PROJECT FINAL REPORT

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1. Final publishable summary report

1.1. Executive summary

Beta-thalassaemia major is one of the most severe forms of anaemia. The recommended treatment consists in regular blood transfusions combined with chelating therapy to remove harmful iron accumulation in the body. The first chelating agent approved for clinical use was deferoxamine that, despite its potentially satisfactory therapeutic effects, is not usable by many patients due to toxicity. Moreover, its subcutaneous route of administration leads to non-compliance in most young patients. On August 1999, the oral iron chelator deferiprone was authorised in Europe where it is currently indicated for the treatment of iron overload in patients with beta-thalassaemia major when deferoxamine is contraindicated or inadequate. Despite a wide experience of deferiprone with thalassaemic patients, limited data are available on its use in 2-10 years old children and the need for additional data in this class of age is expressly stated in the 2009 PDCO (the Paediatric Committee at the European Medicines Agency) Priority List. In addition, the anticipated benefit in controlling cardiac iron overload in all the paediatric population as well as in other chronic transfusion-dependent anaemias, has led the PDCO to expand the request for additional data to the cited patients populations.

The DEEP Project has been developed with the specific intent to integrate the existing information on deferiprone use in paediatric patients, thus covering the lack of information and providing a valid support to the use of the drug in this class of age. According to the opinion expressed by the PDCO, the Project includes the whole paediatric population affected by beta-thalassaemia major and other chronic transfusion-dependent anaemias. The aim of DEEP is to provide data on deferiprone pharmacokinetics in younger children, to evaluate the safety of deferiprone in the clinical setting through a long-term observational study and to generate new comparative efficacy/safety data to be used to grant a Marketing Authorisation (MA) of a new liquid formulation of the drug, specifically developed for children use. At the end of the proposed set of studies, deferiprone will be available as first line treatment with the description of efficacious dosages in children under 18 years. The collection of prospective cost-efficacy data is also foreseen in the project to be incorporated in an HTA (Health Technology Assessment) report that will be of help for the Public Health managers and decision makers in guiding the inclusion of the drug in the current protocols and guidelines.

The condition under study in the DEEP project is rare. This poses special difficulties in the conduct of the studies due to the small patient population and the need to involve a large number of recruiting centres. However, being dedicated to develop an orphan drug, DEEP has been also recognised in the context of IRDiRC, the International Rare Diseases Research Consortium devoted to accelerate medical breakthroughs for people affected by rare diseases. As a result, a dedicated page on the DEEP project has been published on the Orphanet website.

Main features of the DEEP project are:

- the innovative design of the clinical studies including pharmacokinetic modelling for the definition of the most appropriate dosage of deferiprone in younger children;
- the inclusion of cardiac MRI T2* within the primary endpoints;
- a three years safety study aimed at evaluating deferiprone, in monotherapy or in combination, in the real world's setting;
- a comparative efficacy-safety trial to compare the two existing oral chelators: deferiprone and deferasirox;

- the DEEP Consortium including European and non-European Countries from the Mediterranean region and UK where the transfusion-dependent congenital anaemia, in particular β-thalassemia major, is particularly widespread: the collaboration within a multinational and multicultural network makes the Project extremely challenging due to many different ethical, methodological and social approaches to be explored and positively addressed;
- the DEEP Project is strongly supported by the TEDDY Network, to which most of the DEEP Beneficiaries adhere. This independent, multidisciplinary, multinational Network, composed by partners from EU and non-EU countries with the aim to perform and support paediatric clinical trials, is of paramount relevance for several reasons: it helps in enlarging the DEEP research partnership in order to reach the recruitment target; supports the development of Study Specific Procedures and age-tailored informative material; contributes to face the regulatory burdens and the ethical issues aiming at reaching the European standards also in not European countries.

1.2. Summary description of project context and objectives

Background

Thalassaemia is among the most common genetic disorders worldwide. An overview of the global distribution shows that beta-thalassaemia is widespread throughout the Mediterranean Region, Africa, Middle East, the Indian subcontinent and Burma, Southeast Asia, including southern China, the Malay Peninsula, and Indonesia. Estimates of gene frequencies range from 3 to 10 percent in some areas [Olivieri, 1999].

Beta-thalassaemias (β-thalassaemias) are a group of inherited blood disorders that are caused by reduced or absent synthesis of haemoglobin and that result in variable outcomes ranging from severe anaemia to clinically asymptomatic individuals.

Beta-thalassaemia major, also called Cooley's anaemia as it was first describe by Thomas Cooley in 1925, is the most severe form of beta-thalassaemias. Beta-thalassaemia major represents the majority of thalassaemia cases that are clinically relevant. While reliable sources estimate that about 1.5% of the global population – 80 million/90 million people – are carriers of beta-thalassaemia, with about 60,000 affected children born annually (the great majority in the developing world), it is certain that these figures are a gross underestimation. According to the TIF records, about 200,000 patients are alive and registered as receiving treatment around the world, underlining the bitter reality that the majority of affected children, born in developing countries, die undiagnosed or misdiagnosed, and receive sub-optimal treatment or are left untreated altogether [Eleftheriou, 2003]. In Table 1 (in attachment), demographic data relative to European and non-EU regions have been collected. Moreover prevalence and distribution varies among countries depending on primary prevention measures and treatment availability.

WHO region	Demography 2003				% of the population carrying			Affected conceptions (per 1000)			Affected births (% of under-5 mortality)
	Population (millions)	Crude birth rate	Annual births (1000s)	Under-5 mortality rate	Significant variant[a]	α^+ thalassaemia[b]	Any variant[c]	Sickle-cell disorders[d]	Thalassaemias[e]	Total	
African	586	39.0	22 895	168	18.2	41.2	44.4	10.68	0.07	10.74	6.4
American	853	19.5	16 609	27	3.0	4.8	7.5	0.49	0.06	0.54	2.0
Eastern Mediterranean	573	29.3	16 798	108	4.4	19.0	21.7	0.84	0.70	1.54	1.4
European	879	11.9	10 459	25	1.1	2.3	3.3	0.07	0.13	0.20	0.8
South-east Asian	1 564	24.4	38 139	83	6.6	44.6	45.5	0.68	0.66	1.34	1.6
Western Pacific	1 761	13.6	23 914	38	3.2	10.3	13.2	0.00	0.76	0.76	2.0
World	**6 217**	**20.7**	**128 814**	**81**	**5.2**	**20.7**	**24.0**	**2.28**	**0.46**	**2.73**	**3.4**

[a] Significant variants include Hb S, Hb C, Hb E, Hb D etc. β thalassaemia, α^0 thalassaemia.
[b] α^+ thalassaemia includes heterozygous and homozygous α^+ thalassaemia.
[c] Allows for (1) coincidence of α and β variants, and (2) harmless combinations of β variants.
[d] Sickle-cell disorders include SS, SC, S/β thalassaemia.
[e] Thalassaemias include homozygous β thalassaemia, haemoglobin E/β thalassaemia, homozygous α^0 thalassaemia, α^0/α^+ thalassaemia (haemoglobin H disease).

Table 1. Estimated prevalences of carriers of haemoglobin gene variants and affected conceptions [Modell and Darlison, 2008]

The signs and symptoms of beta-thalassaemia major appear within the first 2 years of life during which period children develop life-threatening anaemia, do not gain weight and grow at the expected rate (failure to thrive) and may develop yellowing of the skin and of the whites of the eyes (jaundice). Symptoms also include enlarged spleen, liver and heart, and misshapen bones (thin, brittle, and deformed); adolescents also experience delayed puberty.

Frequent transfusions are the recommended treatment for beta-thalassaemic patients in order to suppress ineffective erythropoiesis and to provide adequate oxygen carrying capacity. Early blood transfusions, moreover, have progressively reduced and sometime eliminated the clinical profiles seen in the past characterised by facial alterations, delay in growth, bone fractures and important haematopoietic actions (production of red blood cells in different sites to the bone marrow).

However, in the most severe forms of transfusion-dependent anaemia, after only few years on regular transfusion regimen, the iron storage capacity of the liver and other organs is exceeded, thus leading, in absence of an adequate intervention, to the development of a multi-system organ dysfunction which, in most cases, is lethal. The rate of iron loading in transfused patients is remarkably rapid and there is no physiological mechanism to excrete the excessive iron associated with regular blood transfusions. The exact mechanism of iron-induced damage is unknown, but it has been established that iron bounds to liver, heart and endocrine organs, leading to organ failure. In particular, cardiac failure associated with tissue iron deposition is the most common cause of death in thalassemia patients (>60%).

Since humans do not have a mechanism to eliminate excess iron, it is essential the use of substances that remove the iron from the body, the so called iron chelating agents.

Iron chelation therapy

The first chelating agent approved for clinical use was deferoxamine (DFO) which still plays a central role in iron overload treatment. Deferoxamine treatment has satisfactory therapeutic effects, improves the overall survival, but the prognosis remains poor because its requirement for prolonged subcutaneous infusion make the drug too burdensome for full adherence, thus leading to poor or noncompliance in a high percentage of patients, particularly in the paediatric population [Giardinia PJ et al., 2001; Kontoghiorghes GJ et al., 1996]. Moreover, 10-15% of subjects are unable to use this chelator due to hypersensitivity or toxic side effects. Finally, socioeconomic reasons (drug distribution, cost, health services availability and organisation) prevent its use in many underdeveloped and developing countries [Ayyub M et al., 2005].

Starting from these considerations, in recent years many orally administrable compounds have been studied. Research has led to the identification of several interesting molecules but, among these, only two agents became available on the European Market: deferiprone and deferasirox.

Deferiprone (DFP) was approved as second line treatment in 1999 and for many years it has been the only oral chelator available in Europe for treating subjects for whom deferoxamine was contraindicated or presented serious toxicity.

Only recently, a new oral chelator, deferasirox (DFX), has been approved as first line therapy in children from 6 years onwards and as second line therapy for younger children.

The introduction of DFP in the chelation schemes increased the compliance, the total survival and the quality of life of thalassaemic patients [Ceci A et al., 2006; Borgna-Pignatti C et al., 2006]. Comparisons with DFO have shown that both drugs are effective in reducing iron overload, when given at an appropriate dose. Deferiprone has shown also to be more effective than deferoxamine in chelating cardiac iron, thus providing greater protection against iron-induced heart disease, [Maggio A et al., 2009] while proportionately to DFP, DFO removes more iron from the liver.

These findings have demonstrated that deferiprone represents a valid alternative to the non-oral DFX and have also stimulated the combined use of the two drugs aimed to obtain a global improvement in treating iron overload.

The DEEP project

Despite a wide experience of deferiprone with thalassaemic patients, limited data are available on its use in 2 to 10 years old children. The need to increase information on the use of deferiprone in all age groups under the safest therapeutic conditions has led the PDCO to include deferiprone in the 2009 Priority list, with the specific request to provide data on PK, efficacy and safety in children from 2 years to less than 10 years.

The DEEP (DEferiprone Evaluation in Paediatrics) project has been developed with the specific intent to integrate the existing information on DFP use in paediatric patients, thus covering the lack of information and providing a valid support to the use of the drug in this class of age.

The primary aim of DEEP is to provide data on deferiprone pharmacokinetics in younger children, and to generate new comparative efficacy/safety data to be used to grant a Marketing Authorisation (MA) of a new liquid formulation of the drug, specifically developed for children use.

Specific aims are:

I. to evaluate pharmacokinetics and pharmacodynamics properties of DFP in children aged less than 10 years; efficacious dosages identified in this study will be used in the efficacy/safety study performed within this proposal;

II. to provide additional information on PKPD properties of deferiprone when used in combination with DFO in order to provide practitioners with more data on safe dosages;

III. to evaluate efficacy and safety of DFP compared to DFX therapy in paediatric patients (from 1 month to less than 18 years of age) affected by beta-thalassaemia major and other chronic transfusion-dependent anaemias;

IV. to provide long-term safety data by analysing all events potentially related to deferiprone use (alone or in combination with deferoxamine) in children;

V. to provide a pharmacoeconomic evaluation of DFP in the concerned aged group and in comparison with other chelating treatments.

At the end of the proposed set of studies, data will be available for the application of a Paediatric Use Marketing Authorisation (PUMA) and to make deferiprone available as first line treatment.

1.3. Description of the main S&T results/foregrounds

The DEEP Project has been developed with the specific intent to integrate the existing information on deferiprone use in paediatric patients, thus covering the lack of information and providing a valid support to the use of the drug in this class of age.

All activities planned and carried out during the 68 months of the project were dedicated to the achievement of the project's specific objectives and the implementation of the developmental plan agreed upon with the Paediatric Committee.

WP1 – PROJECT COORDINATION

WP1 final aim is to provide the overall scientific strategy, the project coordination and the establishment of the general framework for the management of the proposed clinical studies across the different European and non-European countries.

The DEEP team developed specific standard operating procedures (SOPs) and guidelines to be implemented by all the 16 DEEP Beneficiaries and by all the third parties at any time.

A Project Scientific Committee (PSC) and two additional independent bodies, the Ethics Board (EB) and the Data Safety Monitoring Committee (DSMC), were also established to monitor all scientific aspects of the project, the safety of the experimental drug and the rights, safety and wellbeing of patients involved in the DEEP studies.

WP2 - FORMULATION DEVELOPMENT AND PREPARATION OF A PAEDIATRIC ORAL SOLUTION

A new better flavoured oral 80 mg/mL liquid formulation specifically tailored for the paediatric population was developed by the pharma partners (Apotex and ApoPharma) of the DEEP Project. Deferiprone 80 mg/mL oral solution is a clear reddish pink solution with a bubble gum flavoured aroma.

The 80 mg/mL strength of the oral solution aims for a balance between accurate measurement of dose for patients of low body weight and manageable volume of administration. The flavouring was chosen to be of broad familiarity and acceptability, and its ability to mask the intrinsically bitter taste of deferiprone is reinforced by the lower concentration of active ingredient compared with the currently marketed 100 mg/mL deferiprone solution. Two pilot (development) batches were manufactured in October 2011 and two full-scale batches for clinical use were manufactured in January 2012 by Apotex Inc. All batches were filled into 250 mL and 500 mL amber coloured polyethylene terephthalate (PET) bottles closed with 24-400 and 28-400 white, polypropylene child resistant caps, respectively.

Stability tests were conducted and experimental batches were manufactured and released to the recruiting clinical centres, both for the DEEP-1 and the DEEP-2 clinical trials.

WP3 - PERFORMING A PK STUDY IN CHILDREN UP TO 6 YEARS OF AGE (DEEP-1)

The primary objective of the DEEP-1 study ("Multi-centre, oral single dose experimental and modelling study to evaluate the pharmacokinetics of deferiprone in patients aged from 1 month to less than 6 years of age affected by transfusion-dependent haemoglobinopathies"; EudraCT No. 2012-000658-67) was to assess the pharmacokinetics of deferiprone in paediatric patients aged from 1 month to less than 6 years.

It was a multicentre study involving 7 clinical centres of which only the 5 based in Italy actually recruited patients.

The study consisted of two phases: 1) an experimental phase, during which patients aged from 1 month to less than 6 years of age, received a single oral dose of DFP; 2) a modelling phase, during which PK data obtained in the experimental phase were analysed in conjunction with historical PK data from adults, older children and adolescents. The total duration of the study for each participant was approximately 30 days (from screening to follow-up visit).

The DEEP-1 clinical trial started in 2012 and the first patient was enrolled in January 2013.

By December 2013 all patients foreseen for the interim analysis (18 evaluable subjects) successfully completed the study and the plasma samples were shipped to Universiteit Leiden for the PK evaluation. On 17 February 2014, the analysis on the first 18 evaluable subjects was performed confirming that:

- no additional patients needed to be enrolled into the study;
- a dosing regimen of 25 mg/kg t.i.d. is recommended for children aged from 1 month to < 6 years, with the possibility of titration up to 33.3 mg/kg t.i.d., if necessary.

DEEP- 1 study report of results (synopsis in attachment) has been officially issued in May 2015.

EudraCT No: 2012-000658-67	
Title: Multi-centre, oral single dose experimental and modelling study to evaluate the pharmacokinetics of deferiprone in patients aged from 1 month to less than 6 years of age affected by transfusion-dependent haemoglobinopathies.	
Rationale: deferiprone (DFP) was investigated as therapy for children from 1 month to less than 6 years of age affected by transfusion dependent haemoglobinopathies. A pharmacokinetic study allowed appropriate evaluation of systemic exposure of DFP in the target population. A model-based analysis of the data enabled pharmacokinetic bridging and dosing recommendation for the subsequent non-inferiority study, during which efficacy and safety will be assessed.	
Phase: II a	
Study Period: 31 January 2013 – 17 February 2014	
Study Design: multi-centre, randomised, single blind, and single dose PK study.	
Centres:	
Site 1 (coordinating centre)	Dr. Giovanni Carlo Del Vecchio A.O.Universitaria Ospedale Consorziale Policlinico Di Bari U.O. Pediatria Federico Vecchio Piazza Giulio Cesare 11 70124 Bari

Site 2	Prof. Amal El Beshlawy Cairo University Paediatric Hospital Egyptian Thalassaemia Association 6 El Mouris St.El Monira,El Sayeda Zeinab Cairo Egypt
Site 3	Dr. Aldo Filosa Azienda Ospedaliera "A.Cardarelli" Di Napoli Uos Talassemia Pediatrica E Emoglobinopatie Pediatriche Via A.Cardarelli 9 80131 Napoli
Site 4	Dr. Soteroula Christou Makarios Hospital Thalassaemia Center Koritsas 6, Strovolos, 1474 Nicosia Cyprus
Site 5	Dr. Maria Caterina Putti Azienda Ospedaliera Di Padova Clinica Di Emato-Oncologia Pediatrica Via Giustiniani, 1 35127 Padova
Site 6	Prof Aurelio Maggio A.O. "V.Cervello" Di Palermo U.O.C. Ematologia Ii Via Trabucco,180 90146 Palermo
Site 7	Dr. Carlo Cosmi A.O. Universitaria Policlinico Di Sassari Viale San Pietro, 12 07100 Sassari
Treatment: patients were randomised according to a stratification scheme in which three different dose levels are used. Dose level 1: 8.3 mg/kg as a single dose Dose level 2: 16.7 mg/kg as a single dose Dose level 3: 33.3 mg/kg as a single dose	
Objectives: The primary objective of this study was to assess the pharmacokinetics of DFP in paediatric patients aged from 1 month to less than 6 years. The secondary objectives of this study were: 1) To identify dose levels yielding deferiprone exposures comparable to adults and define the dose rationale in children aged from 1 month to less than 6 years. 2) To evaluate safety and tolerability of deferiprone after single dose administration in children aged from 1 month to less than 6 years. 3) To evaluate the effect of demographic covariates on DFP disposition and estimate the clearance distribution across the population. It should be noted that in order to fully evaluate the effect of demographic covariates, further integration with prospective data on a larger population may be required.	

Pharmacokinetic analysis:

Model building: the time course of deferiprone concentrations was analysed with Nonlinear mixed effects modelling in NONMEM, version 7.2.0. Model building criteria included: (i) successful minimisation, (ii) standard error of estimates, (iii) number of significant digits, (iv) termination of the covariance step, (v) correlation between model parameters and (vi) acceptable gradients at the last iteration. Goodness of fit was assessed by graphical methods, including population and individual predicted vs. observed concentrations, conditional weighted residual vs. observed concentrations and time, correlation matrix for fixed vs. random effects, correlation matrix between parameters and covariates and normalised predictive distribution error (NPDE). Comparison of hierarchical models was based on the likelihood ratio test. A superior model is also expected to reduce inter-subject variance terms and/or residual error terms. Standard error of the parameter estimates were approximated using the asymptotic covariance matrix.

Covariate analysis: *The relationship between individual PK parameters (*post-hoc *or conditional estimates) and covariates was explored by graphical methods (plot of each covariate vs. each individual parameter). Relevant demographic covariates (i.e., body weight, age, height) were tested one by one into the population model (univariate analysis). After all significant covariates have been entered into the model (forward selection), each covariate was removed (backward elimination), one at a time. The model was run again and the objective function recorded. The likelihood ratio test was used to assess whether the difference in the objective function between the base model and the full (more complex) model was significant. The difference in twice the log of the likelihood (∆OBJF) between the base and the full model is approximately* χ^2 *distributed, with degrees of freedom equal to the difference in number of parameters between the two hierarchical models. Because of the exploratory nature of this investigation, for univariate analyses, additional parameters leading to a decrease in the objective function of 3.84 were considered significant (p<0.05). During the final steps of the model building, only the covariates which resulted in a difference of objective function ≥7.88 (p<0.005) were kept in the final model.*

Validation *of the final model was based on graphical and statistical methods. First, a bootstrap procedure was performed in PsN v3.5.3 (University of Uppsala, Sweden). Bootstrap was used to identify bias, stability and accuracy of the parameter estimates (standard errors and confidence intervals). PsN does so by generating a set of new datasets by sampling individuals with replacement from the original dataset, and fitting the model to each new dataset.*

Subsequently, parameter estimates were used to simulate plasma concentrations in paediatric patients with the similar demographic characteristics, dosing regimens and sampling scheme as in the original clinical studies. Furthermore, an internal validation of the final model, based on simulation techniques such as Visual Predictive Check (VPC) and Normalised Prediction Distribution Errors (NPDE), was performed to assess the predictive ability of the model.

Secondary PK parameters: In addition to the final model parameter estimates, secondary pharmacokinetic parameters were derived based on the individual predicted concentration vs. time profiles. Area under the concentration vs. time curve (AUC_{∞}), area under the concentration vs. time curve during the dosing interval ($AUC_{0\text{-}8h}$), time to peak concentration, concentration at steady-state (Css) and trough concentration (i.e., at 8 hours post dose) (Cmin) were listed for each patient and summarised per dose level.

PK bridging and dosing recommendations: To optimise DFP dosing regimen in the target population, simulations were performed to obtain systemic exposure values similar to the adult reference population. Simulations were carried out to explore how differences in demographic covariates might affect steady-state exposure to DFP treatment. Sampling frequency and times were based on a serial sampling scheme for the purposes of estimating AUC, Cmax and Css over the dosing interval. Integration of the concentration time data was applied according to the trapezoidal rule to ensure realistic estimates of variability. The adequacy of the simulated dosing regimens was

assessed graphically by determining the fraction of the paediatric population reaching systemic exposure comparable to the target range based on PK reference values in adults.

Safety analysis:
Descriptive statistics were used to summarise adverse events, vital signs and clinical lab data (haematology, biochemistry and virology). Findings arising from medical history, ECG monitoring, physical examination and concomitant medication were recorded for each patient and presented as listings or summary tables, where appropriate. As clinical chemistry (haematology and biochemistry) measurements were not performed by a central lab, a list of normal ranges from each participating centre was used for reference values. All other clinical measures and procedures, e.g. ECG measurements, were performed in each centre according to standard clinical practice.
All the medical occurrences that started prior to the drug administration were recorded as medical events. Assessment criteria for the classification of safety findings included causality, intensity, pattern, outcome, action taken with regard to IMP and other action taken.

Study Population: children from 1 month to less than 6 years of age affected by transfusion dependent haemoglobinopathies.

Number of subjects	
Planned, N	30
Enrolled, N	23
Dosed, N	18
Completed, N	18
Number of screening failures, N	2
Number of premature discontinuations, N	3
Demographics	
N (All subjects dosed – PK analysis population)	18
Males/Females	9/9
Age (Years) (mean and SD)	3.62 (1.33)
Weight (Kg) (mean and SD)	16.08 (3.18)
Height (Cm) (mean and SD)	98.95 (9.16)

Pharmacokinetics (PK) Endpoints: (All subjects dosed, i.e., PK analysis population)

Deferiprone PK parameter, median (5^{th} and 95^{th} quantiles)	**Dose 1 – 8.3 mg/kg**	**Dose 2 – 16.7 mg/kg**	**Dose 3 – 33.3 mg/kg**
N of subjects per dose group	6	6	6
AUC_{0-8} (µM/L*h)	116.7 (90.6-129.0)	210.0 (173.1-266.6)	428.8 (291.4-547.8)
Cmax (µM/L)	61.7 (45.1-80.7)	119.8 (106.0-154.0)	229.5 (179.7-278.1)
Tmax (h)	0.33 (0.19-0.92)	0.33 (0.21-0.63)	0.37 (0.27-0.42)
Css (µM/L)	2.1 (1.6-2.3)	3.7 (3.1-4.9)	7.7 (5.1-10.0)
Cmin (µM/L)	1.5 (0.92-2.6)	1.9 (0.79-5.5)	6.8 (3.1-13.9)

Safety results (Safety population N=21): All adverse events (AEs) occurring before or after dosing were recorded

Adverse Events:	
N	3
No. subjects with AEs, N	3
Serious Adverse Events (SAEs):	
No. subjects with any SAEs	0

Conclusion:

DFP showed a very favourable safety profile in children younger than 6 years of age after administration of single oral doses of 8.3, 16.7 and 33.3 mg/kg. No serious adverse events were observed during the study. The pharmacokinetics of the new oral formulation of DFP was successfully characterised by a model-based approach. A one-compartment open model with first-order absorption and elimination processes accurately described the PK profile of the drug under investigation, allowing the estimation of the main PK parameters of interest. In addition, the inclusion of body weight on CL/F and V/F according to fixed allometric scaling showed that differences in size explain part of the variability in the data. As such, body weight was found to be a good predictor of inter-individual differences in the population under investigation.

Bridging concepts were applied to evaluate the exposure in the paediatric population with the objective of defining dosing recommendations that yield DFP levels comparable to those observed at efficacious doses in adults. Using the pharmacokinetic model developed for the paediatric population in this study in conjunction with a model previously developed for adult subjects, simulations were performed to evaluate drug exposure in children below 6 years of age and in adult patients. AUC and Css distributions were found to be comparable at 75 mg/kg/day and 100 mg/kg/day. Differences in Cmax were not considered clinically relevant. Based on these findings, a dosing regimen of 25 mg/kg t.i.d. (75 mg/kg/day) is recommended for children aged from 1 month to < 6 years, with the possibility of titration up to 33.3 mg/kg t.i.d. (100 mg/kg/day), if necessary.

WP4 - PERFORMING AN EFFICACY/SAFETY TRIAL TO COMPARE DFP VERSUS DFX (DEEP-2)

The primary objective of the DEEP-2 study ("Multicentre, randomised, open-label, non-inferiority active-controlled trial to evaluate the efficacy and safety of deferiprone compared to deferasirox in paediatric patients aged from 1 month to less than 18 years affected by transfusion-dependent haemoglobinopathies"; EudraCT No. 2012-000353-31) is to assess the non-inferiority of deferiprone (DFP) compared to deferasirox (DFX) in terms of changes of ferritin levels and heart iron concentration in paediatric patients affected by hereditary haemoglobinopathies requiring chronic transfusions and chelation.

The total duration of the study for each participant is approximately 14 months (from screening to follow-up visit). Both study treatments are administered orally, at a starting dose which depends on the patient's weight and on the previous chelation treatment. DFP must be taken daily 3 times-a-day, possibly at consistent times. DFX must be taken once a day on an empty stomach.

The DEEP-2 study has received the ethical approval in 24 experimental centres (both European and non–European). The list of the 23 centres activated out of the 32 involved, with the related status of the patients for each centre, is detailed in Table 2 (in attachment).

Site ID	Town/Country	Planned	Randomized (V3)	Ongoing (V3-V15)	Completed (V15)	Early Termination
01	Palermo/Italy	10	11	6	5	0

Site ID	Town/Country	Planned	Randomized (V3)	Ongoing (V3-V15)	Completed (V15)	Early Termination
02	Cairo/Egypt	130	133	43	61	29
03	Athens/Greece	12	11	4	5	2
04	Tirana/Albania	20	27	14	12	1
05	Nicosia/Cyprus	12	8	4	0	4
06	Naples/Italy	14	13	0	10	4
07	Tunis/Tunisia	30	56	54	0	2
08	Padua/Italy	9	9	0	8	1
09	Bari/Italy	12	6	3	3	0
10	Palermo/Italy	4	3	0	0	3
11	Cosenza/Italy	4	1	0	1	0
12	Lentini/Italy	6	1	1	0	0
13	Modena/Italy	3	0	0	0	0
14	Sassari/Italy	5	5	0	4	1
15	Cagliari/Italy	7	5	1	2	2
16	Florence/Italy	4	3	2	1	0
17	Catania/Italy	6	2	1	1	0
18	London/UK	20	19	18	0	1
19	London/UK	5	4	4	0	0
20	London/UK	5	0	0	0	0
23	Zagazig/Egypt	40	40	37	0	3
24	Alexandria/Egypt	25	23	17	0	6
31	Lushnja/Albania	12	12	12	0	0
		Total	**393**	**221**	**113**	**59**

Table 2. Patients' status in DEEP-2 centres at the end of October 2016

The first visit of the first patient was held on 17 March 2014 and the last patient was randomised on July 15th, 2016. As of October 2016 a total of 393 patients were randomized, 113 patients have successfully completed the study and further 221 patients are under treatment with one of the two IMPs.

An interim analysis was performed at the beginning of November 2016, evaluating the first 57 patients that completed the 1 year of study and the 245 patients that completed 6 months of study. The evaluation of the primary efficacy endpoint (ferritin) allowed us to conclude that:

- the percentage of success in the two protocol' arms (DFP and DFX) is similar;
- while the sample of 57 patient that concluded the study is too small to demonstrate the non-inferiority, this latter is fully demonstrated in the 245 patients group observed for 6 months.

On the basis of these preliminary results, we are confident that DEEP-2 study will be successfully completed and its results will be respondent to the DEEP project objectives and commitments.

WP5 - PERFORMING A LONG-TERM SAFETY TRIAL IN CHILDREN UP TO 18 YEARS (DEEP-3)

In order to establish the safety profile in paediatric patients, we performed the DEEP-3 safety study: a long-term observational safety study to evaluate the nature and incidence of adverse effects of deferiprone treatment in children with β-thalassaemia major, who are aged from one month to less than 18 years when deferiprone treatment commences.

The study's main objective was the generation of safety data in terms of nature and incidence of serious and non-serious adverse drug reactions (ADRs) to DFP in children and adolescents with beta-thalassaemia major and transfusional iron overload. Secondary objective was the analysis of potential risk factors for ADRs and therapy discontinuations.

DEEP-3 was a multi-centre, retro- and prospective, non-interventional, observational cohort field study and was implemented in 16 hospitals in six Mediterranean countries: Albania (1), Cyprus (1), Egypt (1), Greece (1), Italy (11) and Tunisia (1). A list of all centres and principle investigators is presented in Table 3 (in attachment). The Universitätsklinikum Erlangen was sponsor of this study and principle study coordination took place at the Department of Paediatrics and Adolescent Medicine, Friedrich-Alexander University Erlangen-Nürnberg.

Centre	Country
Qendra Spitalore Universitare Nene Tereza, Tirana	Albania
Cyprus Ministry of Health, Nicosia Thalassaemia Center, Nicosia	Cyprus
Cairo University, Cairo, Egypt	Egypt
National and Kapodistrian University of Athens, Athens	Greece
Azienda Ospedaliera di Rilievo Nazionale AntonioCardarelli, Naples	Italy
Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo	
Azienda Ospedaliera di Padova, Padua	
Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari	
ARNAS-Civico G. di Cristina-Benfratelli, Palermo	
Azienda Ospedaliera di Cosenza, Consenza	
Ospedale Civile di Lentini, Lentini	
Policlinico di Modena, Modena	
Azienda Mista Ospedaliera-Universitaria di Sassari, Sassari	
Ospedale Regionale per le Microcitemie-ASL8, Cagliari	
Azienda Ospedaliero-Universitaria Meyer, Florence	
Centre national de Greffe de Moelle Osseuse, Tunis	Tunisia

Table 3. DEEP-3 participating centres

The study started in 2012 and data collection was stopped in April 2016.

Three hundred and ten patients were enrolled into the study. The complete observation period was from March 1994 to October 2015 with 717.4 person-years (PY) follow-up, mostly retrospective (663.7 PY, 92.5%). Collectively, 3,213 study visits were recorded by the investigators. Median follow-up per patient was 1.7 years (IQR 0.8-3.5) and ranged from two days to 15.2 years. Further details are outlined in Table 4 (in attachment).

	Albania	Cyprus	Egypt	Greece	Italy	Tunisia
Study sites	1	1	1	1	11	1
Start of recruitment	Sept 2013	Mar 2015	Apr 2013	Nov 2012	May 2013	Feb 2015
Enrolled subjects	5	13	154	23	101	14
With complete records	5	13	148	23	97	11
Age (median, range, in years)[1]	13.3 (10.3-14.4)	11.1 (5.0-14.1)	4.6 (0.6-17.6)	10.5 (3.3-16.9)	10.5 (1.1-17.4)	7.5 (4.0-12.6)
Follow-up (total person-years)	13.7	30.8	253.6	73.6	326.2	19.3
Retrospective observation	11.3	29.4	230.9	70.3	302.6	19.3
Prospective observation	2.4	1.5	22.7	3.4	23.6	0
Per patient (median, IQR)	3.3 (1.9-3.5)	1.6 (0.7-3.7)	1.2 (0.7-2.1)	2.7 (1.4-4.8)	2.7 (1.4-4.9)	1.1 (0.3-3.4)
[1] *P*-value <0.001 (Kruskal-Wallis test).						

Table 4. Study characteristics

Patient age at start of DFP therapy ranged from 0.6 to 17.6 years (median 8.5, IQR 4.0-12.2) and was significantly different between participating sites. The majority of patients (59.9%) was below the age of 10 years and 37.7% below the age of 6 years at baseline (Table 5, in attachment).

Patients, analysed	297 (100.0)
Age (years)	8.5 (4.0-12.2)
< 6 years	112 (37.7)
6-10 years	66 (22.2)
> 10 years	119 (40.1)
at diagnosis of β-TM	0.8 (0.4-1.2)
at start of transfusion therapy	0.7 (0.5-1.2)
at start of chelation therapy	2.8 (2.0-4.5)
Gender	297 (100.0)
Female	145 (48.8)
Male	152 (51.2)
Origin	297 (100.0)
Europe	131 (44.1)
North Africa	154 (51.9)
Rest of Africa	1 (0.3)
North America	6 (2.0)
Latin America	1 (0.3)
Asia	4 (1.4)
β-TM type	84 (100.0)
β^0 / β^0	23 (27.4)
β^0 / β^+	28 (33.3)
β^+ / β^+	30 (35.71)
Hb Lepore / β^0	1 (1.2)
Hb Lepore / β^+	1 (1.2)

δβ / β^+	1 (1.2)
Transfusional iron intake (mg/kg/day)	293 (100.0)
Low (< 0.3)	46 (15.7)
Intermediate (0.3-0.5)	197 (67.2)
High (> 0.5)	50 (17.1)
Annual blood requirement (mL pure RBC/kg/year)	125 (117-156)
Spleen status	289 (100.0)
Normal	51 (17.7)
Splenomegaly	168 (58.1)
Splenectomised	70 (24.2)
Serum ferritin (ng/mL)	268 (100.0)
< 2,000 ng/mL (n, %)	143 (53.4)
2,000-4,000 ng/mL (n, %)	93 (34.7)
> 4,000 ng/mL (n, %)	32 (11.9)
HIV seropositive (n = 183)	0 (0.0)
Hepatitis B seropositive (n = 237)	10 (4.2)
Hepatitis C seropositive (n = 242)	41 (16.9)
Values are median (IQR) and number of patients n (%), if not stated otherwise.	

Table 5. Patient demographics and baseline characteristics

DFP-related ADRs were ascertained by an independent expert team. Incidences and incidence rates for serious and non-serious ADRs were calculated and analysed using Kaplan-Meier failure function. Potential risk factors for ADRs and treatment discontinuations were explored using multivariate logistic regression and Cox proportional hazards methods.

A total of 491 adverse events (AEs) including 158 serious AEs in 183 patients underwent the ADR causality assessment. One-hundred-seventy-two AE episodes in 104 patients were deemed at least possibly related to DFP and therefore considered as ADRs for further analysis (Table 6, in attachment). This corresponds to an ADR incidence of 35.0% and incidence rate of 24.0 episodes per 100 PY. After 13 months on DFP, the ADR probability is one out of four and after 74 months every other patient experienced at least one ADR. In patients with at least one ADR, 18 suffered from two different ADRs, four patients from three different ADRs and one patient experienced four distinct ADRs. ADR incidence did not differ significantly in a subgroup analysis of Egyptian patients using *Ferriprox* or *Kelfer* (P-value 0.491, Chi-square test). As for serious ADRs, the incidence and incidence rate was 14.8% and 9.5 per 100 PY, respectively. In three patients we observed two distinct serious ADRs whereas in all other 41 patients not more than one serious ADR was seen. The probability of having a serious ADR was 20.6% after 36 months of treatment.

MedDRA SOC / Preferred Term	**ADRs / Patients**	**Severity** mild / moderate / severe	**Seriousness** non-serious / serious	**Incidence**[1] (95% CI)	**Incidence rate**[2] (95% CI)	**DFP discontinuation**[3] (95% CI)
Blood and lymphatic system disorders						
Agranulocytosis	2/2	0/2/0	0/2	0.7 (0.1-2.4)	0.3 (0.0-1.0)	0.7 (0.1-2.4)
Leukopenia	3/2	3/0/0	3/0	0.7 (0.1-2.4)	0.4 (0.1-1.2)	0.3 (0.0-1.9)
Neutropenia	38/25	26/12/0	0/38	8.4 (5.5-12.2)	5.3 (3.7-7.3)	5.1 (2.9-8.2)
Thrombocytopenia	1/1	1/0/0	0/1	0.3 (0.0-1.9)	0.1 (0.0-0.8)	0.3 (0.0-1.9)
Gastrointestinal disorders						
Abdominal pain	9/8	6/3/0	9/0	2.7 (1.2-5.2)	1.3 (0.6-2.4)	1.0 (0.2-2.9)
Diarrhoea	1/1	1/0/0	1/0	0.3 (0.0-1.9)	0.1 (0.0-0.8)	none
Dyspepsia	4/4	4/0/0	4/0	1.3 (0.4-3.4)	0.6 (0.2-1.4)	0.3 (0.0-1.9)
Nausea	3/3	1/2/0	3/0	1.0 (0.2-2.9)	0.4 (0.1-1.2)	0.3 (0.0-1.9)
Salivary hypersecretion	1/1	1/0/0	1/0	0.3 (0.0-1.9)	0.1 (0.0-0.8)	none
Vomiting	14/10	3/11/0	14/0	3.4 (1.6-6.1)	2.0 (1.1-3.3)	2.7 (1.2-5.2)
General disorders and administration site conditions						
Fatigue	1/1	0/1/0	1/0	0.3 (0.0-1.9)	0.1 (0.0-0.8)	0.3 (0.0-1.9)
Investigations						
Transaminases increased	42/31	35/7/0	17/25	10.4 (7.2-14.5)	5.9 (4.2-7.9)	6.4 (3.9-9.8)
Weight increased	1/1	1/0/0	1/0	0.3 (0.0-1.9)	0.1 (0.0-0.8)	none
Musculoskeletal and connective tissue disorders						
Arthropathy	43/35	10/30/3	41/2	11.8 (8.3-16.0)	6.0 (4.3-8.1)	8.4 (5.5-12.2)
Bone pain	5/5	2/3/0	5/0	1.7 (0.5-3.9)	0.7 (0.2-1.6)	1.3 (0.4-3.4)
Renal and urinary disorders						
Chromaturia	1/1	1/0/0	1/0	0.3 (0.0-1.9)	0.1 (0.0-0.8)	none
Skin and subcutaneous tissue disorders						

MedDRA SOC / Preferred Term	**ADRs / Patients**	**Severity** mild / moderate / severe	**Seriousness** non-serious / serious	**Incidence**[1] (95% CI)	**Incidence rate**[2] (95% CI)	**DFP discontinuation**[3] (95% CI)
Rash	2/1	2/0/0	2/0	0.3 (0.0-1.9)	0.3 (0.0-1.0)	none
Urticaria	1/1	0/1/0	1/0	0.3 (0.0-1.9)	0.1 (0.0-0.8)	none
TOTAL						
Any ADR	172/104	97/72/3	104/68	35.0 (29.6-40.7)	24.0 (20.5-27.8)	23.2 (18.6-28.5)
Any serious ADR	68/44	48/19/1	0/68	14.8 (11.0-19.4)	9.5 (7.4-12.0)	9.1 (6.1-13.0)

[1] Number of patients with at least one ADR from the corresponding group divided by all exposed patients in percent (95% CI); [2] Number of ADR episodes divided by total observation time per 100 PY (95% CI); [3] Number of patients permanently discontinuing DFP due to the ADR divided by all exposed patients in percent (95% CI). PY: person-years; CI: confidence interval

Table 6. All identified adverse drug reactions to deferiprone

The safety profile and ADR incidences found are consistent with information in the latest EU and US summary of product characteristics (SPC). No unexpected ADRs or specific risk factors for ADRs were identified. Most ADRs were of mild or moderate severity. Similar to adult data, agranulocytosis is the most serious ADR to DFP with incidence of 0.3% in children and adolescents.

Mild-to-moderate neutropenia, arthropathy, increased transaminases, and gastrointestinal disorders are other important ADRs and led to therapy discontinuation in up to 23.2% of patients. Single cases of mild thrombocytopenia and leukopenia were identified, which are not described in the current SPCs but reported in the literature. Patients generally recovered shortly from ADRs upon dose reduction, temporary interruption or permanent therapy discontinuation. There was no greater risk for ADRs in patients below the age of 10 years or on combined iron chelation therapy with DFO.

The safety profile of DFP in children and adolescents obtained from this study is in accordance with the latest information in EU/US SPCs and manufacturer post-marketing data. There was no increased risk for ADRs in children under the age of 10 years or in patients with combined therapy with DFO. The risk for agranulocytosis in children treated with DFP is comparable to older patients. Close monitoring of neutrophil count remains mandatory in every patient. However, further mechanistic studies are needed to identify potential risk factors and ethnic differences for the occurrence of agranulocytosis.

WP6 - MANAGEMENT OF REGULATORY AND PHARMACOECONOMIC ISSUES

In compliance with the Paediatric Regulation (EC) 1901/2006, a PIP was submitted to the Paediatric Committee (PDCO) in February 2011. Its regulatory and scientific evaluation process led to the approval of the deferiprone Paediatric Investigation Plan in November 2011 and a final EMA decision in December 2011. In August 2014, a request for modification (RfM) of the agreed PIP was submitted to the European Medicines Agency (EMA) and its Paediatric Committee (PDCO). The procedure ended in November 2014 (Figure 1, in attachment).

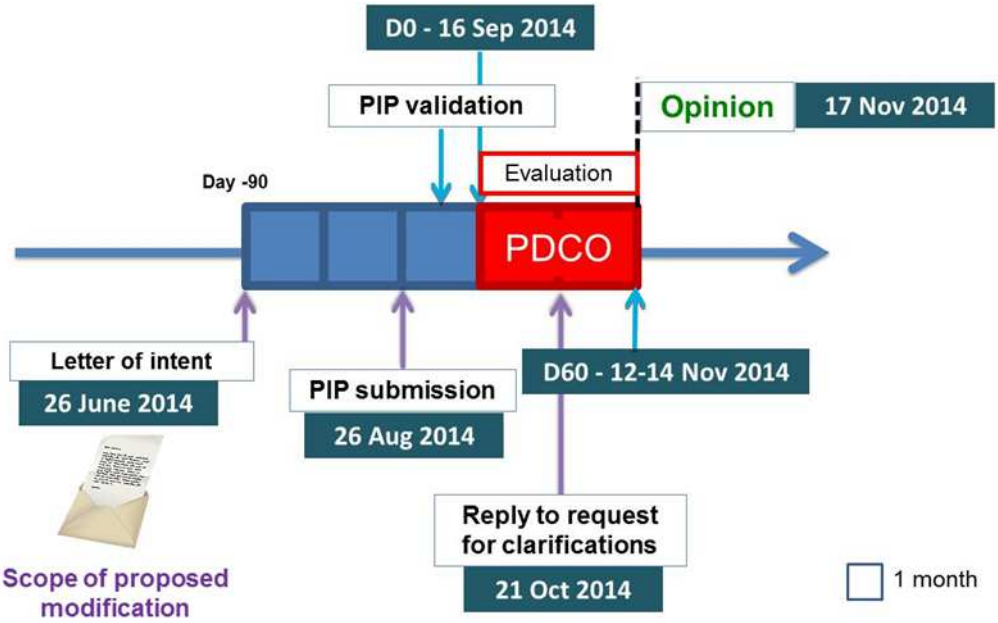


Figure 1. Request for modification of an agreed PIP

The PIP modification was motivated by both the need to implement the results of the modifications introduced by the scientific coordination group into the DEEP-2 protocol and by the intention to clarify minimal aspects on timing and use of data with reference to DEEP-1 and DEEP-3 studies.

The DEEP final clinical plan agreed with the EMA-PDCO includes the following main aspects:

a) Condition: β-thalassaemia and other conditions requiring long-term blood transfusion therapy and chelation;

b) Age Groups: entire paediatric population;

c) Pharmacokinetic study (WP3, DEEP-1): formal PK study in children < 6 years, modelling phase for generating data on deferiprone appropriate dosage in young children;

d) Efficacy/Safety study (WP4, DEEP-2): the other oral chelating agent deferasirox (DFX) is used as comparator for evaluating safety and efficacy of DFP in paediatrics, in the framework of a clinical trial involving 388 patients for a period of 13-14 months;

e) Long-term safety study (WP5, DEEP-3): a retrospective and a prospective cohort of at least 300 patients, exploring serious and non-serious adverse events associated to the use of DFP;

f) Pharmacoeconomic evaluation: prospective comparative data on health care resource utilization, compliance and quality of life (QoL) are collected in patients admitted to DEEP 2 study, to provide a pharmacoeconomic evaluation that will be part of a HTA report.

The DEEP project pharmacoeconomic evaluations of deferiprone is based on the collection of real costs generated by the use of the chelators and of compliance and QoL data during the DEEP-2 study period. In particular the Child Health Questionnaire (CHQ) is used to evaluate the health-related quality of life (HRQoL) from the perspective of parents/guardians. All these data will be of help for the Public Health managers and decision makers in guiding the inclusion of the drug in the current Protocol and Guidelines.

To collect, discuss, compare and summarise information and evidence on iron chelators, the Health Technology Assessment (HTA) approach has been adopted. HTA is *a form of policy research that systematically examines the short- and long-term consequences, in terms of health and resource use, of the application of a health technology, a set of related technologies or a technology-related issue*. To this aim, the most relevant domains have been investigated and results included will be in a HTA report (Health problem and current use of technology, CUR; Description and technical characteristics of drugs and therapies, TEC; Safety, SAF; Clinical effectiveness, EFF; Costs and economic evaluation, ECO).

Moreover, to estimate how a change in the current mix of drugs used to treat iron overload in paediatric patients could impact on budget decisions, a Budget Impact Analysis – i.e. *a financial evaluation technique able to estimate the short-term financial consequences of the adoption and diffusion of a new health technology in a specific geographical area* – will be produced.

WP8 - COMMUNICATION STRATEGY AND THE KNOWLEDGE MANAGEMENT

Work package 8 (WP8) was aimed to ensure efficient communication with stakeholders outside the project in order to raise awareness about DEEP activities and results and to use the results of the project for a PUMA application and for marketing exploitation. In this sense, dissemination plays an essential role in the DEEP project in contributing to its cohesion and success both in terms of well-planned coordination among the stakeholders and of results to be released to a public not involved in the project.

Dissemination activities carried out in the context of the DEEP project included:

- the set-up and maintenance of means of dissemination through the design of a dedicated graphical identity, the definition of communication channels (electronic mailing list, the project website, external conferences, Partners' website and other portals);
- the production of communication materials (website contents, newsletter, press releases and other informative materials);
- the production of informative materials (age appropriate booklets and assent forms as well as the booklet entitled "Living well with thalassaemia").

A **Communication Plan** was developed to identify the communication activities to be performed in the framework of the DEEP project and to make the projects results public among the different stakeholders in an appropriate, effective and efficient manner.

Communication activities have been designed for specific target audiences in order to give maximum visibility to the project and its results. Progresses and results of the DEEP studies have been disseminated by means of scientific publications, presentation of oral communications, abstracts, posters at scientific meetings, other publication and press releases. All members of the Consortium have contributed to these dissemination activities by participating and giving presentations at conferences, publishing papers, networking and similar activities within the range of their scientific networks and affiliations, in order to ensure that the foreground of which they have ownership is disseminated as swiftly as possible, as requested by the European Commission. To this aim, a variety of channels such as a project website, scientific publications, partners' websites and other portals, social networks and the DEEP newsletters have been used, as reported below.

1. Project website. The DEEP project website (Figure 3, in attachment) is available at the following link: www.deepeproject.eu and has been used as the main dissemination tool, covering

the project's goals, objectives, accomplishments, background information and partner's role and contribution. It is an interactive website, accessible to the public and different stakeholders with an easy-to-use interface, based on the project's graphical identity.

The DEEP logo (Figure 2, in attachment) is characterised by several cubes of different colours evoking the children's game. A stylised child's face also appears in one of the cubes together with the EU's stars representing the EU contribution to the project.

Figure 2. DEEP logo

DEEP visual identity is the "soul" of the Project and represents its personality and philosophy, helping the project to be easily recognisable also outside the Consortium and allowing a wide dissemination of its results. It has been applied to all communication materials.

The DEEP website underwent a complete renewal in 2014: the graphic features were improved, the website was rendered more dynamic and user-friendly and new pages, specifically devoted to patients and families, with simplified texts describing the project scope and aims were introduced.

The website and in particular the sections "News" and "Events" under the "Updates" main menu have been regularly updated with project news, articles, press releases and downloadable versions of public documents. Furthermore, a section entitled "**Studies**" has been created and regularly updated for each study, aimed at providing information on the study objectives, centres involved and recruitment status. A counter has also been published on the DEEP homepage to provide timey updates on the DEEP-2 patients recruitment status.

The dedicated pages are available here:

- DEEP-1 study (http://www.deepproject.eu/deep-1-performing-a-pharmacokinetics-trial-of-deferiprone-in-children-up-to-6-years/)
- DEEP-2 study (http://www.deepproject.eu/deep-2-performing-an-efficacysafety-trial-to-compare-deferiprone-with-deferasirox/)
- DEEP-3 study (http://www.deepproject.eu/deep-3-performing-a-long-term-safety-study-of-deferiprone-use-in-paediatric-patients/)

A specific **section for families and children** was created; here the main reasons and characteristics of iron chelation treatments are explained in language and wording appropriate to age and using the iconic format.

In particular, the DEEP-2 information booklets have been published on the page dedicated to children, and the booklet entitled "Living well with thalassaemia" has been published in the "Results

& Publications" section of the DEEP website. All these informative materials are available in the 6 project languages (Albanian, Arabic, English, French, Greek and Italian).

Figure 3. Snapshot DEEP website

In the period from October 2013 to October 2016 (Figures 4 and 5, in attachment), there have been a total of 20.439 visits with an average of 16 visitors per day per session (a session is a visit

by a visitor, both as a new user and a returning visitor). The table shows also the monthly number of accesses.

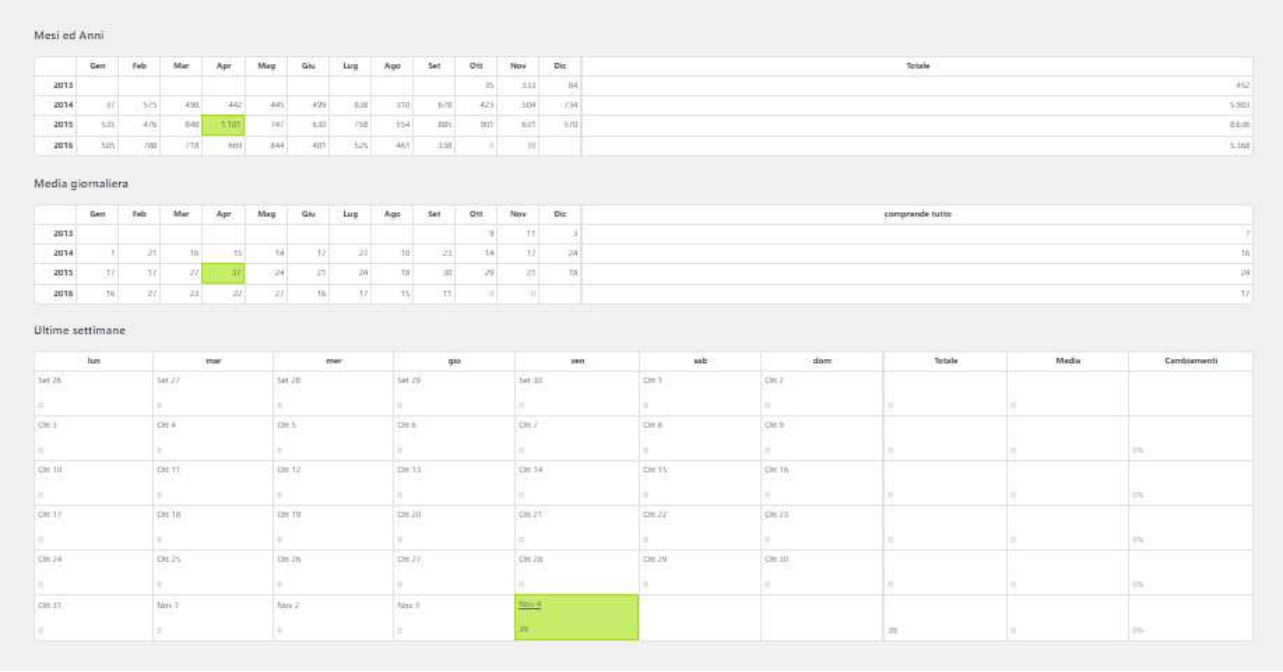


Figure 4. Number of users visits to the website up to November 4th, 2016

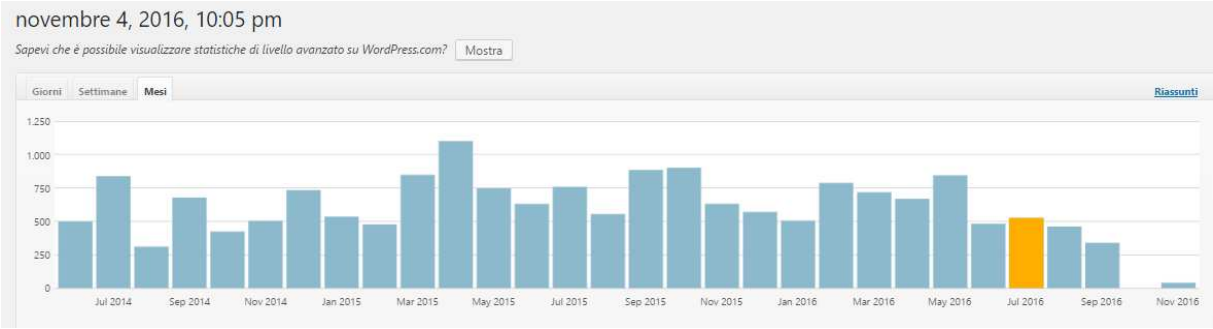


Figure 5. Trend of the project visits up to November 4th, 2016

The record of 119 visitors, who clicked links from Search Engines pages (Google Search) to get to the DEEP website, has been recorded on March 19th, 2015.

2. **Social network.** To give further visibility to the project and to reach also a non-scientific audience as well as patients and parents associations, the following social network channels have been created: DEEP Facebook profile (https://www.facebook.com/DeepFP7, Figure 6, in attachment) and DEEP Google+ (https://plus.google.com/+DeepprojectEuFp7; Figure 7, in attachment). These social network channels were aimed to help the project to reach and be reached by that range of people where social networks are more popular, included dedicated groups, patients/families and the parents associations. By exploiting these very useful two-way

communication forms of media, all project activities and results have been shared more quickly with a wide public audience.

Figure 6. DEEP Facebook page

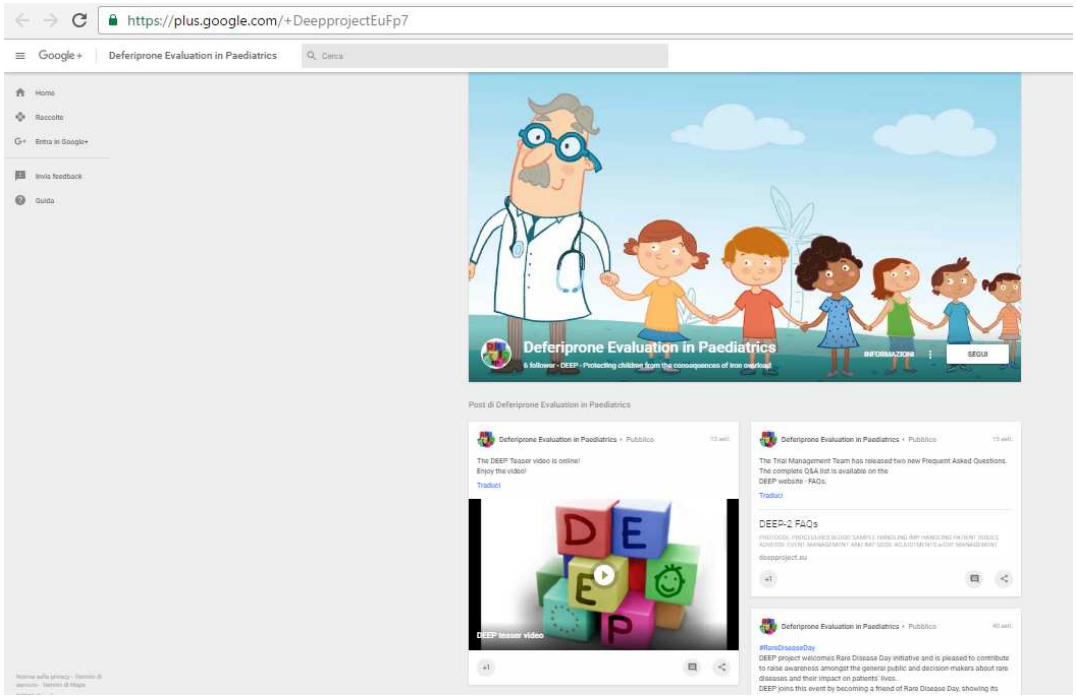


Figure 7. DEEP Google+ page

All interviews realized during the sixth General Assembly in Tirana (2015) with key DEEP staff and opinion leaders as well as the DEEP promotional video are available on a dedicated YouTube channel (https://www.youtube.com/c/DeepprojectEuFp7; Figure 8, in attachment).

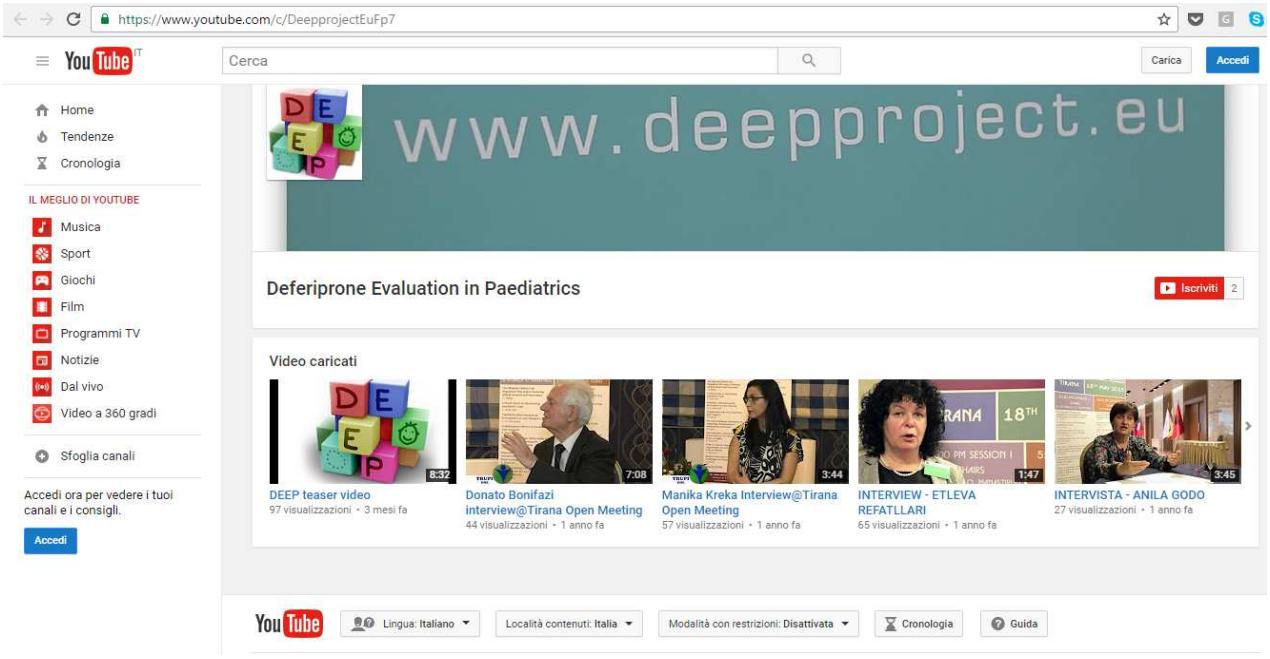
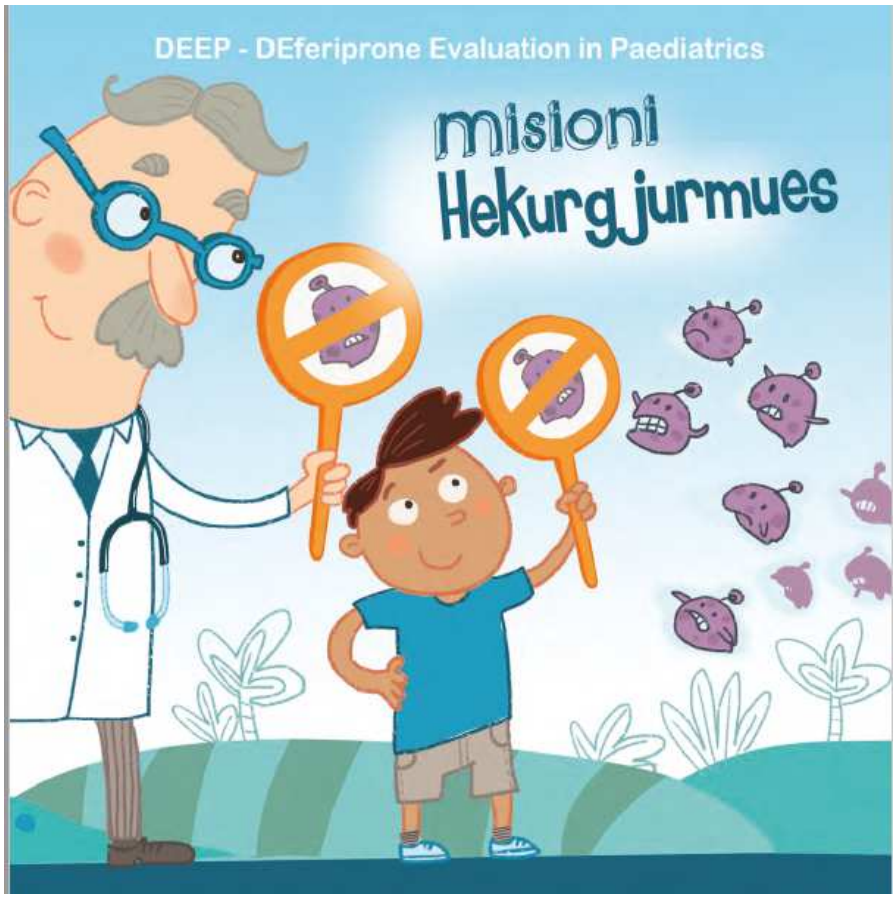


Figure 8. DEEP YouTube Channel

3. Promotional teaser video. A promotional teaser video has been developed with the aim to describe with an "emotional" cut and a dynamic style, the scope and the objectives of the project through the voice of scientists, patients and the management team, focusing on the prospects for an enhancement of the patients' quality of life. It includes touching moments resulting from the personal and direct experiences of children affected by thalassaemia, who were interviewed in May 2015 in Tirana with the collaboration of University Hospital Center "Mother Teresa"– UHCT (Albania), reporting their situation, describing how their diseases are affecting their daily life and how they live with their diseases. The DEEP Project has entered in their homes and in their private lives, and it has provided with the possibility to understand how DEEP can really support them and how clinical studies can definitely help in finding a suitable cure. The video has been published on the DEEP YouTube channel and is available at this link: https://youtu.be/94U08_jQ99Q.

4. Informative booklets. Children have the right to know in advance which medicines they need and why. They should be allowed to express their own views and granted the right to participate in the decision-making process concerning their own health. Moving from such assumptions, the DEEP Project has developed **age-tailored information booklets and assent forms** to explain the clinical trial procedures to the children involved in DEEP-2 in the six languages of the Project. The materials have been developed within a collaborative effort between pharmacologists, paediatricians, child psychologists and illustrators. Their aim is to inform children on deferiprone use, on the final objectives of the trial they are involved in, and on the importance of such research.

Three different booklets explaining the DEEP-2 aims and procedures and what children are going to experience and two different assent forms have been realised (Figure 9, in attachment).



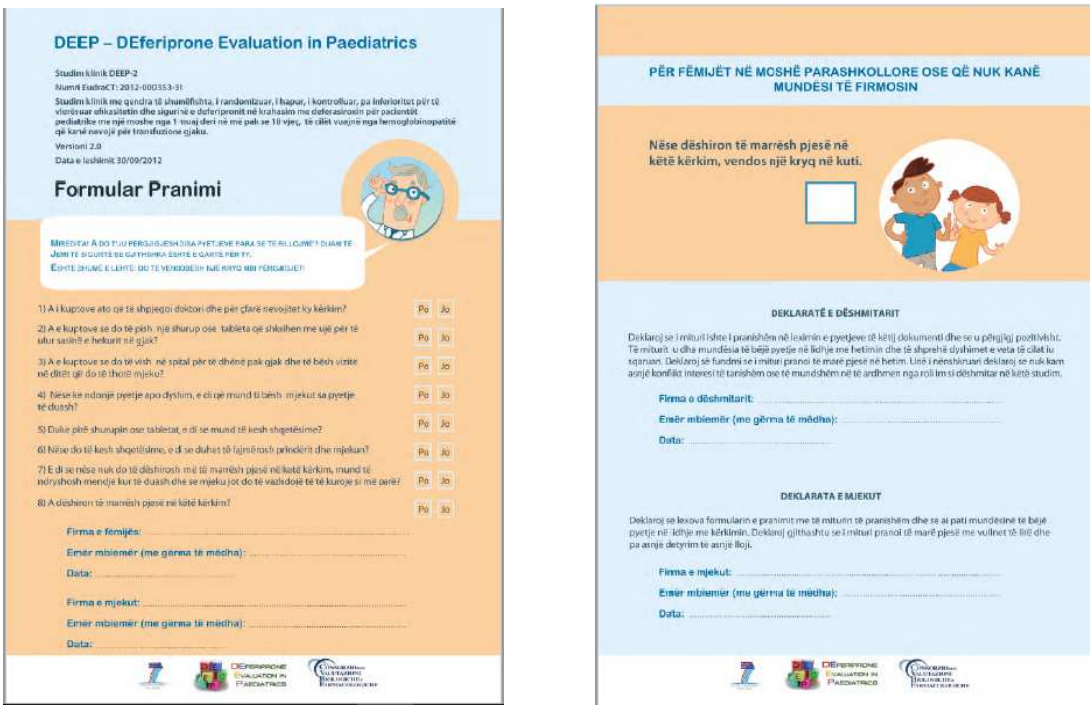


Figure 9. Example of DEEP Informative materials and assent forms

To investigate the quality of the informative material addressed to paediatric patients involved in DEEP-2 study, the **QuBo substudy** ("Quality evaluation of the informative booklets for patients involved in the DEEP-2 trial") has been conducted in some patients. The overall aim of this study was to evaluate the level of comprehension and the likeability of the informative documents proposed in the clinical trial to paediatric patients.

Particularly, QuBo has foreseen the filling in of an age-tailored structured questionnaire (one for 6-11 years old patients and another one for 11-18 patients) that has been used to directly collect the children's and adolescents' opinion on the DEEP-2 informative material. The study has involved centres adhering to DEEP-2 and all patients receiving the DEEP-2 informative material. Children have only been asked to provide their feedback about the age-appropriate informative documents produced to explain key aspects of the clinical study. The study has demonstrated that the use of informative booklets has favoured the understanding and participation in the clinical trial.

Furthermore, the Gianni Benzi Pharmacological Research Foundation prepared a booklet entitled "**Living well with thalassaemia**" (Figure 10, in attachment), available in the 6 project languages (Albania, Arabic, English, French, Greek, Italian) and aimed to provide patients with direct access to knowledge and understanding of the numerous problems related to the treatment and cure of thalassaemia. The publication did not intend to provide general information that are already available in other publications and from other sources (including the worldwide web), but to give detailed information in answer to those questions asked most frequently by the patients, at the same time trying to eliminate the prejudices and common misconceptions about the illness.

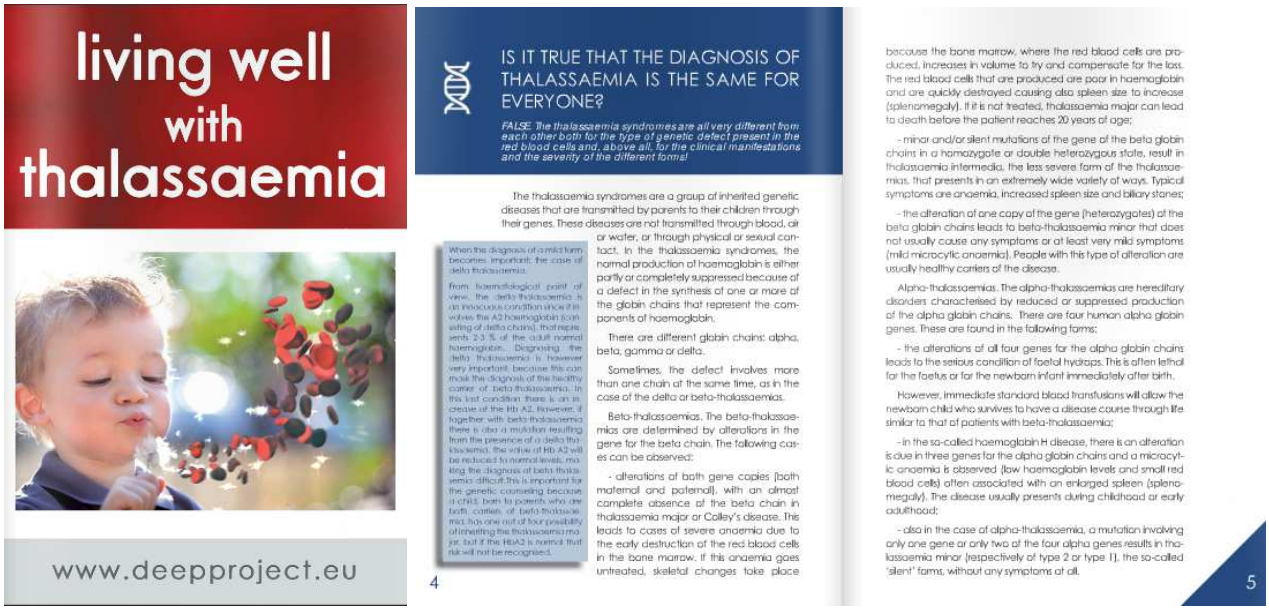


Figure 10. Living well with thalassaemia booklet in English

5. Newsletters. Two different types of newsletters have been produced in the course of the Project. The study newsletters (per each study) were sent periodically to all scientific partners (PI, CRAs, Clinical Monitors, etc.) to keep them updated about the study conduction/alerts and recommendations. The Project newsletters were sent to a general and wider audience in order to provide them with updates on the main project results and accomplishments in a plain language. Newsletters have been edited in English and are available to read on the webpage and in a downloadable version in the "Results & Publications" section. To date, the following newsletters' issues have been released:

- 2 DEEP-1 study newsletters
- 22 DEEP-2 study newsletters
- 4 DEEP-3 study newsletters
- 6 DEEP Project newsletters.

In particular, the project newsletters have been distributed to more than 1,000 contacts.

6. Scientific publications and press releases. Producing scientific publications is an important activity to disseminate project progresses and results and has been pursued throughout the whole project. In order to coordinate the publication strategy, ensure transparency within the Consortium, boost the publication activities of project results and define the procedure for preparing, reviewing, submitting and maximizing diffusion of scientific publications and dissemination material, a SOP for "Scientific publications and dissemination activities" has been prepared.

Progresses and results of the DEEP studies are disseminated also by means of publication of abstracts, posters and articles. The detailed list of scientific (peer reviewed) publications related to the foreground is available in the Table 1 "list of all scientific publications" attached to the report.

Moreover, information on the DEEP project and press releases have been published on many websites. The detailed list is available in the Table 2 "list of all dissemination activities" attached to the report.

7. Presentation at scientific events. DEEP Project dissemination goals have been achieved by efforts of all the partners in exploiting occasions and opportunities to generate exposure of the project and all of the partners have been encouraged to get involved in the dissemination activities. In particular, according to the Grant Agreement, Annex II, art.II.30, each beneficiary shall ensure that the foreground of which it has ownership is disseminated as swiftly as possible and all dissemination activities shall be compatible with the protection of intellectual property rights, confidentiality obligations and the legitimate interests of the owner(s) of the foreground.

All members of the Consortium have contributed to the dissemination activities by participating and giving presentations at conferences and other major events related to the main topics of the project, publishing papers, networking and similar activities within the range of their scientific networks and affiliations, in order to give rise to deeper discussions on its results and benefit from possible feedback from other experts in the DEEP research area.

8. Networking. Dissemination activities have also been fostered through the participation in national and international professional networks that can allow project visibility as well as the sharing of their channels and in particular the use of their existing mailing lists, newsletters and meetings to cover a wider dissemination. Members of the DEEP Consortium are in fact members of various paediatric scientific and clinical research associations as well as national, international and specialty networks. These networks' platforms have been used to disseminate the progresses and results of the project as well as to foster access to the wider professional community. In particular, DEEP is member of the TEDDY Network (European Network of Excellence for Paediatric Clinical Research), which is an independent multidisciplinary, multinational Network aimed at facilitating the performance of good quality paediatric studies and research. TEDDY is a member of the Enpr-EMA, the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA).

Project website address: http://www.deepproject.eu/

Name, title and organisation of the scientific representative of the project's coordinator:

Consorzio per Valutazioni Biologiche e Farmacologiche

Prof. Adriana Ceci, Project Scientific Coordinator

1.4 Potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results

The European Commission defines dissemination as "a planned process of providing information on the quality, relevance and effectiveness of the results of programmes and initiatives to key actors". It occurs as and when the results of programmes and initiatives become available. Dissemination activities have consequences in terms of both financial and time expenditure, therefore the development of communication tools and the execution of dissemination activities are essential in order to raise awareness of the project as a whole, and specifically of its results, among different stakeholders.

As a consequence, dissemination is playing an essential role in the DEEP Project in contributing to its cohesion and success.

The collaboration developed between the project partners has been so effective and intense that at the end of the funded project period, on August 31st, 2016, they have decided to sign a new consortium agreement aimed at:

- continue the project activities;

- regulate the dissemination activities of the results;

- plan the creation of a stable International network for the paediatric haematological research.

In this sense, the main purposes of DEEP dissemination activities have been and will be to:

- ensure that efficient communication with stakeholders outside the project is implemented;
- raise awareness of the project, its activities and outcomes, to build an identity known by all the stakeholders;
- target communication activities to those who can benefit from it and make the project understandable for the general public;
- create networking and sharing opportunities within the scientific community;
- disseminate results to parents' organisations and lay media.

Following the launch of the European Commission open access pilot in FP7, grant beneficiaries, like the DEEP Consortium, are expected to deposit peer-reviewed research articles or final manuscripts resulting from their projects into an online repository and make their best efforts to ensure open access to those articles within a set period of time after publication.

The DEEP Grant Agreement and Consortium Agreement contain provisions aimed at defining the procedure for the dissemination of project results, ensuring transparency and safeguarding of the legitimate interests of all beneficiaries. Therefore, results from the DEEP clinical trials shall be published and made accessible online to ensure free internet access to these research outputs. The principal objective of an open access policy in the seventh framework programme (FP7) is to provide researchers and other interested members of the public with improved online access to EU-funded research results. This is considered a way to improve the EU's return on research and development investment.

In reference to Article II.29 of the GA, the Beneficiaries shall use the Foreground which they own, or ensure that it is used. "Use" means the direct or indirect utilisation of Foreground in further research activities other than those covered by the Project, or for developing, creating and marketing a product or process, or for creating and providing a service. Direct utilisation is done by

the Beneficiary owning the Foreground while indirect utilisation is done by other parties (e.g. through licensing). It is clear that commercial Use must only be undertaken if it makes sense from an economic point of view. When ownership of Foreground is transferred, one of the obligations to be passed on is the obligation to use the Foreground concerned.

In order to implement the dissemination activities, also at the end of the DEEP Project, in a consistent manner with the European Commission criteria, the Project's dissemination agenda has included the design of a communication plan aimed to raise awareness of the Project as a whole, and specifically of its results, among different stakeholders. Subsequently, communication tools identified by the communication plan have been and will be developed and adapted as needed, keeping in mind the actions, audiences and objectives to which these tools should serve as supporting materials. All the developed materials shall include the following disclaimer: "The research leading to these results has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 261483 (DEEP – DEferiprone Evaluation in Paediatrics)".

Though patient/family communication and civil society information are dissemination areas in strong development in the framework of the Project, dissemination undertakings will entail primarily scientific interactions that will include, at least:

- **Publication of scientific papers**. Preference will be given to the generation of publications related to the project activities and results, which will be mainly submitted for publication in international scientific journals with as high an impact as possible.

- **Presentations at relevant events** (Congresses, meetings, workshops, e-learning activities, etc.). An important dissemination activity will comprise participation in the organisation of relevant events where the presentation of the project, its approaches and results, can take place.

Presentations can take the form of oral communications, participation in poster sessions or any other format foreseen as appropriate.

- **Organisation of scientific Open Meetings.** So far, four scientific Open Meetings have been organised in the framework of the DEEP Project in Albania, Cyprus, Greece and Italy. A fifth Open Meeting was planned to be held in Tunis first in December 2015, then in February 2016, but unfortunately terrorism, that has left almost no Country spared, hit Tunisia at those periods forcing the DEEP Consortium to cancel the meeting.

The DEEP Open Meetings have been a crucial dissemination activity as they have allowed to people not directly involved in the DEEP Project to talk about the goals of the DEEP project and to raise the attention on the progresses achieved by the clinical research and the challenges to be faced in conducting clinical trials in paediatrics, also highlighting the importance of the international cooperation through European Networks and the global initiatives to create synergies and foster clinical research. In particular, the meeting in Tirana has been an important way to promote the clinical research in paediatrics and a sort of window on the Mediterranean area stressing the concept that the international activities promoted in the clinical research field and in collaboration with an international research consortium could, indeed, provide support for aligning Albanian as well as the North African countries standards and practices with those present in the European Union for establishing working procedures to make innovation feasible.

It is remarkable that the DEEP-2 Safety/Efficacy Study (EudraCT: 2012-000353-31) represents the first paediatric clinical trial ever performed in Albania and in which the University Hospital Centre "Mother Teresa" of Tirana (which represents the main and most important Albanian Hospital, being also a tertiary level Hospital and the only academic and Research Hospital Centre in Albania) is officially involved, after the entry into force of the new Albanian law concerning clinical trials. DEEP-2 is also conducted at the Hospital of Lushnja (Albania), participating as Third Party in the DEEP Project, in accordance with a signed agreement between the General Direction of the Hospital and the no-profit Sponsor, CVBF.

Beyond the administrative management of the study, in the conduct of this clinical trial, the Coordinator CVBF is extensively supporting the Albanian study team both in the start-up phase and in the trial progression, ensuring the performance of the trial in compliance to the ICH GCP. This represents a valid example of how to respond to European Commission (EC) Research policies promoting networking and public-private partnership, providing a new model for clinical research and disseminating competencies and technologies in non-European Countries.

The model proposed by DEEP focuses on therapeutic needs in paediatric and the integration of research and culture, adopting a global regulatory framework and patient-tailored transparent communication tools and has to become an example and the first milestone in developing the clinical research in Albania.

- **Individual presentations and meetings with key stakeholders**. To raise the interest and gain support of key actors, such as regulatory authorities, individual contacts will be established as needed. This task will provide an important connection with the future use of the project results, insofar as the ultimate aim of DEEP is to boost the adoption of regulatory decisions on the use of deferiprone for the treatment of iron overload in children.

- **Informative materials tailored to patients and parents**. Informative packages for patients/parents have been created, specifically tailored to this audience. In addition, a report tailored for patients and parents will be prepared at the end of the studies with the aim to inform patients enrolled in the DEEP studies and their parents on the Project results. At present, while DEEP-1 and DEEP-3 have been concluded, the efficacy/safety DEEP-2 trial is still running, as the enrolment was closed on July 2016 and the last patient will end the treatment on July 2017. The report will have an easy to manage format and a charming graphic and will provide patients and parents with the results of all the three studies and will foresee their direct involvement according to a "participatory design" methodology. In order to foster the dissemination of results and reach and inform all participants in the studies and their family as well as a large target audience as possible, the report will be translated in the six languages (Albanian, Arabic, French, Greek, Italian and English) of the Project. An electronic and a printable version will be realised and distributed to the project partners and uploaded on the project and partners' websites. The report will be sent to the European Commission as soon as it will be finalised.

Some tools considered essential will also be developed in order to support and make the most out of the planned dissemination activities throughout the Project. A brochure will be produced, as well as a generic poster, with the intention to reflect the status of the project and to support the presentations at events and the individual meetings. In order to attract a wider audience, press releases will be developed according to the needs of the different stakeholders. A website has been set up, intended to support and reinforce all of the above mentioned dissemination. The website

will be further updated with project news, and downloadable versions of all public documents generated by the project are being made available.

Finally, looking in to the future, the DEEP consortium is working to promote an international network in Paediatric Haematology based on the achievements and progress made in this years:

- contribution to the harmonisation of clinical and diagnostic standards for trials in thalassaemia/SCD patients in a large geographic area including Mediterranean area;
- ability to fulfil GCP requirements for paediatric clinical trials improving the quality and aligning the services, standards and procedures offered by each centre.

Expected advantages of creating a stable Network will be: the cooperation will be enforced; the Network could candidate in the ongoing initiatives in EU such as the Paediatric Research Infrastructure and the pan-European Paediatric Clinical Trials network, and to be part of Enpr-EMA.

The pathway towards the **international network in paediatric haematology** perfectly fits the international scenario where, following the entry into force of the Paediatric Regulation, EU paediatric networks gathered in Enpr-EMA (the European Network of Paediatric Research at the European Medicines Agency), to grant an efficient inter-network and stakeholder collaboration and foster high-quality ethical research on medicinal products in children. One of the most important duty of a specialty network is to define/revise and agree priorities for the conditions of interest according to the arising scientific, social and healthcare needs and to cover the gap in paediatric clinical trials and research.

To date, Enpr-EMA includes in this area only the Paediatric Diseases Working Party as subgroup of EBMT European Blood and Marrow Transplantation, while a specific Paediatric Haematology Network is not included.