Liver Safety Monitoring Working Group

Co-Chairs:

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Rationale: Liver Safety Monitoring WG

- **Spontaneous, immune mediated disease flares (e.g. ALT flare) unique feature of untreated CHB**
  - **Surge in HBV replication followed by enhanced host immunity**
  - **Can lead to acute/ subacute liver failure (death) or**
  - **Can precede beneficial transition to ↓HBV replication state**

- **Idiosyncratic DILI: infrequent, independent of drug dose/ duration, and difficult to predict**
  - **GWAS: HLA associations with individual drugs**
    - **? Failure to adapt/ abberant immune response**
  - **DILI is a leading reason for drug development failure**

- **The challenge is to distinguish DILI vs therapeutic flare in an HBV drug development program**

Liver Safety Working Group

- **AIMS: Develop consensus recommendations regarding definitions and criteria to distinguish DILI event vs therapeutic flare vs other (e.g. spontaneous, breakthrough/ resistance) in HBV treatment trial with newer agent(s)**
- **Drug mechanism(s) of action**
  - **“Direct- acting” agents (core modulators) vs immune/ host modulators**
  - **RNAi can rapidly ↓ sAg and ↑CTL response**

LSM WG White Paper

- Idiosyncratic DILI (Avigan, Fontana, Stern)
  - Causality, severity scales, risk factors
- Spontaneous flares (Janssen, Wat)
  - Grading, frequency, risk factors
- NA and pegIFN flares (Brown, Gaggar, Wat)
  - Early vs late, off treatment, consequences
- Future clinical trials (Regev, Brown, Poonam)
  - Single vs combo trials
  - Phase 1: I/E, non-cirrhotic, Nuc sup vs naïve
  - Phase 2/3: Nuc sup vs naïve, lab schedule/ duration, stopping rules
- Liver safety signal assessment (Fontana)
  - Diffl dx/ testing, F/U, causality, liver biopsy, expert panels
- Unmet needs (All)
  - Immune assays, DILI biomarkers, new HBV assays

LSWG Timelines

- **4/18: White paper outline**
  - **Section assignments**
  - **Monthly conf calls**
- **Fall 2018: Manuscript Draft**
  - **Tables/ figures**
  - **Recommendations for best practices**

Questions