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DEEP

Deferiprone Evaluation in Paediatrics

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Deferiprone Evaluation in Paediatrics

4-years research project funded by the European Commission within the 7th Framework Program (Health 2010.4.2-1)
Why DEEP as a case study?

- DEEP trials are investigator-driven… but **registrative studies** which are PIP compliant
- The condition under treatment is a **rare condition**
- The concerned population is **paediatrics**
- The studies are **multicentre, multinational and…multicultural**
- Include **PK, efficacy** and (long-term) **safety** evaluations
- A **paediatric formulation** is to be tested
- The envisaged MA is a **PUMA**

…so DEEP includes many of the difficulties which hamper the development of paediatric medicines!
What is deferiprone?

- First oral iron chelator
- Very competitive on the market in comparison to more expensive (thus often unaccessible) oral iron chelator
- Authorised for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate
- Was associated with increased incidence of neutropenia and agranulocytosis which prevented its widespread use notwithstanding its distinct efficacy profile in preventing cardiac iron accumulation
- A PUMA will give to the product 10 years of data protection
- Obtaining a “first line” approval will open the door to a similar indication in adults
In 2008 Deferiprone was included in the PDCO Priority List

SEVENTH FRAMEWORK
PROGRAMME
THEME [HEALTH.2010.4.2-1]
FP7-HEALTH-2010-single-stage]
Grant agreement for: Collaborative project*

Project acronym: DEEP
Project full title: Déferiprone Evaluation in Paediatrics
Grant agreement no: 261483
Date of preparation of Annex I (latest version): 2010-11-22
### From the Priority List to the project funding

<table>
<thead>
<tr>
<th>Need in the Priority list</th>
<th>DEEP Project:</th>
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<tbody>
<tr>
<td><strong>Deferiprone:</strong></td>
<td><strong>Deferiprone:</strong></td>
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<tr>
<td>1. condition Thalassemia</td>
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<tr>
<td>2. need: PK, efficacy and safety</td>
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<tr>
<td>3. age subsets: from 2 years to less than 10 years</td>
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**Additional features:**
- a paediatric formulation
- deferiprone to first line indication
- long-term safety data
- market analysis
How to respond to such need?

• Formulation development of a paediatric oral solution
• Pharmacokinetic study in children 2-6 yrs (DEEP-1)
• Efficacy and safety study in children 2-10 yrs (DEEP-2)
• Long term safety study in children < 18yrs (DEEP-3)
• Market analysis

DEEP started on January 1st, 2011
Project plan and timelines

Formulation/Stability programme

DEEP-1

DEEP-2

DEEP-3

Market analysis

study reports

PIP compliance check

Jan 2011

Dec 2014
The steep path: from funding to first patient’s recruitment

1. Project approved by EC
2. Development plan approved by EMA-PDCO
3. Studies’ protocol approval by ECs and CAs
4. Studies’ protocol IMPLEMENTATION!
In compliance with the Paediatric Regulation (EC) 1901/2006 and within the remit of the call “FP7 Cooperation Work Programme “Health-2010-4.2-1” on February 14th 2011, a PIP (Paediatric Investigation Plan) was submitted to the Paediatric Committee (EMA-PDCO).
## Impact of PDCO requests on trials: the DEEP-2 case study

<table>
<thead>
<tr>
<th>Efficacy-Safety</th>
<th>PIP APPLICATION</th>
<th>APPROVED PIP</th>
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<tbody>
<tr>
<td>CONDITION</td>
<td>Beta-Thalassemia</td>
<td>Haemoglobinopathies requiring transfusion</td>
</tr>
<tr>
<td>AGE GROUPS</td>
<td>2-10 yrs</td>
<td>Up to 18 yrs</td>
</tr>
<tr>
<td>TOTAL PATIENTS</td>
<td>254</td>
<td>310</td>
</tr>
<tr>
<td>STUDY AIMS AND DESIGN</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>
Revised DEEP-2 trial: the overall impact

- Enlargement of the condition
  - Increase heterogeneity of the population
- Enlargement of the concerned age subsets
  - Need for stratification in the study design
- Change of study aim
  - Comparator, with associated substantial increase of costs
  - Composite endpoint:
    - Significant increase of sample size
    - Introduction of complex and expensive assessment (cardiac MRI)
- Inclusion of patients < 6yrs of age possible only after completion of DEEP-1 PK study
  - Delay of recruitment closure
**DEEP-2 final protocol**

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 of age affected by transfusion-dependent haemoglobinopathies.

**Pts eligible for randomisation**

(n = 344)

- Pts allocated to **DFP** liquid formulation
  NEW STRENGHT 80 mg/ml
  (n = 172)

- 1 year of treatment
- 16 hospital visits
- Several observational and instrumental assessments

- Pts allocated to **DFX**
  (n = 172)

Data collection and analysis
First obstacle: large patient population …and PAEDIATRIC!
The answer: a large research network

A large researchers-driven Network including centres from:
- EU: Albania (1), Cyprus (1), Greece (1), Italy (12), UK (3, new)
- non-EU: Egypt (3), Tunisia (1), Morocco (2, new)
- probably new centres will be activated in Lebanon (1) and Turkey (3)
Next steps: study approval by ECs and Cas in Italy

1. Study registration in EudraCT portal
2. Study registration in the “Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (OsSC)”
3. Study submission to the Ethics Committee of the Coordinator Centre
4. Study submission to the ECs of the other Italian Centers
5. Formal approval by each Competent Authority of each involved recruiting centres

Centres opened  Recruitment starts!
Next steps:

study approval by ECs and CAs (2)

Despite EMA-PDCO and coordinating centre approval… each EC may put forward specific request for changes:

• integrations to the text of the Informed Consent and Informed Assent documents in relation to blood volumes and contraceptive measures
• specification on use and storage of biological samples
• provision of additional administrative information
• clarifications requested on study design, study funding
Next steps:

study approval by ECs and CAs (3)

Additional hurdles have to be faced in other Countries:

- Egypt ⇒ the approval from National Security granted with restriction for sending samples abroad
- Greece ⇒ insurance must cover foetus damages even though contraceptive measures are indicated in the informed consent form
- Tunisia ⇒ a ‘special’ authorization from the Ministry of Health is necessary for paediatric trials before EC submission
- Albania ⇒ specific rules on CTs were lacking until 07/14; DEEP-2 approval set the path
Learned lesson: study approval by ECs and CAs is a lengthy and wearilying procedure!

DEEP-2 experience highlighted the wide heterogeneity in approach and timings (from 1 month to > 6 months) present not only outside Europe but also among MSs.

Reflection paper on ethical and GCP aspects of CTs outside EU/EEA (EMA/121340/2011)

Paediatric Ethical Recommendations (EC, 2008)

EudraLex Vol. 10

Directive 2001/20/EC

Directive 2005/28/EC
Next steps: protocol implementation

Most of the hurdles around the conduct of a paediatric clinical trial are embedded in the DEEP-2 protocol...
Problem: delivery of transparent information to a wide audience

Solution: respect of diversity and patient’s empowerment

• Not only parents and legal guardian were properly informed of the aim and procedures of the study, but significant efforts were devoted to build suitable communication tools for children

• Informative materials were produced adopting a patient-tailored approach by stratifying the population (< 6yrs; 6-11 yrs; > 12 yrs)

• Any tool delivered to patients and family was translated into native language: Albanian, Arabic, English, French, Greek, Italian
Problem: delivery of transparent information to a wide audience (2)

Solution: respect of diversity and patient’s empowerment
Problem: delivery of transparent information to a wide audience (3)

Solution: respect of diversity and patient’s empowerment…

…not only at start, but also when they finish the study, to increase their motivation and to recognise the value of the collaboration and the potential additional burden to their day-to-day life.
Problem: comparator drug supply

Solution: comparator provided as standard of care

• As PDCO considers deferasirox the only other suitable comparator to deferiprone in paediatrics to its oral formulation, this has to be considered standard of care and be supplied by the national Health System:

  – This is acceptable in some countries (Italy, Albania, Tunisia)
  – In those countries where this is not acceptable (because of high cost) the comparator is supplied with project funding with additional and significant economic burden
Problem: conduct of laboratory assessments in several local settings

Solution: centralisation of analysis key for primary endpoints and harmonisation and quality assurance of local laboratories

A complex clinical operations infrastructure had to be in place to manage:

– Local and central medical procedures
– Pharmacovigilance
– Drug supply
– Sample shipments and logistics
– Regulatory and Ethics
– Data management and statistics
**Problem: conduct of laboratory assessments in several local settings (2)**

**Solution: centralisation of ferritin**

Ferritin is assessed in duplicate:

- for patient’s management and dose adjustments ⇒ local laboratories
- for the evaluation of the primary endpoint ⇒ centralised laboratory

- Respect of maximum volume of blood allowed in compliance with the Paediatric Ethical Recommendations (EC, 2008)
- Shipment of biological sample to a central laboratory
- Obtain consent, when applicable to export samples form the given Country
- Disposal of any remaining sample
- Associated costs
Problem: conduct of laboratory assessments in several local settings (3)

Solution: centralisation of cardiac MRI

Cardiac MRI is conducted on every child >10 yrs of age provided sedation is not needed, using a unique MRI protocol sequence:

• locally, if a suitable MRI equipment is present

or alternatively…

• patients are referred to one of the trial references centres for MRI

All the scan analyses are centralised in ONE unique analytical centre to ensure consistency of results
Learned lesson:

*conduct of laboratory assessments in multicentre trial requires harmonisation and/or centralisation*

Harmonisation and/or centralisation of procedures and assessments…

…ensure consistency and robustness of data

…but…

…is very expensive!

Careful budget management is critical to the success of any trial!
DEEP responds to several open questions

- EC Research policies
  - **Networking action:** a very large scientific community is sharing competencies and skills.
  - **Public-private** integration and support to SMEs
- Specific medical needs (Paediatric Medicines)
  - **Development of Paediatric Plans**
  - **Consistent representation of paediatric patients**
  - An appropriate drug for treating iron overload in children
- Scientific community expectations
  - **Innovative elements** included in the trials: modelling studies
  - **New competencies** acquired and disseminated (regulatory, trial management, ethics, communication)
FOCUS ON THERAPEUTIC NEEDS IN PAEDIATRICS

Communication to the patient

DEEP proposes an innovative model for clinical research in terms of

Integration of research and culture

Global regulatory framework
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