FDA Guidance for HBV November 2018

KEY POINT 1

The development of new therapies is targeted at developing treatment regimens of finite duration with low risk of virologic relapse and minimal risk of liver disease progression after the treatment is stopped (Lok et al. 2017).

KEY POINT 2

Nonclinical combination studies of an investigational drug plus an approved drug or licensed biological product generally are not recommended. Therefore, unless data from nonclinical studies of an investigational drug suggest a potential for serious synergistic toxicity with an approved drug or licensed biological product, combination toxicology studies are not anticipated.

KEY POINT 3 - siRNA

Identify potential off-target matches in the human transcriptome, regardless of tissue expression; for each of these, describe available information on mouse knockouts and human genetic diseases.

A plan for monitoring for significant off-target effects should be included in clinical trial protocols.

Determine the conservation among the investigational off-target human genes with their respective mouse genes that are three or fewer mismatched bases different from the drug to determine if these sites are sufficiently conserved in the mouse such that toxicities related to off-target matches would be present in mice.

Identify potential off-target matches in the human mitochondrial transcriptome.

Determine the variation within the off-target matches in the transcriptomes of different populations in the United States to assess whether different populations would be more susceptible to off-target effects than others.

Determine the effect of different mismatches with respect to off-target effects (i.e. comparing purine to purine versus other mismatches).

KEY POINT 4 - Host Targeting Agents

For drugs targeting host factors, polymorphisms in the gene encoding the target should be assessed to determine if the drug will be more effective or less effective in different populations.

KEY POINT 5 - Early Stage endpoints

- Change in quantitative HBsAg (qHBsAg) concentration at various time points on treatment
- HBeAg concentration
- HBV RNA
- HBV core-related antigen (HBcrAg)
- cccDNA quantification
- HBsAg fragments
- HBsAg-anti-HBs immune complex

KEY POINT 6 – Phase 3 considerations

safety database of about 1,000 to 1,500 patients exposed to the proposed dose and duration of treatment.

Single population

Separate populations

2 well controlled trials to support NDA

KEY POINT 7 – Endpoints, Functional Cure, Partial Cure

NUC Suppressed

HBsAg loss (<0.05 IU/ml)

Partial cure – Sustained HBV DNA (LLOQ, TND) suppression off treatment (at least 6 months after stopping)

NAÏVE

Superiority study versus SOC
Same endpoints

KEY POINT 8 – Other considerations

Safety

ALT Flare Plan

Resistance testing plan including cross-resistance

Long term follow up to show clinical outcomes improvement for accelerated approval

Special populations – HIV, HDV co-infection, pediatrics