Berkeley School of Public Health

EASL European Association for the Study of the Liver

Forum for Collaborative HIV Research

Regulatory Updates

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Regulatory update from Europe:

Paediatric NASH

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Regulatory update from Europe - Overview

- Paediatric Regulation in Europe
  - Principles
  - Paediatric Investigational Plan (PIP)
  - Obligations and incentives
  - Comparison EU-US
- Currently agreed PIPs:
  - Indication NASH
  - Other indications including NASH; other procedures
  - Problems 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“)

Regulatory update from Europe – Paediatric Regulation

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 very 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)
- Currently ongoing procedures:
  - 1 PIP application for NASH (currently in clock stop)
  - 1 Paediatric Scientific Advice in preparation of PIP submission

- 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

- Simtuzumab PIP (EMA/PDCO/35844/2015)
- Proposed indication/condition:
  - Treatment of advanced hepatic fibrosis and cirrhosis
- Waiver:
  - Patient population less than 28 days of age (no significant benefit over existing therapies expected)
- Measures agreed:
  - Development of an age-appropriate strength for s.c. injection
  - Pre- and postnatal development and juvenile tox. studies in rats
  - Open-label trial to evaluate efficacy and safety and PK in children 28 days to 18 years with advanced heaptic fibrosis or cirrhosis.
  - Underlying potential diseases: NASH, PSC, post-Kasai BA, CF, HBV- and HCV-associated fibrosis

Regulatory update from Europe – Ongoing PIP procedure:

- Substance XXX
- 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
  - Need for (repeated) biopsies
- Proposed deferral:
  - Time to be determined
  - Availability of complete results in adults
  - 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 YYY
- Proposed indication/condition:
  - Treatment of NASH
- Proposed Waiver:
  - Patient population less than 2 years of age
- Proposed deferral:
  - Time to be determined
  - Availability of interim results in adults
  - 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

Regulatory update from Europe – PIPs in NASH:

- Problems identified:
  - Need for natural history studies
    - 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:
      - 2/6/12 years
  - Proposed target population:
    - NASH vs NAFLD; stages of fibrosis, NAS activity?
  - Features of trial design:
    - Need for placebo control, Study duration?
  - 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

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Regulatory update from Europe – PIPs in NASH:

A remarkable citation from one of the PIP assessments of the PDCO:

„Discussion involving regulatory agencies such as EMA or FDA is ongoing, through the Liver Forum, in order to determine what is the most appropriate endpoint for clinical trials in the NAFLD/NASH indication, and notably if a histological endpoint is considered as a gold standard for paediatric trials as for adults. Detailed paediatric trials will therefore be proposed for this PIP as soon as a consensus is found on this endpoint.“

Thank you for your attention!

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