Federal Institute
for Drugs
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EMA perspective on optimal trial design for Phase 3 trials of novel therapies for Chronic Hepatitis D

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Clinical phase 3 trial design considerations - chronic HDV

Goal of therapy in patients with **HBV/HDV coinfection:**

- **Clearance** or **long-term suppression** of **both viruses**
- **Loss of HBsAg** may ultimately lead to the **clearance of HDV infection**

  → currently **not possible** with treatment options

Approved drugs for the treatment of chronic HDV in the EU

- One **conditionally apporved** chronic HDV treatment in **the EU**
- **Heplcudex®** (bulvertide), approved in July 2020

Indication:

"Treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease"

- Conditional approval was based on results of **two small expolatory phase II** studies (Myr 202 and Myr 203)
- **Exploratory primary endpoint** in both studies: **HDV RNA negativation** or a **decrease in HDV RNA by ≥2 log10 IU/mL**
- More clinical evidence from **phase III study 301** will become available
- **Study design** of phase III study 301 was discussed and **agreed by EMA**

Clinical phase III trial design considerations – chronic HDV

Trial Design:

- Double-blind, **active comparator-controlled** superiority or non-inferiority trial

Trial population:

- Documented **chronic HDV infection** with HDV RNA quantifiable for **at least 6 months**
- **On NUC suppressive therapy** before HDV treatment start due to the risk of HBV reactivation

Randomisation/Stratification factors:

- Presence/absence cirrhosis, baseline HDV RNA and/or genotype/region

Clinical phase III trial design considerations – chronic HDV Primary efficacy endpoint

- **Surrogate endpoint** that is reasonably likely to **predict clinical benefit**
- Should provide evidence of both a **decline in virologic replication** and an **improvement** in associated **liver inflammation** as evident by biochemical response

Composite endpoint:

- **undetectable serum HDV RNA** (defined as less than the lower limit of quantification (LLOQ) or **≥ 2 log10 IU/ml decline in HDV RNA** and **ALT normalization**

Note:
Any **other proposal** would **need to be justified,** with respect to **surrogacy** for **clinical endpoint,** supported by **clinical phase II data** prior to study start

Clinical phase III trial design considerations – chronic HDV
Secondary efficacy endpoint

The following secondary endpoint should be considered

- Greater than or equal to 2-log10 decline in serum HDV RNA
- Undetectable HDV RNA
- HDV RNA less than LLOQ (TND)
- ALT normalization
- Histological response or change in liver stiffness
- Change in Model for End-Stage Liver Disease

Clinical phase III trial design considerations – chronic HDV Timing of assessment

- Dependent on the treatment strategy used

Chronic treatments:

- Assessment at **week 48 on-treatment** with **sufficient FU** of **96** and **144 weeks**

Finite treatments:

- Assessment at **24 weeks off-treatment** with **FU time** of additional **48** and **96 weeks** to evaluate sustainability of response

Conclusion

- HBV lifecyle is complex and development of appropriate clinical trial design for new HBV or HDV therapies is challenging
- **No „one-fits-all“ approach**
- Regulatory guidance will continue to evolve based on the available/emerging data
- Use one of the regulatory pathways to **seek regulatory guidance early** and throughout the drug development program
- EMA is committed to provide timely advice in designing feasible, ethical, and scientifically valid trials through all phases of clinical development program
- Collaborative interactions between regulatory agencies, academia, industry, and patient communities are crucial to move forward to achieve WHO goal of elimination of viral hepatitis!

Thank you very much for your attention!

Contact

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