Experience from the DEEP trial

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Deferiprone (DFP)

- Oral iron chelator drug
- Requires three or four times daily dosing for adequate 24 hr. drug levels
- Wide experience of DFP in patients with iron overload (specifically thalassaemia)
- Limited data are available for younger children
- DFP still approved only for second line treatment.

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Context

- Additional data on DFP included by the Paediatric Committee at the EMA in the 2009 PDCO Priority List
- An independent research Consortium (DEEP-Deferiprone Evaluation in Paediatrics) funded under the FP7 Framework Research program "HEALTH-2010.4.2-1: Off-patent medicines for children".

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Main objective

- To undertake a 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:2012-000353-31)

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Components

- Pharmacokinetic study in children (DEEP 1)
- RCT comparing deferiprone with the other licensed oral chelator, deferasirox (DEEP-2)
- 3 yr. retrospective and prospective Phase 4 safety study of deferiprone in children (DEEP 3)

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Novel aspects

- Pharmacokinetic study in children age <6 yrs. before inclusion in DEEP 2
- Evaluation of chelator safety and efficacy in very young children (<2 yrs. old)
- Use of oral chelators as first line therapy in chelation-naïve patients
- Using composite primary end point of iron overload (serum ferritin and myocardial iron T2*)
- Health care utilization and QOL assessment incorporated to enable HTA assessment

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Challenges-EU and non-EU countries

- Varying national and local requirements and delays in obtaining trial authorizations
- Timeliness of recruitment
- Centralization of sample analysis
- Trial monitoring in very different health care settings across EU and Mediterranean

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Achievements

- Development of a consortium of specialist centres treating transfusion-dependent anaemia
- Collaboration with pharmaceutical company (Apopharma) in developing a new liquid formulation for paediatric use
- Collaboration with Resonance Health in use of standardised and centralised MRI protocols for measuring iron overload (Liver and myocardial iron)

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Outcomes so far

- PK study (DEEP-1) shows comparable pharmacokinetics in children age <6 and older subjects, justifying standard mg/kg dosing across all age ranges
- Recruitment target met- 21 centres, 393 patients randomized
- At the end of October 2016, 113 patients have successfully completed the study as per protocol and further 221 patients are in treatment with one of the two IMPs.

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Experience in the UK: Set-up

- REC and NHS R and D authorizations
- Redrafting of patient information sheets , consent and assent forms
- Local institutional contract with sponsor
- DEEP adopted onto NHS CRN portfolio
- Approximately 15 centres approached, 4 agreed to participate

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Conducting the DEEP-2 trial

- Recruitment at our centre was quite easy and we met recruitment target by Aug 2016
- Two of four centres did not recruit
- With adoption on the NIHR Clinical trials portfolio we were able to utilize paediatric clinical trials infrastructure (nurses, administration, radiology support)

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Problems

- Very time consuming for PI
- Staffing – three dedicated nurses at our site alone
- Funding- contract does not cover actual costs of activity
- Trial protocol too detailed, resulting in multiple protocol violations not relevant to end points
- Trial monitoring- rather unpredictable and erratic

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Overall reflections

- Oral medication three times daily was challenging for school-age children
- Participation in a clinical trial helps with long-term management of adherence to medication
- Useful experience for design of future trials in this patient group, and collaboration with international centres

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Thank you

CVBF

DEEP Partners

Paediatric clinical trials unit, Royal London Hospital