical site as well as the conduct of a PILOT study in adults to ensure optimal workflow prior to 1st paediatric patient was successfully performed.

The central laboratory developed low-volume and microassays and sampling schedules for pharmacokinetic and pharmacodynamic RAAS parameters at highest ethical standards. All developed

assays had received certification by external reference laboratories. The central laboratory had been certified as GCP/GCLP-compliant.

Top-line pharmacokinetic analysis for WP07 was performed in time. A paediatric dosing regimen for enalapril ODMTs and sampling schedule for WP08, WP09 and WP10 trials was delineated and after successful determination of enalapril and enalaprilat concentrations as well as pharmacodynamic parameters (aldosterone, renin, and plasma renin activity) in WP08, WP09, and WP10, the bioavailability in the paediatric population and the effect of enalapril on the RAAS neurohumoral system could be assessed.

## Statistics and Data Management (WP6)

The statistical concept including the descriptive statistics methodology, the calculation for sample size definition and exploratory statistical testing has been developed and implemented in the study and regulatory documents like study protocol, Case Report Forms (CRF) for WP07 and eCRFs for WP08-WP10, statistical analysis plans etc. in accordance with ICH E9 and other applicable standards.

A database was set up and validated by a comprehensive quality assurance and safety system. All sites and trial management have been provided with SOPs, trained and supported with data entry and monitoring, respectively.

To facilitate successful patient recruitment and a high quality in study conduct and data entry regular reports on key performance indicators have been provided to the consortium. These included monthly site-quality-reports (to WP4) monthly patient disposition reports (to WP5), monthly blood sample CryoID reports (to WP1) and periodical adverse events (MedDRA coded), concomitant medication for monitoring and DSUR (Development Safety Update Report).

Data Completion and Data Cleaning was performed for WP08 to WP10 studies. In addition to the automated inconsistency and completeness checks programmed into the eCRF, semi-automated and four eyes checks have been done to raise queries to the clinical sites and monitors for data correction and completion between 26.9.2018 and 21.12.2018.

Data Analysis was performed in accordance with the statistical analysis plans and Statistical Reporting. The analyses and visualizations results have been discussed with the consortium (Data Review meeting, 6.3.2019) and the advisory board (General Assembly meeting, 27.3.2019). The final reports have been provided to lead beneficiaries 1, 2, 3, 5 and 6 for the implementation into the clinical study reports, project reports, the pharmaceutical development and scientific publications by 24.04.2019.

Simulation based training of “LENA” study teams

An innovative simulation-based training of study teams in study specific communication and pre analytical skills was developed, utilized and systematically evaluated by a survey.

## Bioavailability and Food Effect in Healthy Adults (WP7)

The main objective for WP7 was to perform a relative bioavailability study in healthy adults of a newly developed Orodispersible Mini-Tablet (ODMT) containing enalapril as Active Pharmaceutical Ingredient versus a standard enalapril formulation. This relative bioavailability was necessary in order to define the need for adjusting the enalapril doses to be used in the paediatric clinical studies of the LENA project. A state-of-the-art protocol and a related informed consent document were developed for review by the Belgian authorities and the Ethics Committee of the University Hospitals KU Leuven and was given a favourable opinion on 09JUL2014. The study was designed as a single-centre, open-label, randomised three-way crossover, three-treatment, three-period study conducted in 24 healthy subjects and was in accordance with the International Council on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice.

On the basis of the pharmacokinetic results, the main conclusion of the study revealed that a dose adjustment of enalapril in the LENA clinical investigations with the ODMT formulation administered to

newborns, infants and toddlers, children and adolescents was not indicated. A detailed clinical study report was developed and finalized in M26 (December 2015).

## Dilated Cardiomyopathy Bridging Study – Orodispersible Minitablets of Enalapril in Children with Heart Failure due to Dilated Cardiomyopathy (DCM) (WP8)

In the initial phase of the WP8 study, the study protocol was designed with input from many required in order to design a study in a very vulnerable population young children with severe cardiac disease. This included the design of a safe dosing scheme within the limitations of the doses available, clear definitions of safety parameters and their acceptable upper and lower limits, as well as the design flow diagrams how to uptitrate enalapril and how to act when the boundaries of safety limits were surpassed. Furthermore, a feasibility analysis was performed, based on the data of the national Dutch DCM cohort. It was clear from the beginning that the demand to include 50 children with DCM would be tight, but when it turned out that one of the centres with an estimated high number of inclusion had severe problems to include it was clear that the required number of 50 would not be made. After renegotiation with the PDCO ultimately 25 children were accepted, which was an achievable goal.
As predicted, the large majority of children included into the study were those who had been pretreated with enalapril and were children with relatively stable heart failure that were mostly followed on an outpatient basis. The inclusion followed a fairly linear pattern. It turned out that obtaining venous blood at each visit was one of the major challenges of the study. It was an important reason for some parents to decline participation, for early termination of the study and it was not always successful. This explains why in 6/32 children a full PK (primary endpoint) could ultimately not be obtained. The success of the study, however, is that despite all these hurdles our goals were ultimately successfully achieved, providing a set of unique data on enalapril, safety and neurohormonal and renin-angiotensin-aldosterone PD in (very) young children with heart failure.

## Study on Orodispersible Minitablets of Enalapril in Young Children with Heart Failure – Orodispersible Minitablets of Enalapril in Young Children with Heart Failure due to Congenital Heart Disease (CHD) – (WP9)

This work package 9 was responsible for establishing the study protocol for paediatric patients with heart failure due to congenital heart disease and for the contribution of this topic into the Paediatric Investigation plan (PIP). Also, the work package was intensively involved in all stage of protocol and licence approval process at the national competent authority.
All members of the clinical sites had been trained not only by the GCP training but also by the simulation training at the simulation center at PMU. Patient recruitment in WP09 started at in January 2016. Because of low recruitment rates at several sites two new clinical sites where included into the LENA Study. One of them was a second site at Belgrade. Due to high performance for study conduct at the Belgrade clinical sites, a higher number of WP09 patients than originally planned (a minimum of 60 than 50 patients in WP09) compensated the number of patients in WP08 which was not recruited in other centres by DoW. The LENA clinical trial study visits were conducted according to the study protocol, at all sites, with only minor deviations. Clinical observations, tests and analysis were performed according to the study protocol without obstacles. No major deviations from protocol were made during whole trial period. During blood sampling, partners did not encounter any problems regardless the patients' young age. Two audit visits were conducted at the clinical sites at the two Belgrade sites. At the site UDK, an audit was done by the Serbian drugs agency (ALIMS) during the 3rd period reporting. At IMD the audit was done by an internal auditor assigned by the sponsor Ethicare during the 4th period of study. Both audits were passed and did not identify any critical or major findings. Last patient last visit occurred in May 2018. Finally, in total, 63 fully evaluated out of 70 patients fulfilled the inclusion criteria for WP9 protocol were recruited at 5 sites. Put of the 70 patients, 56 (89%) of the recruited patients in WP9 belonged to the vulnarable subgroup of young children age from 0 to <12 months. Data cleaning and line listings, resolving of queries, filling in some open pages

and resolving eCRF inconsistencies lasted until October 2018. All sites did their best to fulfil the expectations and enable final database closure. In March 2019 first trial results were obtained by the data management and the modelling and simulation team and delivered to project leaders. Studx outcomes were discussed in a face to face meeting in March. The main results were presented at the Final Summit Meeting at end of March. All coordinators and principal investigators of WP09 trial were present at this meeting. An intensive period of writing the clinical study report started with the contribution of all relevant work packages leader. Even more, WP coordinators participated actively in weekly teleconference in order to discuss and manage arisen issues.

## Clinical Safety Study with Longer Observation – Follow-up Safety Trial in Children with Dilated Cardiomyopathy (DCM) and Congenital Heart Disease (CHD) Receiving Orodispersible Minitablets (WP10)

Work package 10 was involved in the study protocol development, the approval processes at the Dutch sites and some scientific discussions about patient follow up. The paediatric investigation which had agreed in August 2015 requested a substantial change in the study duration of WP10 from 6 months as agreed in the initial LENA workplan to 10 months follow up. The patient recreuitment which had started in March 2016, however, revealed by the end of 2016 that a follow up for a total number of 40 patients in WP10 for the whole time period appeared to be not achievable. The sponsor together with the scientific coordinator and the trial management negotiated a modification of the paediatric investigation plan in June 2017. This resulted in realistic minimum numbers of patients followed up with n=10 for a minimum of 10 months, n=10 for a minimum of 6 months and n=10 for a minimum of 3 months. All these patients had to be below 12 months of age at the entry into WP08 or WP09. The principal investigators in WP10 were the same people as for WP08 and WP09 and they rolled over the patients from the previous LENA paediatric trials to follow up the safety of patients. Finally, 86 children from the WP08 and WP09 trials who received at least three days of enalapril ODMT treatment were enrolled into this follow-up study. All PDCO required criteria were met with this patient cohort. The primary endpoint of this WP10 trial was to demonstrate safety was the primary endpoint. Acceptability and palatiability, single concentrations for enalapril and enalaprilat as well as the RAAS pharmacodynamic parameters were secondary endpoints. The majority of patients (72%) originated from the WP9 trial and were diagnosed with congenital heart disease. The remaining 28% of all patients originated from the WP8 trial and thus were diagnosed with a dilated cardiomyopathy. At the start of WP10, 80 (93.0%) of patients entering WP10 were still on enalapril ODMT treatment. Last patient finished the study in July 2018. Thereafter, a process of data cleaning and data analysis followed. Since March 2019 outcomes of the study were discussed. Subsequently, a clinical study report was written with contributions from all work packages involved. All phases of the trial development and conduct were accompanied by telefone conferences to solve issues that were raised during the process.

## Ethics and Dissemination to Parents, Patients and Society (WP11)

The “LENA” partner Children’s Heart Federation is the leading UK children’s heart charity and works with individuals and organisations concerned with children and young people with health and educational needs due to acquired or congenital heart conditions. CHF shared information, knowledge and experience in order to improve access to the best possbile care and treatment for all the people affected by Congenital Heart Disease (CHD) in Europe. Best practices and Lessons-learnt from the activities of the Children’s Heart Federation (CHF), the “LENA” partner disseminating to parents, patients and the wider public will improve future collaborations between patient and parent groups and clinicians / professionals. Numerous activities went well as the design and publication of flyers and posters, talks, presentations, and exhibitions to patient groups and interested clinicians, the design and publication of accessible and age appropriate assent. Challenges were overcome because CHF adapted its strategy in collaboration with the board to the European Congenital Heart Disease

Orgnisation (ECHDO). There was little interest from parents in joining a parent-led steering group. The ECHDO Board, therefore, took on that role. The original plans envisaged recruiting an expert parent advisor in each country participating in the clinical trial. There was no interest in parents taking on this role, and so CHF, based in London, UK, using a translation service took on this role. It was a little used service because parents participating in the trial appeared satisfied in the information provided by the trial clinicians. The publication of a newsletter for parents was trialled over two editions, but there was little take-up, partly because of the small number participating in the trial but mainly because participating parents were satisfied by the information provided by the clinicians. Other people were satisfied by information provided through publics, flyers, conferences and exhibitions.

## Education of the Scientific and Clinical Community (WP12)

While the benefits of pharmacotherapy in adult heart failure (HF) are well established, efficacy in paediatrics has yet to be confirmed. Therapeutic strategies are largely based on the extrapolation of adult data and own experience. Little is known about drug treatment routines in everyday practice. Great uncertainty exists regarding optimal use of angiotensin-converting enzyme inhibitors (ACE-I) in HF children. Thereore, a European survey was performed. This survey characterised heart failure maintenance pharmacotherapy for children across Europe and investigated how angiotensin-converting enzyme inhibitors are used in this setting. This Europe-wide web-based survey was conducted between January and May 2015. Out of 200-eligible, 100 European paediatricians dedicated to cardiology representing 100 hospitals in 27 European countries participated. In a subsequent Delphi survey, a selected group of 13 paediatricic cardiologists from across Europe and the United States of America conducted a formal discussion on controversial aspects regarding the European survey, facilitated consensus, and highlight areas of agreement and disagreement. Of these experts, 92% had a working experience in the field of more than 10 years and were working in a specific paediatric cardiology unit.

Most important results of the surveys were that a) ACEI are key in paediatric heart failure therapy, even for children with single ventricle physiology, in apparent contradiction with current paediatric evidence; b) ACEI used as first class therapy for the paediatric age groups in patients among European hospitals indicated that enalapril and captopril are prioritarily used in children throughout all age groups. Enalapril is first line in children above 2 years of age and that captopril is first line in children below 2 years of age; c) many physicians avoid using ACEI in neonates and disparate usage criteria suggest significant differences may exist in the risk-benefit profile children are exposed to; d) no standardization in dilated cardiomyopathy-related heart failure pharmacotherapy exists, and there appear to be marked deviations from conditions of use that current adult data support; e) in the Delphi survey the experts had found areas of common thinking and motivation, which can provide a means of triggering scientific collaboration; f) The Delphi survey results might also contribute to disseminate available paediatric evidence and promote reducing unjustified variability in everyday practice.

## Regulatory Interactions & Paediatric Development Strategy (WP13)

Data consolidation and preparation in the regulatory required format for a PUMA and regulatory procedures and approvals had been performed and achived throughout the LENA project. The respective procedures and approvals are listed:

- Approved paediatric investigation plan (PIP) with two approved requests for modification (2015/2017/2018).
- Preparation and approvals for study protocols version 1.0, 2.0, 3.0, 3.1 and 3.2 for all four studies in 6 countries (WP07: Belgium; WP08, WP09, WP10: Austria, Germany, Hungary, Serbia, The Netherlands)

- Preparation and approvals by competent authorities and ethics committees for 2 substantial amendments for WP08, Wp09 and WP10 in all countries plus two national substantial amendments due to change of principal investigator
- Pharmacovigilance system implemented and executed as required in the clinical trials.
- Preparation and submission of Annual Safety Reports (DSURs) to all competent authorities and ethics committees (last DSURs submitted in this reporting period).
- Preparation and annual updates of the Investigator Brochure. The last Investigator Brochure update was submitted in this reporting period.
- Preparation, approval and approved updates to the Investigator Medicinal Product Dossier (IMPDs) for both ODMT dose strengths.
- End-of-Study Declarations sent to the competent authorities and ethics committees in all countries involved (in this reporting period).
- Medical Monitor contribution to data review before database lock.
- Ensuring suitable clinical study report structure and complete content for a PUMA application through ongoing advice to clinical study report preparation team
- Clinical Study Reports for all 4 clinical trials in the LENA Project completed according to PUMA application requirements (3 clinical study reports for WP8, WP9 and WP10 trials prepared and submitted to the European Commission in this reporting period).

## Pharmacoeconomics and Commercialization (WP14)

The need for a child-appropriate dosage form of Enalapril was clearly demonstrated. An Economic Target Product Profile was established and highly acknowledged by the potential commercial partners during the discussions. Recent political decisions required several updates of this document. Despite the ongoing discussion on reimbursement of PUMA products, various small and medium-sized companies expressed their interest in the LENA ODMT products. CDAs were signed with five companies to give more insight in the state of the pharmaceutical and clinical development. Further negotiations will be continued when the clinical study reports are completed and can be shared under CDA.

## Project Management (WP15)

In “LENA”, the overall objective of this WP led by UDUS is two-fold with a clear share of management tasks and responsibilities between UDUS and ARTTIC: (1) assuming its responsibility of the overall strategic management as well as contractual and financial administration and (2) the day-to-day operational management in view of financial, contractual and logistical aspects.

At project start, a dedicated project office was set up by ARTTIC in close exchange with the scientific coordinator at UDUS to establish the management infrastructure consisting of the project committees (SC and GA), external advisory boards (ESAB and DSMBT), management procedures, project management tools (i.e. project management plan, budget and effort indicators, deliverable and milestone indicators) and a secure password-protected internal data repository. This infrastructure was regularly updated, as needed. Throughout “LENA”, the project office acted as central contact point for all project partners.

In view of meetings, UDUS chaired eight Executive Board web conferences and seven six-monthly General Assembly meetings with a focus on progress review, strategy and decision-making (see 4th Periodic Report, chapter 2.4). ARTTIC provided logistics support and electronic tools (via private part of webspace, conference service, etc.) for these meetings and for WP and inter-WP web conferences.

In addition, the project office maintained and updated all contractual documents (i.e. seven amendments of the “LENA” grant agreement), provided regular financial control for the project, and managed all financial reporting aspects. ARTTIC supported UDUS with the distribution of EC payments.

Rules and regulations as stipulated in the Grant Agreement and Consortium Agreement were implemented throughout the project.

In “LENA”, project quality control was ensured through continuous monitoring of the project progress against contractual commitments (deliverables and milestones) by UDUS with the support of ARTTIC. All project deliverables were monitored on a continuous basis and submitted together with each EC periodic report. All four contractual periodic reports were submitted to the European Commission on time on a regular basis, including scientific/technical reporting and financial statements.

## 1.4 Potential Impact

This collection of views on the impact is derived from each of the work package leaders and reflects all experiences throughout the 5.5 years of collaborative work in the LENA team. It was regarded as important to have all the original comments and views listed from each work package. Thus, repititions were warrented and the different wording of even similar topics was regarded as additional value.

### Scientific Management & Joint Data Analyis (WP1)

The LENA project had proven that an academic consortium is able to develop and perform a paediatric drug development program succesfully. The jointly analyised "LENA" data might be used by one of the pharmaceutical companies identified for a PUMA submission (see WP14). With the approval of the enalapril Orodispersible Minitablets there is the potential to change the Standard of Care for Paediatric Patients with Heart Failure in Europe.

### Pharmaceutical Development (WP2)

The LENA consortium has developed a child-appropriate dosage form, orodispersible minitablets (ODMTs), with Enalapril maleate as the active substance at two different dose strengths (0.25 mg and 1.00 mg). The two products are stable, show good bioavailability of the active substance, are easy to prepare individualized doses and can be taken by children of all ages. So far, there is no product with this new dosage form on the global market. LENA ODMTs are easy to use, patient- and parent-friendly and would close the gap for child-appropriate formulations of ACE inhibitors. Even small paediatric sub-populations would benefit from the ODMTs, as very small doses can be prepared as aqueous dispersions to administer directly into the mouth or via nasogastric tubes.

### Non-clinical safety (WP3)

Enalapril is a relatively safe, untoxic substance. The excipients used in the ODMTs are safe for children of all ages, as being confirmed by the experts of the PDCO at the EMA.

### Clinical Trial Management, Pharmacovigilance and Safety (WP4)

For the first time a publicly funded consortium was able to perform the complete set of clinical trials required to generate the PK, PD, and safety data set for demonstration of the suitability of ODMTs as a galenic formulation in paediatric patients with heart failure of all age groups requiring reliable and optimally dosed enalapril treatment. In the context of training of medical staff for clinical trials, a simulation-based training of study teams in study specific communication and pre analytical skills is an innovative approach that can be transferred to other studies with similar challenges in patient recruitment and sample handling.

### Pharmacokinetic & Modeling and Simulation (WP5)

Within this work package an academic partner took over the responsibility of the central laboratory and set up a functioning GCLP infrastructure for paediatric trials. The development of low-volume and microassays and sampling schedules was enforced. This lowered the burden of patients for the study procedures and adapted the study protocol to the highest ethical standards of EMA and FDA guidelines. It allowed to measure 6 parameters in total, 2 for pharmacokinetics and 4 four for pharmacodynamics in each child at the same time. This was a major step to finally achieve meaningful results for pharmacokinetics and pharmacodynamics. As the study design had precluded a control group in enalapril as off-patent drug, this unique set of six parameters was able to prove bioavailability of the drug and the inhibition of the neuro-humoral system in the paediatric population with heart

failure. The stimulation of the neurohumoral system is regarded as driving pathophysiological force in children with heart failure. To perform this unique PK/PD approach throughout the study at each site and to lower the burden for the patients, work package 5 together with work package 6 developed and conducted a simulation training to familiarize all team members with the complex PK/PD sampling and communication tasks of the LENA paediatric studies.

## Statistics and Data Management (WP6)

The main contribution of WP6 to the LENA project is the data management framework that allowed to provide a data quality that fulfils international standards not only from a scientific but also from a regulatory aspect in the context of drug approval. This for the successful utilization of the ODMTs and the gathered data in terms of PUMA market application, commercialisation and scientific publication of the data. The implementation of these standards was particularly challenging in the financially and time wise limited frame of an EC-supported Health project and in a consortium with many partners that so far predominantly worked in academic research not in industry driven drug development. By this our project in general and the cooperation of data management and trial management, in particular, can be a role model for similar projects. The need for this is clearly illustrated by the low overall success rate in this EC Health call. Finally, the simulation-based training of study teams in study specific communication and pre analytical skills is an innovative approach that can be transferred to other studies with similar challenges in patient recruitment and sample handling.

## Bioavailability and Food Effect in Healthy Adults (WP7)

The current WP07 was the first clinical study planned in the LENA project. By developing a new Orodispersible MiniTablet, the LENA project aimed to change the Standard Care for Paediatric Patients with Heart failure. The availability of a suitable formulation of enalapril adapted to the specific needs of children with heart failure will have a significant impact on the way of treatment of these children.
The WP7 project showed that the pharmacokinetics of enalapril of the ODMT in adults were very similar to a standard enalapril formulation so that a dose adjustment in the LENA clinical investigations in children was not needed.

## Dilated Cardiomyopathy Bridging Study – Orodispersible Minitablets of Enalapril in Children with Heart Failure due to Dilated Cardiomyopathy (DCM) (WP8)

Heart failure secondary to dilated cardiomyopathy is a relatively rare disease in children, while the prognosis is guarded. Transplantation free survival at 1- and 5 years after diagnosis has been reported around 75% and 50%, respectively. While treatment strategies that have proven efficacious in adults with heart failure, are widely accepted and used in children with heart failure a formal demonstration of its efficacy is lacking.
The most important impact of this study is twofold. First, for the first time in very young children with heart failure, data will be provided on the dose-exposure relationship of enalapril. Assuming similar underlying pathophysiological mechanisms in pediatric and adult heart failure secondary to cardiomyopathy, this allows to define dose recommendations for young children to obtain exposures that are similar to those in adults. Furthermore, data are provided on the interaction of enalapril with the neurohormonal systems it is, potentially, interacting with.
The second major impact is that a formulation is provided that has proved to be very well suited to deliver drugs even the youngest age groups in an easy and reliable way. This important for these children to optimize treatment, for parents to facilitate the care for their children as the burden of this disease on parents is already high. The advantage of using ODMTs in young children to deliver drugs has potential impact far beyond the use of enalapril.

## Study on Orodispersible Minitablets of Enalapril in Young Children with Heart Failure – Orodispersible Minitablets of Enalapril in Young Children with Heart Failure due to Congenital Heart Disease (CHD) – (WP9)

The LENA studies have provided, for the first time, scientific evidence for the use of orodispersible mini tablets in paediatric patients with heart failure due to congenital heart disease. This is a unique paediatric population of all age groups which highly deserves reliable chronic treatment. There is currently no licensed formulation of enalapril available in Europe suitable for use in children below 20 kg (about 6 years of age) with heart failure, resulting in the administration of extemporaneously compounded oral preparations. Therefore, with the LENA trials, the patients will be given a child size product with known quality attributes (dose, stability, bioavailability, safety etc.) which is portable, easy to handle and does not require the use of a measuring device.

## Clinical Safety Study with Longer Observation – Follow-up Safety Trial in Children with Dilated Cardiomyopathy (DCM) and Congenital Heart Disease (CHD) Receiving Orodispersible Minitablets (WP10)

First, these outcomes provide important impact to better treat children with safe and optimized dosing of enalapril as long-term safety data for the use of enalapril in children with heart failure had been obtained. The second major impact is that a formulation is provided that has proved to be very well suited to deliver drugs even the youngest age groups in an easy and reliable way ove a long period of time. This important for these children to optimize treatment and be adherent to therapy. It is also for partents important as this lowers the burden of disease for them. The advantage of using ODMTs in young children to deliver drugs has potential impact far beyond the use of enalapril.

## Ethics and Dissemination to Parents, Patients and Society (WP11)

Information on the LENA clinical study was disseminated in an accessible language primarily to people, particularly parents/patients, interested in medicines for congenital heart disease, secondary to people interested in mini- tablets and oral dispensible tablets. Also, information on the assent (consent) was provided to children and their parents considering participating in the LENA study.
In sum, parents, patients and patient / parent organisations as well as medical professionals's feedback is focused on these aspects:

1. A small number of parents were interested in specific project – the parents of those children likely to be eligible
2. Many parents and professionals were interested in the principle of developing medicines for children
3. The idea of a mini-tablet and its adaptability to other medicines raised high interest

## Education of the Scientific and Clinical Community (WP12)

"LENA" project held responsible for the education of young scientists, working in an interdisciplinary environment. The project consortium trained clinical research staff on the complex "LENA" proceedings based on the "LENA" study protocols and on interactions with patients and parents (i.e. at the "Medical Simulation Trainings" at PMU in Salzburg, Austria), which will help them in their future careers. A total of four PhD and two Diploma theses were supported by the "LENA" consortium. All LENA General Assembly meetings, Steering Committee meetings and meetings for specific topis such as study protocol development, Quality Team meetings, meetings for the development and conductance of the Medical Simulation Training helped to build up a network for (young) scientists working in the fields of paediatric clinical pharmacology, pharmaceutical technology, paediatric heart failure, and modelling and simulation. First insights into the newly generated knowledge could be presented and discussed with the "LENA" Ethical and Scientific Advisors, each a renown expert in their

field. Moreover, by publishing and presenting the results in academic journals, researchers had the opportunity to enlarge their network and their reputation in the area of paediatric clinical pharmacology, paediatric cardiology, pharmaceutical technology for paediatric formulations, and clinical trial performance in studies for children.

## Regulatory Interactions & Paediatric Development Strategy (WP13)

The smooth run through all regulatory requirements and approvals concerning study approvals, competent authority appovals, several interactions with the paediatric Committee about the content of the LENA trials helped to increase acceptance in academic consortia who normally are not familiarized with the regulatory requirements in the heavily regulated field of drug development in children. The LENA project is a proof that academic consortia al also competent to align with the regulatory requirements as pharmaceutical industry.

## Pharmacoeconomics and Commercialization (WP14)

LENA ODMTs with Enalapril maleate will be made available after the completion of the EU-funded project period in the European Union and beyond.

### 1.4.1 Socio-economic Impact

This collection of views on the socio-economic impact is derived from each of the work package leaders and reflects all experiences throughout the 5.5 years of collaborative work in the LENA team. It was regarded as important to have all the original comments and views listed from each work package. Thus, repititions were warrented and the different wording of even similar topics was regarded as additional value.

**Scientific Management & Joint Data Analyis (WP1)**

The LENA project has provided data for the first orodispersible mini-tablet ever for neonates (impact on European families). The minitablet was convenient and easy to handle, and highly appreciated by parents and patients. The parents did not need to use extemporaneous drug formulations, causing non-adherence and impeding the effective use of medications. Non-adherence can lead to hospital admissions and this might impact the economic wellbeing of the family. Thus, mini-tablets might have alleviated the socioeconomic burden of disease for the family.

**Pharmaceutical Development (WP2)**

LENA ODMTs help children who suffer from heart failure and their parents. Preparation of enalapril capsules at community or hospital pharmacies can be omitted as it may provide erratic doses due to difficult manufacturing, administration as powders emptied from hard capsules and unknown stability. As ODMTs are small scaled tablets which are produced with smaller yields and tabletting speed than bigger tablets, the cost of goods are higher. However, due to the rare indication of heart failure in children it will not significantly contribute to the drug product costs in our health systems.

**Non-clinical safety (WP3)**

The low toxicity, but high efficacy makes enalapril an ideal candidate for drug treatment of heart failure in children.

**Clinical Trial Management, Pharmacovigilance and Safety (WP4)**

Creating the clinical trial management and quality infrastructure for the performance of the LENA clinical trials within the strictly limited timelines and budget enabled the generation of reliable data required for marketing authorisation of enalapril ODMTs as a more reliable and acceptable galenic formulation for paediatric patients with heart failure. Lessons learned from establishing and implementing a clinical trials management and quality infrastructure in a publicly funded, successful, paediatric project will help other consortia in future to better plan and more efficiently execute their publicly funded clinical trial projects.

**Pharmacokinetic & Modeling and Simulation (WP5)**

Adhering to the highest ethical standards with microassays, PK/PD training of the medical staff for the conduct of the study lowered the burden of thepatients and helped to gain the benefits of reveiving better care while participating in a clinical trial in quite a lot of European countries.

**Statistics and Data Management (WP6)**

The implications of the above described impact is rooted in the excellent chance to successfully apply for a PUMA market authorization and by this in the potential future availability of a enalapril formulation that is safe and efficient in patients from neonates to adolescents. Furthermore, this

positive example may motivate other projects that also could improve the availability of high-quality medicines for children. The scientific publications that will be published on these data may have substantial impact on the rational use even of other enelapril formulation already on the market. The use of our simulation-based training strategy could improve the success of future studies with similar challenges.

### Bioavailability and Food Effect in Healthy Adults (WP7)

The greatest challenge in paediatric formulation development is to create dosage forms with measurable and easy-to-administer dosages. Some drug formulations for adults are associated with a risk of aspiration or choking, depending on the size and shape of the tablet or capsule. The LENA project has taken up this challenge by developing a new enalapril minitablet to treat children, from neonates to adolescents, with chronic heart failure. This condition was chosen as the EMA Expert Group on Paediatric Heart Failure considers enalapril to be a first-line treatment for chronic heart failure in children. By this project, LENA promotes the concept of drug development of age-specific formulations. At the end, LENA will have paved the way for the pricing, marketing and distribution of the novel age-appropriate solid drug formulation of enalapril in paediatric patients.

### Orodispersible Minitablets of Enalapril in Children with Heart Failure due to Dilated Cardiomyopathy (DCM) (WP8), due to Congenital Heart Disease (CHD) (WP9), and Follow-up Safety Trial Receiving Orodispersible Minitablets (WP10)

With better treatment of heart failure in children, less health care resources (including rehospitalizations and heart transplantation) may be needed and children's and family's welfare will be greater. Also, when children are in better health they can go to school, which ultimately increases their chances to contribute to the society as adults.
Moreover, when children are in better health, parents can also be more productive economically. Finally, WP10 data contribute to a PUMA which may contribute to a marketable product which may also generate revenue.

### Ethics and Dissemination to Parents, Patients and Society (WP11)

Parents have commented that it was very easy to administer the ODMT medicine. Also, less wastage was noted and a reduction in conflict with and/or challenge of getting pharmacists to dispense enalapril in a format that can be taken safely and accurately by children was mentioned several times.

### Pharmacoeconomics and Commercialization (WP14)

Enalapril maleate will enter the pharmaceutical market in a child-appropriate dosage form and dose strengths for the treatment of heart failure. Due to the innovative concept, the prices can be moderate and acceptable for reimbursement bodies. Introduction of the LENA products may encourage pharmaceutical companies to follow this process. The minitablet concept might be transferable to other drug products. The LENA project might serve as a blueprint for future PUMA or NCE products.

### 1.4.2 Wider Societal Implications

This collection of views on the societal implications is derived from each of the work package leaders and reflects all experiences throughout the 5.5 years of collaborative work in the LENA team. It was regarded as important to have all the original comments and views listed from each work package. Thus, repititions were warrented and the different wording of even similar topics was regarded as additional value.

**Scientific Management & Joint Data Analyis (WP1)**

Paediatric patients will be supplied with a child appropriate formulation which helps to maintain health, avoids hospitalisations, and avoids familiar disasters as parents need to care intensively for hospitalised children. LENAs mini-tablets are ideal medicines for children with limited access to clean potable water (impact on other parts of the world). Thus, minitablets are ideal medicines for developing countries and countries with limited access to the fresh, clean water necessary to administer drugs. With the data obtained in clinical trials of mini-tablets for neonates, infants, and young children and the subsequent application to other drugs, the LENA achievements can strengthen the pharmaceutical industry and small- and medium-sized enterprises (SMEs) of the European Union, which can then become more competitive and increase their economic power by offering novel and superior products.

**Pharmaceutical Development (WP2)**

LENA ODMTs may serve as a positive example and blue copy for academic and industrial institutions aiming at the development of a PUMA product. Patients and parents can be encouraged by the LENA project that there are novel concepts and products to be developed, even if the disease affect only few children and only in a hard period of their lives.

**Clinical Trial Management, Pharmacovigilance and Safety (WP4)**

Having been able to provide the infrastructure for creating evidence by generating a comprehensive set of quality data on pharmacokinetic, pharmacodynamic, safety and acceptability of enalapril ODMT administration by the other consortium partners will make the treatment with enalapril more reliable and dosing more adequate for paediatric patients with heart failure in all age groups.

**Statistics and Data Management (WP6)**

The high-quality data of the LENA trials. The ODMTs (if marketed) successful project cooperation as a role model and the innovative simulation training contribute to improvements in the research for and the development of high-quality medicines for neonates, infants, children and adolescents.

**Bioavailability and Food Effect in Healthy Adults (WP7)**

Children deserve medicines that are adapted to their needs. Dosage forms that are designed for adults are often inappropriate for children. For example, tablets that allow for adult doses may need to be split before being given to younger children, assuming that the active substance within the tablet is uniformly distributed within the tablet. A large proportion of medicines were given to children in an “off label” manner, or even without a license/marketing authorisation. The LENA project provides ODMT’s of enalapril in age-appropriate formulation that allows a reliable and constant dosage treatment in neonates and children.

## Orodispersible Minitablets of Enalapril in Children with Heart Failure due to Dilated Cardiomyopathy (DCM) (WP8), due to Congenital Heart Disease (CHD) (WP9) and Follow-up Safety trial in those children reveiving Orodispersible Minitablets (WP10)

We have shown that such a long-term safety study is feasible. Hence this can provide guidance for future similar studies in this population and thereby ultimately impact many-fold more children and their families. We have shown that medicine can be produced in a format that can accurately be given to very young children. This methodology could be adapted to other medicines taken by children/vulnerable adults and also that such a methodoly could be adapted to medicines used for vetinary purposes.

## Pharmacoeconomics and Commercialization (WP14)

The minitablet concept might bridge the gaps in paediatric medicines, as it may be applicable to many other drug substances which are desperately needed in paediatrics.

### 1.4.3 Main Dissemination Activities

The dissemination and exploitation activities of the "LENA" Consortium can be divided into to the following two domains:

**(1) CLINICAL AND SCIENFITIC DISSEMINATION:**

From the first funding period on, the "LENA" consortium implemented a multi-stakeholder dissemination strategy that targeted clinicians, researchers and scientists (particulary in paediatric clinical pharmacology and paediatric cardiology) at local, national and international scientific meetings, seminars, workshops, and congresses. To ease and harmonise the generation of dissemination material, corporate "LENA" design elements were created and made available to all consortium members. Based on these elements, local and national dissemination strategies were implemented and adapted to the respective audiences, ranging from the lay public to the clinical, political and scientific communities. These activities comprised talks, interviews, and a total of 26 peer-reviewed publications, and aimed at creating maximum awareness for the project, its overall vision and objectives, thus raising awareness and last but not least increasing participant referral to the recruitment sites.

LENA took great care in drafting a complementary and collaborative dissemination strategy that involved all PhD students and postdocs engaged in "LENA", thus leading to a large number of posters and oral presentations at the major scientific meetings of the field. Furthermore, in the last funding period, the first major paper on "Orodispersible minitablets of enalapril for use in children with heart failure (LENA): rationale and protocol for a multicentre pharmacokinetic bridging study and follow-up safety study" was published in "Contemporary Clinical Trials Communications".

**(2) PATIENT AND PARENT DISSEMINATION:**

Right from the project start, basis for a close interaction with stakeholders of relevance to the LENA project by creating a best practice dissemination guide and the corporate project identity was defined by considering the voice of patients and parents, professionally represented by the Children's Heart Federation (CHF). A project website (www.lena-med.eu) and detailed print material were created to ensure patients and parents are fully informed about the possibilities of this study and recognize the LENA partners as competent experts in the field of paediatric cardiology.

CHF has worked closely with the Board of ECHDO (The European Congenital Heart Disease Organisation) to ensure that information about the LENA project is communicated in a harmonized manner across Europe and the information about this important study is accessible to patients in all countries. CHF has disseminated information on LENA project across to a wide range of audience, although its priority audience has been patients and their parents or caregivers. It has used a range of media including:

- Leaflets: The flyer has been completed and is in English but will be translated into appropriate languages.
- Presentations at meetings and exhibitions for either or both clinicians or parents/caregivers
- Websites and Social Media (www.lena-med.eu, www.echdo.eu, www.chfed.org and CHF'S twitter and facebook accounts)
- A short animated film, with a narrative that can easily be translated into other languages and that is appropriate for publication on the web-site of patient organisations, on social media such as Twitter and on sites such as YouTube. The film emphasises the need to develop medicines for children using the LENA study as the main example, thus ensuring that the film has a long life

enabling it to reach a wide audience. It has been produced in a manner that allows easy translation into other national languages


*Figure 3: "LENA" and #meds4kids animated video created by LENA partner 8, Children's Heart Federation*

Beyond project duration, the LENA website (www.lena-med.eu) presents the "LENA" concepts, the methods and the teams to medical professionals and scientists as well as patients and parents of hospitalised children.

## 1.5 The “LENA” Consortium

**Labeling of Enalapril from Neonates up to Adolescents**

*Figure 4: The “LENA” consortium partners at the Kick-Off in 2013 (above) and at the Final Meeting in 2019 (below)*

Each of the 14 involved organisations from seven countries has been carefully selected to bring particular expertise or facilities to the “LENA” Consortium. The combination of such experience and know-how ensures proper up-take in the academic and clinical fields as well as subsequent capitalisation of results (see Table 1).

*Table 1: List of „LENA" consortium partners*

| Partner | | # | Short Name |
|---|---|---|---|
| | Heinrich-Heine-Universität Düsseldorf (Germany) | UDUS | 1 |
| | Ethicare GmbH (Germany) | Ethicare | 2 |
| | Pharmaplex bvba (Belgium) | Pharma-plex | 3 |
| | Gottsegen György Hungarian Institute of Cardiology (Hungary) | HPHC | 4 |
| | Erasmus MC – Universitair Medisch Centrum Rotterdam (Netherlands) | EMC | 5 |
| | Univerzitetska Dečja Klinika (Serbia) | UDK | 6 |
| | Paracelsus Medizinische Privatuniversität Salzburg (Austria) | PMU | 7 |
| | Children's Heart Fedeartion (United Kingdom) | CHF | 8 |

| Partner | | # | Short Name |
|---|---|---|---|
| | *GABO:mi Gesellschaft für Ablauforganisation :milliarium mbH & Co. KG (Germany)* | *GABO:mi* | *9** |
| | *Great Ormond Street Hospital for Children NHS Trust (United Kingdom)* | *GOSH* | *10** |
| | Katholieke Universiteit Leuven (Belgium) | KU Leuven | 11 |
| | Medizinische Universität Wien (Austria) | MUW | 12 |
| | University Medical Center Utrecht (Netherlands) | UMCU | 13 |
| | ARTTIC SAS (France) | ARTTIC | 14 |
| | Institut za zdravstvenu zaštitu majke i deteta Srbije „dr Vukan Čupić" (Serbia) | IMD | 15 |
| | Universitätsklinikum Hamburg-Eppendorf (Germany) | UKE | 16 |

* Terminated partner

Each of the involved organisations has been carefully selected to bring particular expertise or facilities to the Consortium. They share a common interest in advancing interdisciplinary research in the field of paediatric clinical pahramcology, paediatric cardiology and paediatric drug formulations. The "LENA" Consortium developed a safe, effective and age-appropriate formulation of enalapril for children which will be first in class as orodispersible minitablet by collaborating in an integrated, synergistic way in the domains of pharmaceutical development, cardiovascular pharmacology, paediatric clinical pharmacology, toxicology leading to results that would not be achievable by any partner on its own.

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