FP7 Projects in Rare Anaemias: DEEP - Deferiprone Evaluation in Paediatrics

Adriana Ceci
DEEP Scientific Coordinator,
on behalf of DEEP Consortium
1- Project Specificities:

2- The Regulatory steps:
   PIP
   Clinical Trials in the project

3- The DEEP CT facilitating strategy

4- Status of the projects and preliminary results
**PROJECT SPECIFICITY: RESPONDING TO EU POLICY NEEDS**  
(*FP7-HEALTH-2010. 4.2.*)

- Only ~30% of marketed drugs are paediatric in Europe
- A large paediatric ‘off-label’ use occurs as:
  - Unapproved formulations
  - Drugs for adults not tailored for children
- Less than 50% of Paediatric Medicines have been studied in children

**Increase drugs and Trials in children**

**Grant a Paediatric Investigational Plan before the trials will start**

**Identify therapeutic needs and Priority for funding**

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**Table:**

<table>
<thead>
<tr>
<th>Age</th>
<th>UK(%)</th>
<th>It(%)</th>
<th>NL(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>33.0</td>
<td>20.0</td>
<td>32.1</td>
</tr>
<tr>
<td>2-11</td>
<td>0.4</td>
<td>1.6</td>
<td>26.4</td>
</tr>
<tr>
<td>12-17</td>
<td>2.0</td>
<td>2.0</td>
<td>42.5</td>
</tr>
<tr>
<td>Total</td>
<td>4.7</td>
<td>7.6</td>
<td>32.4</td>
</tr>
</tbody>
</table>

Neubert and al, on behalf of TEDDY NoE, Pharmacol Res. 2008 Nov-Dec;58(5-6):316

**Image:**

TEDDY - European Paediatric Medicines Database  
Medicines approved to be used in the paediatric population  

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**Diagram:**

REGULATION (EC) No 1901/2006
Measures in the Paediatric Regulation

- ensuring that **new products (or variations)** will be developed to meet paediatric needs according to PIPs agreed by the Paediatric Committee (art.7- art.8)

- Give a new MA (PUMA) to the **existing** medicines (OFF-PATENT) willing to developing at least one paediatric study (art.30). **PIP is needed**

All the needs:

~ 20 therapeutic classes
~ 400 active substances

Funding of studies **into off-patent medicinal products** should be provided through the EU FRPs (art. 40) with the aim to develop a PUMA
## Why Ferriprox was included in the Priority List

<table>
<thead>
<tr>
<th>The legal status</th>
<th>Ferriprox obtained the EU MA under exceptional circumstances in Oct. 1999 ‘Off-patent drug’</th>
</tr>
</thead>
<tbody>
<tr>
<td>The relevance of the therapeutic Area</td>
<td>To be used in <strong>rare and more severe</strong> forms of anaemia in the world</td>
</tr>
<tr>
<td>The scarcity of approved chelators in some paediatric ages: <strong>Therapeutic Need</strong></td>
<td><strong>Age:</strong> ( &gt;2 \text{ and } &lt; 6 \text{y} )  <strong>SmPCs information:</strong> the only approved drug in this group of age is DFO. Oral chelators can be used if DFO is refused, inadequate or contraindicated</td>
</tr>
<tr>
<td>The scarcity of clinical evidence</td>
<td><strong>Few data</strong> in children (&lt;10 \text{ years})  No controlled comparative trials</td>
</tr>
</tbody>
</table>
| The expected **therapeutic benefits:**  \(\begin{align*}
\text{Optimal doses of SC DFO or PO DFX are less effective than DFP in reducing cardiac iron and improving cardiac function} \\
\text{Reduced cardiac mortality and morbidity if the drug used as first line} \\
\text{Possible preventive effect if used in younger children before iron accumulation}
\end{align*}\) |
SEVENTH FRAMEWORK
PROGRAMME
THEME [HEALTH.2010.4.2-1]
FP7-HEALTH-2010-single-stage]
Grant agreement for: Collaborative project*

Annex I - "Description of Work"

Project acronym: DEEP
Project full title: DEferiprone Evaluation in Paediatrics
Grant agreement no: 261483
Start date: 2011-01-01
The DEEP consortium

A large research-driven network including:

- 15 Partners
- 17 recruiting centres from 6 Countries:
  - EU Centres: Cyprus, Greece, Italy
  - non-EU Centres: Albania, Egypt, Tunisia
- industrial partners: to guarantee the future commercial development of the drug (Apopharma-Apotex)
The DEEP project

**Objective** to perform paediatric studies on *deferiprone* and to develop a new liquid formulation specific for the paediatric population

**Project contents:**

New Liquid Formulation

2 Clinical Trails:

- PK trial providing dose definition (DEEP-1)

- efficacy-safety multicentre, controlled, active comparator trial (DEEP-2)

2 post marketing studies

  long-term safety non-interventional study (DEEP-3)

  pharmacoeconomic study

A new Marketing Authorisation (PUMA)
DEEP Project: Regulatory Steps

- FP7 project approval: March 2010
- PIP granted: May 2012 - ongoing
- CTs Application and conduct: November 2011
- PUMA Application

FP7 project approval

CTs Application and conduct

PUMA Application

DEFERIPRONE EVALUATION IN PAEDIATRICS - FP7 PROJECT - SP1 - COOPERATION HEALTH-F4-2010-261483
REGULATORY REQUIREMENTS IN DEEP: PUMA AND PIP

PIP: a document aimed at ensuring that the necessary data are generated for the **conditions** in which a MP can be authorised to treat the paediatric population (all ages)

**Paediatric Investigation Plan Application**

*for Deferiprone*

EMEA procedure number: EMEA-001126

`Scientific documentation (Parts B-F)`

Applicant: Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) - Coordinator for DEEP (Deferiprone Evaluation in Paediatrics) Project (HEALTH-F4-2010-261483)

**1 month**

- **Letter of intent**
- **PIP submission and validation**
- **Requests of modifications**
- **PDCO**
- **Clock stop**

**Revised PIP evaluation**

⇒ **120-day procedure**

DE*FIRPR*OE EVALUATION IN PAEDIATRICS - FP7 project - SP1 - Cooperation HEALTH-F4-2010-261483
<table>
<thead>
<tr>
<th>CONDITION</th>
<th>Beta-thalassemia</th>
<th>Haemoglobinopathies requiring transfusion and chelation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE GROUPS</td>
<td>2-10 years</td>
<td>Up to 18 years</td>
</tr>
<tr>
<td>STUDIES and PATIENTS</td>
<td>PK study: 18 pt</td>
<td>18 pt</td>
</tr>
<tr>
<td></td>
<td>Efficacy-Safety: 254</td>
<td>344</td>
</tr>
<tr>
<td></td>
<td>Longterm Safety: 400</td>
<td>400</td>
</tr>
<tr>
<td>STUDY AIMS AND DESIGN</td>
<td>• To study PK in a trial with patients receiving multiple oral doses of DFP</td>
<td>• To study PK through an experimental phase and a modelling phase</td>
</tr>
<tr>
<td></td>
<td>• To assess the non-inferiority of DFP in reducing serum ferritin levels compared to DFO</td>
<td>• To assess the non-inferiority of DFP compared to DFX in terms of changes in ferritin levels and cardiac iron concentration</td>
</tr>
</tbody>
</table>
Innovative approaches in CTs: **DEEP-1** PK modeling/simulation study to define the drug exposure and appropriate dosage of deferiprone for children aged < 6yr

- Deletion of the age-cut off. Inclusion criteria based only on number on *transfusional Fe* intake
- First time comparison between the **two oral available comparators**: **DEEP-2**: the larger RCT in *paediatric patients* comparing deferiprone vs deferasirox
- Cardiac MRI-T2* as primary endpoint

- Multiple serum ferritin levels evaluated in all patients throughout the study
- Cardiac MRI T2* included as **co-primary endpoint** for children above 10 year and liver MRI-R2 included to measure LIC as a **secondary endpoint** in all patients not requiring sedation.
## Clinical Trials in DEEP

<table>
<thead>
<tr>
<th>FP7-HEALTH-2010</th>
<th>HEALTH-2010-4.2-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For clinical trials, EC contribution will be limited to phases I and II and only exceptionally to further studies</strong></td>
<td><strong>Consideration may be given to studies including up to Phase III clinical trials</strong></td>
</tr>
</tbody>
</table>

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**Researchers-driven not for profit project**

- **Paediatric population** (involves children of different ages)
- **A rare and disperse population involving different Rare Congenital Anaemia**

- **Multi-ethnic population with different cultures and Law**

- **‘Registrative’ CTs with**
  - GCP-ICHE11 obligations
  - Ethical stringent provisions
  - Economic burden
3- challenging matters in CTs

Paediatric population (involves children of different ages)

A rare and disperse population involving different Rare Congenital Anaemia

Multi-ethnic population with different cultures and Law

‘Registrative’ CTs with
- GCP-ICHE11 obligations
- Ethical stringent provisions
- Economic burden

RESEARCHERS-DRIVEN NOT FOR PROFIT PROJECT
The ethical and legal framework of CTs in DEEP

Specific approach to be adopted taking into account the cultural characteristics and the possible diversities in human subject protection regulations

**EU framework**

- Directives 2001/20/EC and 2005/28/EC implementing GCP
- Directive 95/46
- EudraLex Vol. 10 Detailed guidance on CTA (EC, 2006, 2010)
- Reflection paper on ethical and GCP aspects of CTs outside EU/EEA (EMA/121340/2011)
- Paediatric Ethical Recommendations (EC, 2008)

**Extra Europe**

*The legal approach is different among Countries: each of them has its own rules governing the submission of CTs*
The legislative context: national provisions governing CTA in DEEP countries

- In EU Countries (Italy, Cyprus and Greece), the Competent Authority authorisation and the Ethics Committee approval is ruled according to Directive 2001/20/EC in terms of CTA form, IMP documents, insurance, informed consent. Specific rules for the paediatric population (e.g. EMA 2008 recommendations, ICH-E11, etc).

- In Albania, specific rules on CTA are lacking; a special decision from the Ministry of Health is required.

- In Egypt, the CTA is largely similar to Europe, but informed consent procedures are different.

- In Tunisia, the Ministry of Health, the National and local ECs shall authorise a paediatric trial.

How to deal with existing differences?

Without compromising the trials' coherence?
The DEEP strategy to deal with diversity

THE DEEP MULTISTEPS APPROACH

1. To implement a unique procedure and a unique CTA ‘package of documents’

2. To organize a ‘trials management plan and infrastructure’ including SOPs preparation, data management, drug management, pharmacovigilance, monitoring, etc

3. To develop a ‘patients tailored approach’ including children, families and association

Partner representative. Loris Brunetta
The DEEP strategy to deal with diversity

STEP 1: THE ‘PACKAGE OF DOCUMENTS’

- Mandatory registration of CTs (EudraCT)
- Preparation for the concerned ECs of the common package including
  - Protocol (according to GCP and ICH Topic E11)
  - IMPs (drugs) information
  - **Insurance** (*not limiting the liability period*)
  - Privacy and confidentiality
  - Trial facilities at each recruiting center
  - Locally-requested documents
- Administrative authorisation

The EU legislative provisions have been assumed as DEEP Standard
# State of art of submission

## in Italy

<table>
<thead>
<tr>
<th>TRIAL SITE</th>
<th>From submission to EC approval</th>
<th>From EC approval to CA authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Az. Osp. Ospedali Riuniti Villa Sofia – Cervello (Palermo)</td>
<td>&lt; 2 months</td>
<td>4 months</td>
</tr>
<tr>
<td>Az. Ospedaliero Universitaria Consorziale Policlinico di Bari</td>
<td>&lt; 2 months</td>
<td>&lt; 6 months</td>
</tr>
<tr>
<td>Az. Osp. di Rilievo Nazionale “Antonio Cardarelli” (Napoli)</td>
<td>3 months</td>
<td>&lt; 1 month</td>
</tr>
<tr>
<td>Az. Osp. G. Di Cristina (Palermo)</td>
<td>1 month</td>
<td>2 months</td>
</tr>
<tr>
<td>Clinica Pediatrica Univ. – ASL 1 D.H per Talassemia – Sassari</td>
<td>&lt; 1 month</td>
<td>3 months</td>
</tr>
<tr>
<td>Policlinico di Modena, Clinica Pediatrica</td>
<td>5 months</td>
<td>2 months</td>
</tr>
<tr>
<td>Presidio Ospedaliero “Annunziata”, Centro di Studi della Microcitemia</td>
<td>&lt; 4 months</td>
<td>&lt; 8 months</td>
</tr>
<tr>
<td>Az. Osp. di Padova</td>
<td>7 months</td>
<td>Under evaluation</td>
</tr>
<tr>
<td>Ospedale Civile di Lentini, Centro di Talassemia, Lentini (SR)</td>
<td>6 months</td>
<td>Under evaluation</td>
</tr>
<tr>
<td>ARNAS Garibaldi (Catania)</td>
<td>1 month</td>
<td>Under evaluation</td>
</tr>
<tr>
<td>ASL Cagliari Ospedale Regionale per le Microcitemie</td>
<td>Under submission</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

### In other countries

- EC approval and CA authorisation expected in October-December 2013

- EC approval granted

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In other countries:

- Greece
- Cyprus
- Albania
- Egypt

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Recruitment and approval: the state of the art

- **DEEP-1** is concluding recruitment with success
- **DEEP-2** approved by the 80% of the Ethics Committees and Competent Authorities and the recruitment in Italy and Tunisia is now starting
- **DEEP-3** observational study has recruited a total of 34 patients
The DEEP strategy to deal with diversity

STEP 2: A COMPLEX (AND EXPENSIVE) ORGANISATIVE INFRASTRUCTURE HAS BEEN SET UP
The language and habits barriers is preventing an easy and free communication with children and parents.

- Participation of Fondazione Giambrone/TIF in the PIP and Protocols design
- Involvement of patients, parents or their organisations in creating the protocol information package
  - Active role in preparing documents for children
  - Contribution in dissemination strategy
- Evaluation of appropriateness of documents in different countries (impact of cultures, languages, social status on readability and acceptability)
The DEEP strategy to deal with diversity

**STEP 3: Patients empowerment in DEEP**

**Patient-tailored communication model:**
- 3 different BOOKLETS explaining CTs aims and procedures and what they are going to experience
- 2 different ASSENT FORMS

**BOOKLET for the younger ones (under 6 years old)**

Translated in the national language: available in Arabic, French, English, Italian, Greek
The DEEP strategy to deal with diversity

**STEP 3: PATIENTS EMPOWERMENT IN DEEP**

BOOKLET and ASSENT FORM for 6-10 years old children
The DEEP strategy to deal with diversity

STEP 3: PATIENTS EMPOWERMENT IN DEEP

BOOKLET and ASSENT FORM for 11-17 years old adolescents
Conclusions

• The projects funded by EC and aimed to develop a PUMA represent the only one tool specifically aimed to translate paediatric research into a new paediatric drug.

• The feasibility of the research-driven trials aimed to develop PUMA still presents critical problems in the context of the Paediatric Regulation implementation.

• Nevertheless, the FP7-funded projects are keeping their promises and deserve to be refinanced in the next EC plan “Horizon 2020”.