Federal Institute
for Drugs
and Medical Devices

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PSC-Forum:
Regulatory update from Europe

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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

Regulatory update from Europe:

- **Content:**

- The regulatory framework in the EU – high level overview
  - Tools for early access to innovative medicines:
    - Conditional approval
    - Accelerated assessment
    - PRIME („proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines")
- Considerations on endpoints in PSC trials
  - Previous presentation (as of EASL/IPSCSG 2015)
  - Advice given to applicants by CHMP (update 2017)
  - Phase III Clinical trials currently ongoing in Europe (EudraCT database)

Current tools for early access

Accelerated assessment

- Medicine is of **major interest** from the point of view of **public health** and in particular from the viewpoint of **therapeutic innovation**
- Objective: **Faster assessment** of marketing authorisation application
- Guidance: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000955.jsp&mid=WC0b01ac05809f843a

Conditional approval

- Medicine fulfills **unmet medical need**
- Medicine targets seriously **debilitating or life-threatening** disease, rare disease or is for use in emergency situations in response to a public health threat
- **Benefit-risk balance of the product is positive**, and benefit to public health of its immediate availability outweigh the risk related to need for additional data
- **Comprehensive data** expected to be provided **after authorisation**
- Objective: **Early Authorisation** on the basis of less complete clinical data
- Guidance: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp&mid=WC0b01ac05809f843b

Current tools for early access

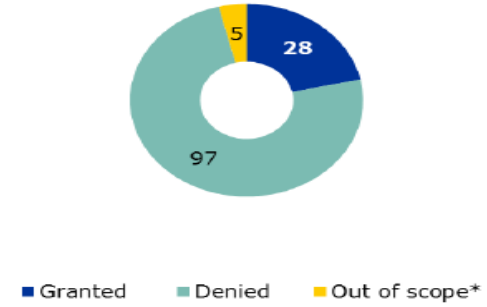
- PRIME
- Procedures:
  - Eligibility assessed by SAWP/CHMP including initial „kick-off“ meeting with all involved network bodies
  - Compulsory repeated Scientific Advice (including multiple stakeholders, e.g. HTAs)
  - Early assignment of CHMP-Rapporteur
  - Early application/decision for accelerated assessment
- Conditions:
  - Product fulfills the conditions for accelerated assessment
    - Major public health interest/unmet medical need
    - Therapeutic innovation
  - Data to support eligibility should show:
    - Potential for major therapeutic advantage
      - » impact on the onset and duration of the condition, or
      - » improving the morbidity or mortality of the disease

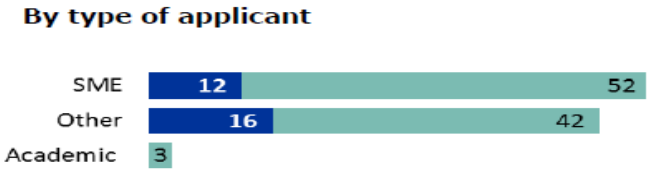
Further reading:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439

Current tools for early access

- PRIME – statistics (September 2017)

Cumulative overview of recommendations on PRIME eligibility requests adopted by 14 September 2017





Current tools for early access

Summary: Comparison FDA-EMA

FDA

- **Accelerated approval**
  Approval of drug for serious lor life threatening conditions based on effect observed on surrogate endpoint reasonably likely to predict clinical benefit
- **Priority review**
  Regulatory review period shortened from standard 10 months to 6 months
- **Fast track designation**
  Facilitate development and expedited review of drugs through more frequent FDA interaction and rolling of review data
- **Breakthrough designation**
  Expedite the development and review through more intensive FDA guidance and commitment to involve senior management

EMA

- **Conditional approval**
  Approval of a drug for serious debilitating/life threatening diseases, less complete data; unmet medical need, positive risk-benefit ratio
- **Accelerated assessment**
  CHMP opinion given within 150 days instead of 210 days
- **PRIME**
  Also: ITF/SME office, Scientific Advice and Protocol Assistance, Biomarker Qualification
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  Also: ITF/SME office, Scientific Advice and Protocol Assistance, Biomarker Qualification

Regulatory aspects of clinical trial end-point considerations in PSC

Outcomes in PSC – Regulatory considerations: General reflections:

- Necessary properties of primary endpoints:
  - "instrument that measures the important aspects of concepts most significant and relevant to the patient's condition"
  - Should be clinically meaningful
  - Should be reliable and well defined
  - Should be sensitive to the effects of an intervention
    - E.g. Pain in malignant disease: Do not use survival
  - Should be "readily" measurable and interpretable
    - E.g. avoid invasive procedures; composites with different weight (e.g. MACE + hospitalisation)
  - Validated surrogate
    - Off-target (e.g. adverse) effects should be covered

Slides presented at IPSCSG meeting at EASL 2015

Regulatory update from Europe:

Regulatory aspects of clinical trial end-point considerations in PSC

Outcomes in PSC – Regulatory considerations: General reflections:

- "Failed surrogates" – examples:
- Maintenance of sinus rhythm after cardioversion for atrial fibrillation
  - No correlation with MACE/death
- Cochrane meta-analysis (Lafuente-Lafuente D et al 2012)
  - Example: Sotalol
  - 12 trials with 1791 (Sotalol) and 1211 (control) patients:
- Outcome with "surrogate" AF recurrence:

No./percentage of events	Sotalol N=1791	Control N=1211	p-value
AF recurrence	1197 (66.8%)	955(78.9%)	<0.001

- Outcome for all cause mortality:

No./percentage of events	Sotalol	Control	p-value
All-cause mortality	34 (1.9%)	5 (0.4%)	0.01

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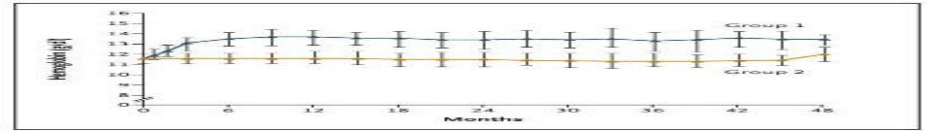
Regulatory update from Europe:

Regulatory aspects of clinical trial end-point considerations in PSC

Outcomes in PSC – Regulatory considerations: General reflections:

- "Failed surrogates" – examples:
- Haemoglobin correction in chronic kidney disease
  - Hb normalisation not correlated with improved CV outcome and death
- TREAT trial (Singh AK et al; 2006)
  - Epoetin alfa targeted to normalisation of Hb (13.5 g/dl) compared with targeted to "subnormal" (11.3 g/dl)
  - 1,423 patients with non-dialysis CKD treated for 3 years
- Outcome with "surrogates" Haemoglobin:



- Outcome for CV events and overall mortality:

No./percentage of events	Normal Hb group	Low Hb group	p-value
Primary outcome (composite)	125 (17.5%)	97 (13.5%)	0.03
All-cause mortality	52 (7.3%)	36 (5.0%)	0.07

Slides presented at IPSCSG meeting at EASL 2015

Regulatory aspects of clinical trial end-point considerations in PSC

Outcomes in PSC – Regulatory considerations: General reflections:

- ALP – also a "failed" surrogate?:
  - Olsson (2005) – Dose: 17-23 mg/kg; n=219; 5 years; primary EP: LTx or death
  - Lindor (2009) – Dose 28-30 mg/kg; n=150; 5 years; primary EP: LTx, death, minimal listing criteria, varices, CCA, cirrhosis
- Outcome with ALP:
  - No statistically significant difference in study Olsson (but numerical difference; reduction higher in Urso)
  - Statistically significant difference in favour of Urso in study Lindor during all 3 years of observation.
- Outcome for primary endpoint:
  - 10.9% vs 7.2% in study Olsson (p=0.368)
  - 25.7% vs 39.5% (p=0.004 in favour of placebo)
- **Conclusions/Questions:**
  - Can ALP still be used as a potential biomarker/surrogate outcome?

Slides presented at IPSCSG meeting at EASL 2015

Regulatory aspects of clinical trial end-point considerations in PSC

Outcomes in PSC – Regulatory considerations: General reflections:

- Conclusion/Preliminary proposal for primary outcome and design of trials in PSC:
  - Study duration of pivotal trial(s) needs to be 5 years
    - or else increase number of patients,
    - or else increase number of patients in later stages (e.g. exclude fibrosis stage 1))
  - Primary evaluation should consist of the following:
    - Histology (stop of deterioration; improvement; manifestation of cirrhosis)
    - LTx, death, and clinical cirrhosis related events should be included
    - Role of malignancies to be clarified but could be acceptable part of primary endpoint
    - Design of the American Urso study could be acceptable:
      - Include histological confirmation of cirrhosis in primary evaluation in addition to clinical endpoints

Slides presented at IPSCSG meeting at EASL 2015

PSC –Phase III trials in Europe:

- Interactions with SAWP/CHMP in PSC:
- Two advices only: 1 in 2014 and 1 in 2016

- 2014 advice:
  - Proposed: Composite response as 35% in ALP and 1 point improvement in Ishak necroinflammatory grading or (with Bonferroni adjustment) or 35% reduction of ALP and no worsening of Ishak fibrosis stage; Study duration 2 years. Potential open-label follow-up
  - Accepted/Recommended: Composite response of 35% reduction of ALP and no worsening of Ishak fibrosis stage. 2 years duration confirmed. Open-label follow-up accepted

- 2016 advice:
  - Proposed: Composite of no worsening of fibrosis (defined as increase in <1.3 kPa from baseline (VCTE) and ALP reduction to < 1.5xULN
  - Accepted/Recommended: Improvement of necroinflammation of 1 grade and no worsening of firosis stage (preferred accord. to Nakamuna). Duration 2 years. Placebo-controlled extension (with endpoints cirrhosis and cirrhosis-related events) recommended

PSC –Phase III trials in Europe (published information from EudraCT database):

- 2014-003942-28 – Initiated 2015
  - Randomized, Global, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Vedolizumab IV for the Treatment of Primary Sclerosing Cholangitis, With Underlying Inflammatory Bowel Disease
  - Primary end point(s):
    - Proportion of subjects with no worsening in Ishak fibrosis staging score, from Baseline to the Week 106 visit
  - Secondary end point(s)
    - Proportion of subjects with a ≥35% reduction in serum ALP from Baseline to the Week 106 visit.
    - Change in Ishak necroinflammatory grading score from the Baseline visit to the Week 106 visit.
  - Open-label follow-up

- 2016-003367-19 – Initiated this year
- Double-blind, randomized, placebo-controlled, phase III study comparing nor-ursodeoxycholic acid capsules with placebo in the treatment of primary sclerosing cholangitis
  - Primary end point(s)
    - Partial normalization of s-ALP and no worsening of disease stage.
  - Secondary end point(s)
    - (Non-invasive) liver stiffness, fibrosis stage, liver histology, s-ALP levels, dominant strictures, quality of life
  - Follow-up:
    - For all patients, treatment decisions after study end (after V22, or in case of premature withdrawal during DB phase: after V14) are at the discretion of the respective investigator. (V14=96 weeks; V22=192 weeks)

Thank you for your attention!

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