Session II

Regulatory Approach in Pediatric NAFLD/ NASH

Federal Institute
for Drugs
and Medical Devices

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory Approach to

Paediatric NAFLD/NASH – European Experience

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The views expressed in this presentation are primarily those of the author and do not necessarily express those of the BfArM, nor of the EMA

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Regulatory Approach to Paediatric NAFLD/NASH – European Experience

- Paediatric Regulation in Europe
  - Principles
  - Paediatric Investigational Plan (PIP)
  - Obligations and incentives
  - Comparison EU-US
- Agreed and ongoing PIPs:
  - Proposals of the applicants
  - Problems identified
- Summary of issues identified

- Paediatric Regulation in Europe
  - Regulation 1901/2006: Set into force on 26 January 2007
    - Objectives: improve the health of children by
      - Increase high quality medical research into medicines for children
      - Increase availability of authorised medicines for children
      - Avoid unnecessary studies in children
      - Not delaying athorisation for adults
  - Set-up of the „Paediatric Committee“; first meeting: 1-2 July 2007
    - Composition: Experts from NCAs (22+alternates); CHMP members (5), patient and health-care-professionals representatives (6)
  - Guideline on „format and content of applications for a PIP“: September 2008 (latest revision 2014)
    - http://ec.europa.eu/health/files/eudralex/vol-1/2014_c338_01/2014_c338_01_en.pdf

- Paediatric Investigational Plan (PIP)
  - Binding to applicants and for all new substances
  - Includes Quality, Safety and Efficacy
  - Contents:
    - Administrative information
    - Waiver requests
    - Overall strategy
    - Details of individual studies (including non-clinical and pharmaceutical development)
    - Timelines (including requests for deferrals)
- Opinion on PIP adopted by PDCO – Decision taken by EMA
  - Procedure: 60 days with potential for 3 months clock-stop and further 60 day extension
  - All opinions and decisions are made public
- Elements of PIP
  - Waiver
    - Legal grounds (Ineffective, unsafe, condition only in adults)
    - Three types: „full“, „partial“, „class waiver“
  - Deferral
    - Avoidance of delaying authorisation of products in adults
    - Defines initiation and completion dates

- Obligations:
  - Submission and agreement of/on PIP for all new medicinal products
  - Submission date: End of Phase I
  - Validation/Compliance-check at the time of submission of MAA
    - An agreed PIP is a pre-condition for MA !
    - Extension of protection period only after compliance check
- Incentives
  - Supplementary Protection Certificate extension of 6 months (patent extension)
  - 1-year extension of market exclusivity protection (if new indication)
  - Extension of Orphan Exclusivity for 2 years (orphan medicinal products only)
  - Scientific Advice to be given free of charge (not binding to PDCO)
  - For off-patent products: 10-year protection period („PUMA“)

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Summary:

	EU (Regulation 1901/2006)	US (PREA 2012)	US (BPCA 2012)
Pediatric development	Mandatory	Mandatory	Optional
Document used	Paediatric Investigation Plan (PIP)	Pediatric Study Plan (PSP)	Written Request (WR)
When	EoP 1	EoP2	EoP2
Who grants a decision	Opinion by Paediatric Committee (PDCO); Decision by European Medicines Agency (EMA)	FDA Review Division and Pediatric Review Committee (PeRC)	FDA Review Division and Pediatric Review Committee (PeRC)
Indications covered	Adult indication as a starting point (other indications can be included depending on a mechanism of action and medical need)	Adult indications	Any indication
Orphan drugs	Included	Excluded	Included
Incentive	6-months Supplementary Protection Certificate (SPC) extension	N/A	6-months exclusivity
Review of pediatric data	Standard	Standard	Priority

- Similar to the overall situation for NASH, the regulatory experience with PIP applications is limited

- Currently agreed PIPs:
  - 1 PIP for the dedicated indication NASH
    - Elafibranor (July 2016)
  - 1 PIP for the indication „Treatment of hepatic fibrosis“
    - Simtuzumab (March 2015); not shown
- Two ongoing procedures:
  - 2 PIP applications for NASH (1 ongoing, 1 currently in clock stop)
- One finalised paediatric Scientific Advice
  - 1 finalised Paediatric Scientific Advice in preparation of PIP submission
- Name of the substances for ongoing procedures/Scientific Advice not shown due to confidentiality reasons

- Elafibranor PIP (EMA/PDCO/231683/2016)
- Waiver:
  - Applies to patients <2 years of age (condition does not occur)
- Proposed inidcation/condition:
  - Treatment of non-alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH)
- Measures agreed:
  - Development of an age appropriate formulation
  - Juvenile tox study
  - Clinical studies:
    - Review of natural history studies
    - Modelling and simulation study to evaluate use in children from 2-18.
    - PK/PD study in 8-18 yr olds
    - Efficacy and safety (DB, placebo-controlled) study in 8-18 yr olds
    - PK/PD study in 2-8 yr olds
    - Efficacy and safety (DB, placebo-controlled) study in 2-8 yr olds
- Timelines (deferral): Completion of the PIP by 2025
  - Deferrals included for one or more measures

- Substance XXX – Applicant‘s Proposals
- Proposed indication/condition:
  - Treatment of NASH with stage 2-3 fibrosis
- Proposed Waiver:
  - Patient population less than 12 years of age due to low prevalence
- Proposed deferral:
  - Time to be determined
  - Availability of complete results in adults
  - Need for (repeated) biopsies problematic; endpoints to be determined on adult data (see below)
  - Need for additional information on natural history of pNASH
- Measures proposed:
  - No further juvenile tox studies (target population adolescents and older)
  - 1 PK/PD study in adolescents aged 12-18; doses investigated to be determined by modelling and simulation;
  - 2-stage design with PK evaluated in first stage, second stage with additional patients will investigate safety and efficacy over 1 year. Efficacy evaluation based on non-invasive evaluation of liver stiffness.

- Substance XXX – Request for Modification
- Clock stop for PIP procedure due to:
- Proposed Waiver:
  - Waiver for children below 12 years of age not acceptable; should included pats. from age of 2
  - Discuss other potential indications
- Need for the development of age appropriate formulation
  - Especially for those aged 2-6; palatability tests needed.
- Need for pre-clinical studies:
  - Conduct juvenile animal studies covering from birth to adolescent age
- Clinical study programme:
  - Include histology as endpoint evaluation
  - Discuss need for dose adjustment in patients with hepatic impairment
  - Need for implementation of body weight control in the study

- Substance YYY – Applicant‘s proposals
- Proposed indication/condition:
  - Treatment of NASH with moderate to severe fibrosis (stage 2-4)
- Proposed Waiver:
  - Patient population less than 8 years of age (justified by the advanced disease status which almost exclusively occurs in patients ≥8 years);
  - no proposal for natural history data generation included
- Proposed deferral:
  - Time proposed: Initiation of studies 2021, completion 2025; completion of adult phase 3 to be awaited.
  - Availability of interim results in adults
  - Availability of additional natural history data in pNASH, intended collaboration with existing registries/databases
- Measures proposed:
  - Appropriate tox studies already available, no further measures proposed
  - Development of a reduced strength tablet
  - 1PK/PD (placebo-controlled) efficacy and safety study in children aged 8-18 (48 weeks duration)

- Substance ZZZ
- Proposed indication/condition:
  - Treatment of NASH
- Proposed Waiver:
  - Patient population less than 2 years of age
- Proposed deferral:
  - Time to be determined
  - Interim results in adults should be available
  - Availability of additional natural history data in pNASH, intended collaboration with existing registries/databases
- Measures proposed:
  - Appropriate juvenile tox studies
  - 1 PK/PD study with staggered approach across the age ranges, 3-months duration; biomarker endpoints
  - 1 Phase 3 trial in the whole age range; efficacy evaluation based on histology in 7-18 old, and on non-invasive fibrosis evaluation and biomarkers in 2-6 years old patients; duration 18 months

- Substance ZZZ – Recommendations of SAWP/CHMP
- Deferral/natural history study:
  - A deferral awaiting more comprehensive natural history data is acceptable, the proposal to decide on target population according to results is also acceptable
  - A further deferral for the population aged 2-6 until the need to treat these patients has been identified more clearly is also acceptable.
- Patient population for natural history study:
  - Patients aged 2 – 18;
  - Agreement/Recommendation on/for the need to include a European population in addition
- Clinical study design/endpoints:
  - Final design and EPs not possible to determine at this point of time, natural history data to be awaited
  - Problem of need for extrapolation identified; development of an „extrapolation plan“ (according to the respective European guideline) recommended.

- Problems identified:
  - Need for natural history studies
    - Are the available databases sufficient for thoughtful description of
      - target population
      - study design (e.g.duration)
      - endpoints
  - Age related waiver:
    - Can the appropriate age range be determined:
      - 2/6/8/12 years
  - Proposed target population:
    - NASH vs NAFLD; stages of fibrosis, NAS activity; differences for type I and II
  - Features of trial design:
    - Need for placebo control
  - Appropriate timing of studies/deferral:
    - How much adult data need to be available?
  - Extrapolation
    - How much extrapolation from adults to adolescents/from adolescents to children is appropriate (or is needed)?
  - Ethical problems:
    - Justification for repeated biopsies

Thank you for your attention!

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