Berkeley School of Public Health

FORUM for Collaborative RESEARCH

HBV Forum 2
April 18th 2017
Hilton Amsterdam

www.forumresearch.org

Berkeley School of Public Health

FORUM for Collaborative RESEARCH

Working Group Update: Surrogate Endpoints

HBV Forum Surrogate Endpoint Working Group

Co-chairs: Oliver Lenz, Marion Peters

Members

- Ryan Taylor Anderson, MS – Forum Intern
- Nat Brown, MD - Hepatitis B Foundation Advisor
- Henry LY Chan, MD- Chinese University of Hong Kong
- Gavin Cloherty, PhD - Abbott
- Eric Donaldson, PhD – US FDA
- Geoffrey Dusheiko, MD -UCL
- Robert Gish, MD - Stanford
- Bettina Hansen, PhD - U Toronto
- Pietro Lampertico, MD, PhD - U Milan
- Oliver Lenz, PhD - Janssen
- Uri Lopatin, MD - Assembly Biosciences
- Eduardo Bruno Martins, MD, DPhil - Eiger
- Brian McMahon, MD – Alaska Native Medical Center
- Charu Mullick, MD – US FDA
- Jeffrey Murray, MD, MPH- US FDA
- Michael Ninburg, MPA - Hepatitis Education Project
- Sandra Palleja, MD - PPD Inc.
- Jean-Michel Pawlotsky, MD, PhD – Henri Mondor Univ. Hospital
- Marion Peters, MD - UCSF
- Leland Ross Pierce, MD – US FDA
- Andrew Vaillant, PhD - Replicor
- Hwai-I Yang, PhD - Academia Sinica

Aims and Objectives

1. Assess the relationship of surrogate endpoints/markers with long-term clinical outcomes, identify gaps, and recommend research to fill these gaps to advance the regulatory process for HBV therapeutic interventions.
2. Review, discuss and formulate evolving consensus on HBV cure definition and appropriate surrogate endpoints for HBV Ph2b and Ph3 clinical studies.

Objective 1: Activity 1

1) Perform a systematic literature review/meta-analysis of references/data describing link between **surrogate endpoints** and **long term clinical outcome**.
   - Starting with:
     A) HBsAg "loss" with or without anti-HBs "gain."
     B) Low level HBsAg and "inactive carrier like state" (low HBV DNA, normal ALT, low HBsAg) .

Objective 1: Activity 1, Current Status

- Excel sheet to capture data from literature has been developed
  - endorsed by Working Group
- Data from 27 papers are included.
- Additional ~60 references have been selected and are being reviewed before inclusion.

Literature Reference: Data Collection

- 67 parameters are collected : Study Information, Baseline, End of Treatment, and Follow-up data, Surrogate Endpoints, Long-term clinical Outcome, Assays.

	Study Information							Long-term Outcome			Endpoints			
Reference	**Study Design**	**Type**	**Tot Pts**	**Age (years)**	**Cohort(s)**	**Treatment Duration**	**Time of Final Follow-up (from start of treatment)**	**New Cirrh (%)**	**Hepato-cellular Carcinoma (%)**	**Death (%)**	**Primary Endpoint**	**Primary Endpoint Result**	**Other Endpoint 2**	**Other Endpoint 2 Result**
Lin et al. J Heptol 2007; 46: 45-52	Retrospective cohort	Long term	466	32 ± 7 31 ± 8	INF-α (n=233) Control (n=233)	4-6 mo None	81.6 ± 38.4 mo 73.2 ± 36 mo	11.0 17.9	2.3 6.1	0.1 5.6	Cumulative incidence of sustained HBeAg/HBV-DNA clearance	74.6% 51.7%	HBsAg Seroclearance	3.0% 0.4%
Kim et al. Cancer 2015; 121(20): 3631-3638	Prospective cohort	Long term	634	45.2 ± 10.6 38.4 ± 11.8	Cirrhosis (n=152) w/o Cirrhosis (n=482)	48 wk TDF or ADV 48 wk TDF or ADV	384 wk 384 wk		3.9 1.7		Observed HCC vs. predicted HCC (SIR, 95% CI)	0.51, 0.23-1.14 0.40, 0.20-0.80	Cumulative incidence of HCC by baseline cirrhosis status	0.65% per year 0.28% per year
Chen et al. JAMA 2006; 295(1): 65-73	Prospective cohort	Long term	3,653	**30-39:** n=1216 **40-49:** n=1014 **50-59:** n=1058 **≥60:** n=365	HBV DNA < 300 copies/mL (n=873) HBV DNA = 300-9,999 copies/mL (n=1161) HBV DNA = 10,000-99,999 copies/mL (n=643) HBV DNA = 100,000-999,999 copies/mL (n=349) HBV DNA > 10^6 copies/mL (n=627)	None	Mean = 11.4 yr		1.3 1.4 3.6 12.2 14.9	10	Risk of HCC associated with HBV DNA level (HR, 95% CI)	Ref 1.1, 0.5-2.3 2.3, 1.1-4.9 6.6, 3.3-13.1 6.1, 2.9-12.7	Cumulative incidence of HCC by DNA level at study entry: all pts (%)	1.3 1.4 3.6 12.2 14.9
Yuen et al. Gastroenterology 2016; 135: 1192-1199	Longitudinal	Long term	298	43.1 (1.9-79.3)	No Rx (n=285), LAM (n=10), or Interferon-α (n=3)	16 wk Interferon-α	108.9 (6.2-319.8) mo				Cumulative risk for the development of HCC in patients with HBsAg seroclearance at age <50 and ≥50 years (%)	**<50:** 0 **≥50:** 10	Liver Stiffness of Patients With HBsAg Seroclearance at Different Age (kPa)	**<40 (n=26):** 5.2(2.9-11.3) **40-50 (n=50):** 5.9(3.3-17.5) **>50:** 6.2(3-22.8)

Objective 1: Activity 2 and 3

2) Determine the regulatory perspective/requirements in terms of evidence needed to accept surrogate endpoints for long term clinical benefit.
3) Gap analyses assessing the available evidence vs. required evidence and determine which additional evidence would facilitate HBV cure development.

Objective 1: Activities 4

4. Identify, promote and facilitate opportunities to create additional evidence (e.g. in collaboration with HBV cohorts (REVEAL), cross pharma initiatives, EASL, AASLD, APASL,…).

Objective 1: Activities 4

- Prof HI Yang has agreed to collaborate with the Working Group with the aim to allow access to the REVEAL data.
  - Complete REVEAL reference list is available and relevant papers are being included in the literature collection.
  - Discussions with Prof. Yang are ongoing to determined the scope of the collaboration and sharing of data.

Objective 2: Activity 1

- Review cure definitions (including surrogate endpoints) and develop/prioritize list of (surrogate) endpoints for Ph2b/3 studies:
  - Review of literature, conference proceedings, etc. from different stakeholders.
  - Achieve consensus within the HBV Forum.
  - Assess the available level of evidence of these surrogate markers with respect to long term clinical outcome (link to Objective 1).

Outcomes and Products

- **Deliverable:**
  - Peer-reviewed manuscript(s).
  - Reference set collection of data (excel sheet has been developed).

Next steps

Objective 1:

- Activity 1: Literature review of clinical outcome data for HBsAg (“loss” and low level) and collection of data – Q2/Q3 2017.
  - Complete Literature Review and data collection Q2.
  - Share literature list and data collection with working group to ensure all relevant studies are included.
  - Perform Meta Analyses Q3-Q4.
- Activity 4: Include relevant data from REVEAL data base (Q2/Q3). Identify other sources of evidence.
- Activity 2: Start taskforce to define regulatory requirements for surrogate marker of “cure” in HBV.

Objective 2:

- Start up activities within working group.

Questions