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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

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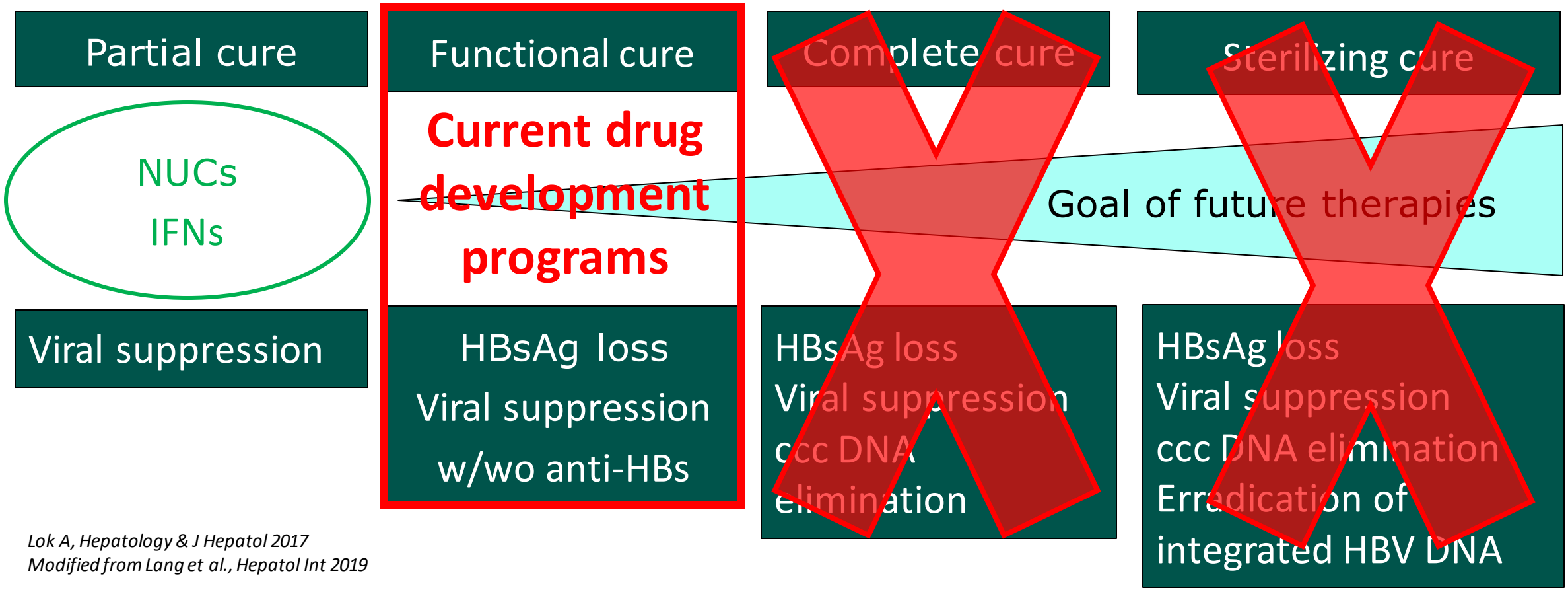
Disclaimer

“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



Lok A, Hepatology & J Hepatol 2017
Modified from Lang et al., Hepatol Int 2019

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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**?

Berg et al., J. Hepatol. 2017, Papatheodoridis et al, Hepatology. 2017
Karakaya et al., Antivir Ther. 2017

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 n**ot 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 recommeded**, 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 withdrawl 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)

→ **Benefit/Risk profile**

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, exlclusion of patients at risk for severe flares)
- Appropiate 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

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