Stopping NUCs – Flares and mitigating risk

Regulatory considerations for clinical trial design for novel combination therapies with a finite treatment duration in CHB patients who are virologically suppressed on NUCs

Dr. Stephanie Buchholz
Clinical Assessor Antivirals
Disclaimer

“The views expressed here are my personal views, and shall in no way be binding for the BfArM or CHMP/EMA.”
Types of HBV cure covered by approved drugs

<table>
<thead>
<tr>
<th>Partial cure</th>
<th>Functional cure</th>
<th>Complete cure</th>
<th>Sterilizing cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUCs IFNs</td>
<td>Current drug development programs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral suppression</td>
<td>HBsAg loss Viral suppression w/wo anti-HBs</td>
<td>HBsAg loss Viral suppression ccc DNA elimination</td>
<td>HBsAg loss Viral suppression ccc DNA elimination Erradication of integrated HBV DNA</td>
</tr>
</tbody>
</table>

**Viral suppression**

**HBsAg loss**

**Viral suppression w/wo anti-HBs**

**HBsAg loss Viral suppression ccc DNA elimination**

**Erradication of integrated HBV DNA**

**Goal of future therapies**

**Lok A, Hepatology & J Hepatol 2017**

**Modified from Lang et al., Hepatol Int 2019**
Trial design considerations –
Finite therapy in CHB patients who are virologically suppressed on NUCs

Well **controlled randomized trials** in the proposed population with an **approved active control arm**

**Trial design:**
Investigational product (s) + NUC vs. NUC alone

**Study population:**
CHB patients **virologically suppressed on NUCs** (most likely HBeAg pos/neg patients)

**Primary efficacy endpoint:**
Sustained suppression of **HBV DNA** (< LLOQ) with **HBsAg loss** (< 0.05 IU/ml) with or without anti-HBs after treatment discontinuation

**Treatment duration:**
**Finite treatment duration** dependent on the **Mechanism of Action** and **half-life** of the drug
Trial design - finite treatment
Criteria for stopping NUCs EOT

Increasing evidence that stopping long-term NUC therapy results in HBsAg-loss rates of up to 20%

Criteria of stopping NUCs in clinical trials should be:

• Applied equally across treatment arms
• Well-defined in the protocol
• Stringent (e.g. HBsAg loss or marked reduction of other biomarkers identified)

Remaining question:
Do baseline demographic or disease characteristics, i.e. HBeAg status or prior duration of suppression with NUC impact the importance of discontinuing NUCs in terms of efficacy and safety?
Criteria for stopping NUCs EOT – variables to consider

- Potential **impact** of **baseline demographic and disease characteristics** on **response rates** after stopping NUCs → effect on efficacy outcome
- **Reflected in the study design** (inclusion/exclusion criteria, stratification criteria and pre-defined subgroup analyses)
- **Variables to consider** for the study design to ensure comparability between IP arm and control arm
  - HBeAg status
  - HBsAg levels at baseline and stopping NUCs
  - Duration of viral suppression
  - Treatment history (duration and type of NUC)
  - Presence/absence of cirrhosis
  - Age, race and HBV genotype
  - HBV DNA levels during reactivation

[→ Potential labelling consequences !!!]
Safety considerations – hepatitis flares

- Stopping NUC treatment is often associated with hepatitis flares
- HBsAg loss is not necessarily associated with severe flares

Assessment of on- and off- treatment hepatitis flares

- Differentiation between beneficial (immune clearance) and severe flares (drug induced liver injury)
- Severe flares associated with increase in bilirubin or prothrombin time can be serious and life-threatening
- Detailed safety monitoring plan for evaluation of hepatitis flares should be included in the clinical study protocol (low bar for monitoring flares recommended, i.e. 2x ULN)
- Definition of unambiguous predefined treatment discontinuation and trial stopping rules
- Treatment re-initiation criteria for NUC should be predefined in the protocol
Safety considerations –
Risk factors for detrimental withdrawal flares

➢ Fibrosis state, cirrhosis
➢ Re-treatment strategy
➢ Serological status: HBsAg < HBeAg neg. < HBeAg pos.
➢ Rise of HBV-DNA
➢ Amplitude of flare
➢ AUC of flare
➢ Comorbidities

→ Impact on the study design (inclusion/exclusion criteria, safety monitoring plan, stopping rules, re-treatment criteria)
Trial design—Safety considerations

- **Benefits** should **outweigh** the **potential risks** for the intended population

- **Avoidance** of **unreasonable** and **significant risks** for clinical trial participants

- All **serious hepatic events** (deaths, liver transplantation, hepatic decompensation, cases of severe hepatitis flares) and **immune system related events** (autoimmunity/extreme immune response) should be **systematically evaluated**

- **Independent safety data reviewing committee** is recommended
Timing and Response rates

Timing of assessment

- **Off-treatment response** for Phase IIb/III trials
- May depend on mechanism of action and half-life of the drug

Response rates

Must be sufficiently high to outweigh the risk for DILI/flare related morbidity and substantial remaining uncertainties in order to support approval

Benefit/Risk considerations for regulatory decision making:

- Benefit: **Magnitude** and **durability** of response
- Risk: **Safety profile**, risk potential
- Relation to approved therapeutic options (Benefit-Risk)
Trial design - Follow-up and long-term follow-up

Adequate long-term follow-up data will be required to support approval

Follow-up evaluation

- Adequate FU to monitor for durability of response and observational clinical data on clinical events (timing is dependent on mechanism of action and treatment duration)
- Post-treatment relapses and resistance development should be evaluated

Post-marketing Long-term follow-up

- Appropriate long-term follow-up should be planned and defined at time of application to assess durability of sustained response and long-term clinical outcome
- Evaluation of incidence of liver-related complications (hepatic failure, HCC, liver transplant and liver-related deaths)
- Documentation of late post-treatment relapses
Conclusion

Stopping NUCs at EOT in clinical trials aiming at functional cure in CHB patients who are virologically suppressed on NUCs with a finite treatment duration, requires careful considerations on the clinical trial design, due to the potential impact of baseline demographic and disease characteristics on response rates after stopping NUCs (efficacy) and the occurrence of hepatitis flares (safety)

**Efficacy:**
- Baseline demographic and disease characteristics should be considered for the study design (i.e. stratification factors, inclusion/exclusion criteria, pre-defined subgroup analyses)
- Criteria for stopping NUCs should be applied equally across treatment arms, well-defined in the study protocol and stringent to allow comparability between the investigational arm and the control arm

**Safety:**
- Safety monitoring of hepatitis flares is considered essential (i.e. detailed safety monitoring plan, clear stopping and retreatment criteria, exclusion of patients at risk for severe flares)
- Appropriate long-term follow-up data required, durability of sustained response, post-treatment relapses, long-term clinical outcome and evaluation of incidence of liver-related complications → Independent safety data reviewing committee is recommended
Thank you very much for your attention!

Contact

Federal Institute for Drugs and Medical Devices
Division 32, Infectiology/Dermatology/Allergology
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn

Contact person
Dr. Stephanie Buchholz
Stephanie.buchholzbfarm.de
www.bfarm.de
Phone +49 (0)228 99 307-4323
Fax +49 (0)228 99 307-3392