Development of drugs in paediatric NMO/NMOSD: Industry perspective

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Aims of session

Given that no drugs have been developed in paediatric NMO/NMOSD to date:

- To describe regulatory requirements
- To give industry perspective
- To discuss possibilities for paediatric development
- To open the topic for discussion

Background: Paediatric regulation in EU

- Based on EU Paediatric Regulation (1901/2006 EC as amended) and European Commission "Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies"(2008/C 243/01)
- Intended to improve the health of children by
  - increasing high quality, ethical research into medicines for children
  - increasing availability of authorised medicines for children
  - increasing information on existing medicines
- To achieve the above
  - without unnecessary studies in children
  - without delaying authorisation for adults
- Aims supported by clinical experts in NMO/NMOSD

Background: Paediatric regulation in EU

- Paediatric Investigation Plan (PIP) or waiver request should be submitted, negotiated and agreed during early clinical development
- Obligation to submit results compliant with agreed PIP at time of marketing authorisation (assuming full waiver not granted) or application is invalid
- Reward: 6-month extension of the patent protection if compliant, if authorisation is in all Member States and if paediatric information is in Product Information
- Orphan drugs - 2 years of market exclusivity added to existing 10 years

Background: Paediatric regulation in US

- Similar aims and requirements in US under Pediatric Research Equity Act (PREA) 2003 and Food and Drug Administration Safety and Innovations Act (FDASIA) 2012 leading to "Draft Guidance for Industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans" (July 2013)
- However paediatric studies may be waived for orphan indications in the US but not in EU
- Paediatric study plan also not required in Japan

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- Regulatory requirement for paediatric studies is from EU
- EU paediatric study requirement depends on epidemiology

Paediatric NMO/NMOSD epidemiology

(Tillema and McKeon 2012)

- Acquired demyelinating disease incidence from 0.66 to 1.66 per 100,000 of which 3 – 4% NMO/NMOSD (based on small numbers so unreliable)
- Median age of diagnosis 10 to 14 years
- Youngest diagnosed under the age of 2 years
- Varying proportions of white to non-white patients in case reports from Europe and the Americas
- NMO-IgG positivity ranges from 16% to 80%
- As in adults, NMO-IgG seropositivity associated with a relapsing course in paediatric patients
- In summary, NMO/NMOSD appears to be considerably less commonly diagnosed in children than adults and a proportion have monophasic disease course (estimates 20 to 80%) therefore not intensively treated with targeted therapies

Starting industry viewpoint on paediatric NMO/NMOSD

- Conducting clinical studies will be very difficult
- Number of patients recruited per site likely to be low, cost to Sponsor per child recruited high and study duration long
- Children may require specific formulations/presentations and/or tox studies, adding to development cost
- Potential to delay adult MA, despite regulatory aims, unless paediatric studies waived or deferred
- Paediatric indication is not likely to be profitable in EU
- Increased potential product liability with use in children

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Not attractive proposition to industry but needs to be addressed

Potential PIP content in NMO/NMOSD: the possibilities

- PIP content or waiver request must cover all paediatric age groups (pre-term, term newborn, infants/toddlers, children 2 – 11 years, adolescents 12 – 16/18 years)
- For each age subset, PIP may propose
  - full, controlled paediatric clinical studies concurrent with adult development,
  - limited paediatric clinical studies with extrapolation from adults,
  - deferred paediatric clinical studies or
  - waiver of paediatric clinical studies
- PIP will depend on the nature of the drug, the amount of adult and paediatric data already available with that drug/class of drug (in terms of PK/PD, efficacy, safety and immunogenicity) in NMO and other indications

Potential for waiver in NMO/NMOSD

- Waiver can apply to condition for the whole paediatric population (full waiver) or to age subsets (partial waiver)
- No class waiver existing in NMO
- Product-specific waiver can be applied for on the following bases:
  - Medication or class of medications likely to be ineffective or unsafe in all or part of paediatric population (unlikely to apply)
  - Disease or condition does not occur in all or part of paediatric population (but does occur in some)
  - Specific medicinal product represents no benefit over existing treatments for paediatric patients (but there are no approved treatments in NMO)
- Some paediatric clinical studies likely to be necessary for most drugs in NMO/NMOSD for EU MA purposes because adult and paediatric disease not fundamentally different

Potential for deferral in NMO/NMOSD

- Company can apply for deferral of initiation and/or completion of some or all of measures in PIP if, for example
  - paediatric studies will take longer
  - appropriate to conduct studies in adults prior to children for ethical reasons
  - adult PK data required to determine dosing regimen for paediatric studies (eg if drug not approved for other paediatric indications)
  - additional non-clinical studies necessary prior to paediatric studies
  - additional formulation work required prior to paediatric studies
- Last 4 bullets drug-specific: depends whether agent has been studied/approved in adults in same indication or in other, extrapolable paediatric indications

Potential for controlled clinical studies in NMO/NMOSD

- Very restricted population available, requiring many sites
- Probably would only involve patients with relapsing, NMO-IgG positive NMO, requiring intensive treatment, depending on drug type, further restricting population
- PDCO favours spread of patients across all age subsets/weights: difficult in NMO when average age of diagnosis is around 14 years
- Multi-company approach (one control group, multiple active arms) could perhaps be considered but not immediately attractive

Potential for multi-company study in paediatric NMO

- Pros:
  - Pooling of resources in terms of finance and limited patients available
  - Might allow controlled study, not otherwise possible
- Cons:
  - Choice of control group (placebo monotherapy or background immune suppression – or include both to show whether background immune suppression works?)
  - Age groups to be studied
  - Inclusion/exclusion criteria re NMO-IgG status, number of prior episodes, NMOSD etc
  - Choice of endpoints
  - Different modes of action/dosing regimens/safety issues/PD markers (blinding unlikely to be possible)
  - Differences in timing re intended MAA dates
  - Sponsors are direct competitors but would need to share confidential information

Potential for extrapolation from adult data in NMO or from other indications

- Aim is to avoid unnecessary studies where feasibility is restricted
- Most common extrapolation is from adults to children or between paediatric subsets
- Requires expected similarity between source and target populations in
  - disease (aetiology, pathophysiology, clinical presentation, diagnosis, treatment, prognosis)
  - PK/PD relationship
  - likely response to study treatment in terms of efficacy, safety and (for biotech) immunogenicity
- Requires plan involving
  - extrapolation hypothesis, probably using PK/PD modelling
  - limited testing of predicted PK/efficacy/safety in target population
  - testing “fit” of results to hypothesis
  - development of dosing recommendations for target population
  - possibly post-marketing commitment to monitor success of prediction

Potential for extrapolation in NMO/NMOSD

- Adult and paediatric NMO/NMOSD appear similar (in terms of aetiology, pathophysiology, clinical presentation, diagnosis, treatment, prognosis) with some minor differences
- Adult treatments have been used in children with success (according to case reports and physician experience) but without clinical studies
- Extrapolability of PK from adult to children also dependent upon individual drug (but for most monoclonals PK affected by body weight)
- Availability of PD markers may depend upon individual drug mechanism of action (no proven, common PD markers for disease as yet)
- Extrapolability of efficacy from adults to children may depend upon individual study population factors eg proportion of NMO-IgG positive/negative patients, background immune suppression or not etc
- EDSS has been used for efficacy assessment in children as in adults; could use TFR, add other validated measures of disability/QOL
- Ability to extrapolate safety/immunogenicity may depend upon experience with same drug/class of drugs in other indications

Summary points for discussion

- Under current regulations, PIP is likely to be required only for EU regulatory purposes in NMO/NMOSD
- Paediatric NMO/NMOSD population is extremely small and seems skewed towards oldest paediatric subset
- Controlled paediatric studies seem unlikely to be feasible unless cooperative (many issues to be overcome)
- Waiver may be possible for some drugs/paediatric subsets
- Extrapolation from adults/older paediatric subsets seems feasible regulatory approach, with limited confirmatory studies (again depending upon individual drug)
- Whether deferral of paediatric studies is valid depends upon available data with drug/drug class: If adult efficacy/safety data already available or paediatric PK and safety data available from other indications, paediatric studies could at least start concurrently with adults
- However desirable for public health/clinicians, paediatric development will be costly for Companies and efforts to agree and comply with PIP may potentially delay approval of drugs for adults unless studies deferred or waived