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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

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Regulatory update from Europe:

- **Content:**

- Regulatory interaction - update
- Considerations on endpoints in PSC trials
  - Review of scientific literature
  - Regulatory position

Regulatory update from Europe:

- **Content:**

- Regulatory interaction - update
- There was no regulatory interaction with EMA for the indication PSC in the time between October 2017 and March 2018
- PSC as part of the planned „reflection paper on chronic liver diseases“
  - First draft envisaged for end of 2nd Quarter 2018
  - Stakeholder interaction update: Currently planned for Dec. 2018
  - The following preliminary proposal is likely to be part of the paper:

Regulatory update from Europe:

- Review of the Scientific Literature:
  - Endpoints in trials for PSC

SPECIAL ARTICLES | HEPATOLOGY, VOL. 63, NO. 4, 2016

Surrogate Endpoints for Clinical Trials in Primary Sclerosing Cholangitis: Review and Results From an International PSC Study Group Consensus Process

Cyriel Y. Ponsioen,[1] Roger W. Chapman,[2] Olivier Chazouillères,[3] Gideon M. Hirschfield,[4] Tom H. Karlsen,[5] Ansgar W. Lohse,[6] Massimo Pinzani,[7] Erik Schrumpf,[8] Michael Trauner,[9] and Gregory J. Gores[10]

  - Still the only dedicated publication

(Publication of the paper „Desgin and endpoints for clinical trials in primary sclrosing chonagitis“; Hepatology 2018; in press by Peniouen/Lindor/Mehta/Dimick not available before the finalisation of the slides)

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Regulatory update from Europe:

- IPSCG proposal for trial endpoints:

Rank	Surrogate marker	Comments	Strength of recommendation
1	ALP	***Potential surrogate endpoint:*** Several observational studies suggest that ALP is a surrogate marker for transplant-free survival. ALP has been employed in all clinical trials in the past two decades (primary endpoint in over 40% of studies), but outcomes are conflicting with regard to the utility as a surrogate parameter for clinical efficacy of ursodeoxycholic acid. ALP is deemed a useful parameter for stratification of patients in clinical trials, although thresholds need to be clarified.	Level 4, RG D
2	TE	***Potential surrogate endpoint:*** Two independent studies have demonstrated that baseline measurements and rate of progression of liver stiffness measurements by TE were strongly and independently linked with patients' outcomes, suggesting that TE may be an attractive surrogate endpoint.	Level 2b, RG C
3	Histology	***Potential to be a robust surrogate endpoint:*** Histology has been used as an outcome parameter in 12 of 26 studies in the past 20 years. Histology is considered less undulating than serum tests; the impact of sampling variability is debated. The invasiveness of the procedure is a disadvantage, whereas its potential for revealing the mechanism of action of the investigational drug is an advantage. Available data indicate that histology is a useful stratification tool for clinical trials in addition to its value as an outcome parameter.	Level 2b, RG B
4	ALP + histology	***Explorative surrogate endpoint:*** In the absence of a convincing single-surrogate endpoint, combining multiple endpoints (either as composite or co-primary endpoints) is considered advisable and should be explored further.	Level 5, RG D
5	Bilirubin	***Unlikely to be suitable:*** Serum bilirubin is part of several prognostic scoring systems and consistently associated with clinical outcome in PSC. However, it only rises permanently in late-stage disease and temporary increases may be due to intercurrent events not reflecting long-term outcome. Hence, it was deemed unlikely to be suitable for clinical trials.	Level 2b, RG C

- Regulatory position:

- **ALP**: Likely to be a reasonbale surrogate, however, doubts based on the URSO results remain (also on Simtuzumab results?)
- **TE**: Reflects the process of the whole liver, but further validation needed.
- **Histology**: Acceptable surrogate from a regulatory point of view – problems with variability (sampling error) remain
- **ALP and Histology combined**: Agreeable from a regulatory perspective
- **Bilirubin**: Unlikely to be acceptable

Regulatory update from Europe:

- Preliminary regulatory position:
  - The combination of ALP ad histology can be used as surrogate endpoint in confirmatory trials for PSC
  - Problems remaining:
    - How to evaluate ALP and histology?
      - Combined or co-primary?
      - Responder-type evaluation or continuous (ALP, mean histology score; which scoring? Staging and grading?)

Regulatory update from Europe:

- Preliminary regulatory position:

  <u>Problems remaining:</u>

  - Evaluation of ALP:
    - » Responder type evaluation preferred (based on DeVries at al Liver International 2016) at a threshold level of 1.3xULN (or 1.3-1.5xULN; or 40% reduction)
  - Evaluation of Histology:
    - » Nakanuma staging (Others possible based on DeVries at al Hepatology 2016)
    - » Remaining issue: Improvement or non-deterioration?
      - Improvement preferred (after revisiting Simtuzumab results)
  - Combined or co-primary:
    - » Co-primary preferred because the relation between the two is largely unclear

Regulatory update from Europe:

- Preliminary regulatory position:

  <u>Problems remaining:</u>

  – Study duration:
    - » At least two years for the proposed surrogate endpoint
  – Study continuation (possible „conditional licensing“)
    - » Two years in placebo-controlled manner
  – Endpoint(s) at trial end:
    - » LTx; all-cause death; liver related events (CCA?)
    - » Confirmatory or not?

Regulatory update from Europe:

- Preliminary regulatory position:

  <u>Problems remaining:</u>

  – Is there a possibility to license treatments for „symptomatic treatments“ only – yes!

  – Requirements:

    » Shorter duration acceptable (6 months?)

    » Symptomatic effect as well as influence on QoL should be shown

    » Unresolved issues:

      - Increased requirements for risks? Long-tem risks?
      - Influence on long-term outcome?

Thank you for your attention!

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