WHAT’S HOT AT THE LIVER MEETING

Edward Gane
New Zealand Liver Transplant Unit
Auckland, New Zealand
Disclosures for Ed Gane

♦ Member of the following Scientific Advisory Boards: AbbVie, ALIOS, ALIGOS, Assembly, Arrowhead, Avalia Immunotherapies, Dicerna, Enanta, Gilead Sciences, GlaxoSmithKline, IMMUNOCORE, Inovio, Novira, Roche and VIR Bio

♦ The opinions expressed today are my own
What’s Hot at the Liver Meeting

1. Basic immunology & virology of HBV
2. Natural history studies
   ▪ Benefit of HBsAg loss
3. Current HBV treatments
   ▪ Is risk for HCC lower with TDF than ETV?
   ▪ NUC Stop studies
4. New HBV therapies
   ▪ Clinical studies
   ▪ Early development
COMBINATION TREATMENT OF LIVER-TARGETED HBV LOCKED NUCLEIC ACID ANTISENSE OLIGONUCLEOTIDE AND TLR7 AGONIST RO7020531 LEADS TO PROLONGED OFF-TREATMENT ANTIVIRAL EFFECT IN THE AAV-HBV MOUSE MODEL

ANALYSIS OF FACTORS INFLUENCING THE EFFICACY AND SAFETY OF GLS4 TREATMENT IN PATIENTS WITH CHRONIC HEPATITIS B

A NOVEL LIVER-DIRECTED LOCKED NUCLEIC ACID TARGETING PD-L1 EXPRESSION REVERTS HBV-SPECIFIC IMMUNE TOLERANCE AND INDUCES SUSTAINED CLEARANCE OF HBV INFECTION

SAFETY, PHARMACOKINETIC, PHARMACODYNAMIC AND VIRAL DATA AFTER 6-WEEKS OF DOSING WITH TLR7 AGONIST RO7020531 IN CHRONIC HEPATITIS B

DUAL AGONIST OF FARNESOID X RECEPTOR AND G PROTEIN-COUPLED RECEPTOR TGR5 INHIBITS HEPATITIS B VIRUS INFECTION

RESULTS AFTER 12 WEEKS TREATMENT OF MULTIPLE DOSES OF GSK3389404 IN CHRONIC HEPATITIS B (CHB) SUBJECTS ON STABLE NUCLEOS(T)IDE THERAPY IN A PHASE 2a DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

DOSE RESPONSE WITH THE RNA INTERFERENC (RNAI) THERAPY JNJ-3989 COMBINED WITH NUCLEOS(T)IDE ANALOGUE (NA) TREATMENT IN EXPANDED COHORTS OF PATIENTS (PTS) WITH CHRONIC HEPATITIS B (CHB)

EFFICACY AND SAFETY OF ORAL TLR8 AGONIST GS-9688 IN VIRALLY-SUPPRESSED ADULT PATIENTS WITH CHRONIC HEPATITIS B: A PHASE 2, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED, MULTI-CENTER STUDY

INTERIM RESULTS OF A PHASE 1 STUDY OF RO7062931, A NOVEL LIVER-TARGETED SINGLE-STRANDED OLIGONUCLEOTIDE (SSO) WITH LOCKED NUCLEIC ACID (LNA) THAT TARGETS HBV TRANSCRIPTS.

PRECLINICAL ASSESSMENT OF A NOVEL CAPSID ASSEMBLY MODULATOR, ALG-001075, DEMONSTRATES BEST-IN-CLASS IN VITRO POTENCY AND IN VIVO ANTIVIRAL EFFICACY

PHASE 2a, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF AN ANTISENSE INHIBITOR (ISIS 505358) IN TREATMENT-NAÏVE CHRONIC HEPATITIS B (CHB) PATIENTS: SAFETY AND ANTIVIRAL EFFICACY

A NOVEL HBV CAPSID INHIBITOR COMPOUND SERIES DEMONSTRATES IMPROVED INHIBITION OF HBV WT AND T33N CORE PROTEIN VARIANT AND SHOWS A UNIQUE BINDING MODE TO CORE PROTEIN

PRECLINICAL ASSESSMENT OF POTENCY AND EFFICACY OF A NOVEL CLASS-II CAPSID ASSEMBLY MODULATOR ALG-001024

LIVER-TARGETED INHIBITION OF PAPD5 AND PAPD7 LEADS TO SUSTAINABLE HBsAg REDUCTION IN THE AAV-HBV MOUSE MODEL.

ONGOING ANALYSIS OF FUNCTIONAL CONTROL / CURE OF HBV AND HDV INFECTION FOLLOWING REP 2139-CA AND PEGYLATED INTERFERON ALPHA-2a THERAPY IN PATIENTS WITH CHRONIC HBV / HDV CO-INFECTION: 3-YEAR FOLLOW-UP RESULTS FROM THE REP 301-LTF STUDY

PERIPHERAL IMMUNE RESPONSES TO TOLL-LIKE RECEPTOR 8 AGONIST GS-9688 IN PATIENTS WITH CHRONIC HEPATITIS B

ANTI-HBV ACTIVITY OF 7-DEAZAADENINE RIBONUCLEOSIDE DERIVATIVE IN IN VITRO AND IN VIVO

AN IN-SILICO DISEASE MODEL FOR THE DEVELOPMENT OF FXR AGONIST EYP001 AS A THERAPY FOR HBV INFECTION

SAFETY AND ANTIVIRAL EFFECT OF THE FARNESOID X RECEPTOR AGONIST EYP001 IN CHRONIC HEPATITIS B PATIENTS: A RANDOMISED PHASE 1b STUDY

META-ANALYSIS OF TWO PHASE 1b RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED CLINICAL TRIALS OF THE HBV THERAPEUTIC VACCINES TG1050 AND T101 DEVELOPED IN EUROPE/CANADA OR CHINA.

IDENTIFICATION OF MIRNAS THAT REGULATE HEPATITIS B VIRUS REPLICATION IN VITRO

CLINICAL FEATURES OF HEPATITIS B PATIENTS AT IMMUNE-TOLERANCE PHASE WITH BASAL CORE PROMOTER AND/OR PRECORE MUTATIONS

SERUM IMMUNOLOGICAL PROFILE ASSOCIATED WITH HBEAG SEROCONVERSION IN CHRONIC HEPATITIS B PATIENTS.
HBV CURE Targets

Reduce Viral Burden

Capsid allosteric modulator
- NVR 3-778
- JNJ-379
- JNJ-440
- ABI-H0731
- ABI-H2198
- ABI-H3733
- AT-130
- BAY41-4109
- HAP-12
- GLS4JH5
- HAP_R01
- SBA_R01
- AB-506
- RG7-907
- EP-027367
- EDP-014
- ALG-001024
- GLP-26

Entry inhibitor
- Myrcludex B

Antibodies
- AB-492

Transcription inhibitors
- DNA Edits
- Epigenetics
- Demethylase inhibitors
- PPAD57 inhibitor
- HB X-inhibitors
- FXR Agonists

Gene Editing
- CRISPR Cas9
- ZNF nucleases
- TALENS

RNA destabilizers
- ASO/LNA
- ARC-520
- ARC-521
- ALN-HBV
- ARB-1467
- ARB-1740
- AB-729
- JNJ-3989
- DCB-NBVS

sAg Inhibitor

Activate Host Immunity

RIG-I inhibitor
- inarigivir

TLR8 agonist
- 1.GS-9668

TLR7 agonist
- 1.GS-9620
- 2.RO6864018
- 3.RO7020531
- 4.JNJ-64794964

Vaccines
- GS-9620
- RO6864018
- RO7020531
- JNJ-64794964

CYTOKINES
- IDO1 Arginase
- CRV431

Metabolic regulation
- TLR7 agonist
- 1.GS-9620
- 2.RO6864018
- 3.RO7020531
- 4.JNJ-64794964

Anti-PD-1/L1
- PD-1 LNA
- Oral PDL1sm

Anti-HBs
- VIR-3434

CD8+ Treg B-Cell NK PD-1/L1 TLR7 agonist 1.GS-9620 2.RO6864018 3.RO7020531 4.JNJ-64794964 TLR8 agonist 1.GS-9668 RIG-I inhibitor inarigivir Anti-PD-1/L1 PD-1 LNA Oral PDL1sm Anti-HBs VIR-3434
Capsid Allosteric Modulators (CAMs)

**CAM-I or A Class**
- RO7049389
- BAY41-4109
- HAP-12
- GLS4JHS
- HAP_R01
- SBA_R01
- RG-7907

**CAM-II or N Class**
- NVR 3-778
- JNJ-379
- JNJ-440
- AT130
- AB-506
- GLP-26
- ABI-H0731
- ABI-H2158
- ABI-H3733
- ALG-001024
- ALG-001075
- TBA #701

1. Fukutomi K, et al. Oral #90
2. Yuen M-F, et al. Poster #LP4
3. Gane E, et al. Oral #89
5. Sulkowski M, et al. Poster #LP1
Oral HBV capsid assembly modulator (CAMs)

- **Antiviral effect during 28 days dosing**

1. **NVR3-778**
   - Yuen M-F, et al. EASL 2016, Barcelona. LBO6
   - ▪ 1200mg $\Rightarrow$ 2log reduction
   - ▪ No effect on HBsAg
   - ▪ Skin rash

2. **JNJ-379**
   - ▪ 250mg $\Rightarrow$ 2.9 log reduction
   - ▪ No effect on HBsAg
   - ▪ Occ ALT elevation

3. **RO7049389**
   - Gane E, et al. EASL 2018, Paris. #LBO-003
   - ▪ 200mg $\Rightarrow$ 3.2 log reduction
   - ▪ No effect on HBsAg
   - ▪ Occ ALT elevation

4. **ABI-H0731**
   - ▪ 1200mg $\Rightarrow$ 2log reduction
   - ▪ No effect on HBsAg
   - ▪ Skin rash
   - ▪ 200mg $\Rightarrow$ 3.9 log reduction
   - ▪ No effect on HBsAg
   - ▪ Occ ALT elevation

HBV Forum 6, Boston Nov 2019
Oral HBV capsid assembly modulator (CAMs)

- Antiviral effect during 28 days dosing

1. NVR3-778

- 2-3 log reduction in HBV DNA after 28 days
- 2 log reduction in HBV RNA after 28 days
- NO change in HBsAg levels after 28 days

Will increased potency/duration achieve this 2’ MoA?

- 1200mg⇒2log reduction
- No effect on HBsAg
- Skin rash

- 250mg⇒2.9 log reduction
- No effect on HBsAg
- Occ ALT elevation

- 200mg⇒3.2 log reduction
- No effect on HBsAg
- ALT elevation in 20%

- 400mg⇒3.9 log reduction
- No effect on HBsAg
- Skin rash

HBV Forum 6, Boston Nov 2019
Oral HBV capsid assembly inhibitor (CpAMs)

AASLD 2019, Abstract #LP14: Increased potency of 2\textsuperscript{nd} Gen CAMs

- ABI-H2158 >10-fold in vitro potency for inhibition of capsid assembly and cccDNA synthesis compared to 1\textsuperscript{st} Gen CAMs

Colonno R, et al. EASL 2019

- ABI-H2158 100mg OD for 14 days in Rx-naïve HBeAg-positive CHB
  - Safe and well tolerated, with no Grade ≥2 ALT elevations
  - Mean HBV DNA decline 2.3 log10 IU/mL [range 1.7 – 3.0]
  - Mean HBV RNA decline 2.0 log10 IU/mL [range 1.5 - 2.6]

- Next cohort of ABI-H2158 300mg OD for 14 days in progress
Oral HBV capsid assembly inhibitor (CpAMs)

AASLD 2019, Abstract #LP1: Longer Duration of 1st Gen CAMs

- Study #211: Open label ETV+ ABI-H0731 for 52 weeks in patients who have completed Studies #201 and #202 (24 weeks ETV + ABI-H0731/Plac)
  - Interim results for HBeAg+ completed ≥ 32 wks ETV + ABI-H0731

1. 27 patients from Study #201 (DNA suppressed on NUCs at Baseline)
   - 11 (41%) are HBV DNA TND, RNA <35 iu/mL and HBeAg <1 IU/mL
2. 22 patients from Study #202 (Rx-naïve, DNA> 5 log iu/mL at Baseline)
   - Mean HBV DNA decline 6.1 log₁₀
   - Mean HBV RNA decline 3.0 log₁₀
   - Mean HBcrAg decline 0.8 log₁₀ (7 pts ≥1.0)
   - Mean HBeAg decline 0.6 log₁₀ (4 pts ≥1.0)
Oral HBV capsid assembly inhibitor (CpAMs)

AASLD 2019, Abstract #LP1: Longer Duration of 1st Gen CAMs

- Study #211: Open label ETV+ ABI-H0731 for 52 weeks in patients who have completed Studies #201 and #202 (24 weeks ETV + ABI-H0731/Plac)
  - Interim results for HBeAg+ completed ≥ 32 wks ETV + ABI-H0731

1. 27 patients from Study #201 (DNA suppressed on NUCs at Baseline)
   - 11 (41%) are HBV DNA TND, RNA <35 iu/mL and HBeAg <1 IU/mL

2. 22 patients from Study #202 (Rx naïve, DNA > 5 log iu/mL at Baseline)
   - Mean HBV DNA decline 6.1 log
   - Mean HBV RNA decline 3.0 log
   - Mean HBcrAg decline 0.8 log
   - Mean HBeAg decline 0.6 log
     - First evidence of cccDNA pool depletion

Will CAM-NUC achieve Functional Cure?

- Mean HBsAg decline 0.4 log (7 pts ≥0.5, 3 pts ≥1.0)
Inhibition of virion and SVP production
- Inhibition of HBV antigen expression could stimulate endogenous immune responses AND increase effectiveness of immunotherapies
Challenges of Translation Inhibitors in CHB

1. What HBV targets are most effective
   - First gen siRNA (ARC-520) had little effect in HBeAg negative patients
     ➔ target sequences downstream from DR1-DR2 region to silence integrated S
     Wooddell C, et al. Sci Transl Med 2017; eaan0241
   - Are multiple targets needed to prevent resistance?
   - Should “X” be targeted as well as “S”?

2. What is best delivery system to hepatocytes
   - 1st Gen NAG-MLP siRNAs (ARC-520/521); LNP siRNAs (ARB-1467/1740)
     required weekly intravenous dosing, infusion reactions and premeds
   ➔ Gal-NAC conjugated: subcutaneous, monthly dosing, no premeds
JNJ-3989 (ARO-HBV) in eAg pos and eAg neg CHB

- MAD Ph1b (AASLD 2018; EASL 2019)
  - Cohorts 1-6: 3 doses Q4W
  - Cohorts 7-8: 3 doses QW or Q2W

- HBsAg declined by 1 log in all patients
- No dose-response from 100-400mg
- 1 Gr 2 ALT elevation, 3 months post-Rx,

- Phase 1b (AASLD 2019 #PS-080)
  - Expanded 100–400 mg cohorts
  - Added low-dose 25, 50mg cohorts
  - Longer follow-up

- Doses < 100mg less effective
- No more ALT elevations

Yuen M-F, et al. EASL 2019, Vienna, Austria. #PS-080

Gane E, et al. AASLD 2019.; #696
Translation Inhibition: other approaches at AASLD

1. Antisense oligonucleotides

- ASOs silence HBV gene expression by hybridising to HBV mRNA and activating host RNase H mediated degradation (not RISC)
- Gal-Nac-conjugation should reduce ASO toxicities of renal dysfunction, low platelets

1. RO7062931: Phase 1a in HVs (Gane #704)
   - Safe, no toxicity

2. GSK3389404: Phase 1b in NUC-suppressed CHB patients (Yuen #695)
   - 12 week dosing 120mg ⇒ HBsAg decline 0.75 log

3. ISIS505358: Phase 1b in treatment naïve-CHB patients (Yuen #700)
   - 3 week dosing 300mg ⇒ HBsAg decline 1.6 log ; HBV DNA decline 1.7 log
   - HBsAg and HBV DNA <LLOQ in 2 pts maintained for 1-4 months post-treatment
Translation Inhibition: other approaches at AASLD

2. mRNA destabilisers

- Small molecules target host poly-A polymerases PAPD5/7 (TENT4A/4B) which destabilise HBV transcripts from both integrated and cccDNA
  - Initial compounds associated with preclinical toxicity

- Gal-NAC LNA ASOs targeting host PAPD5/7
  - POC study in AAV-HBV mouse model (Poster #704)
  - Subcut injection Q2 weekly x3
  - Decrease HBsAg in all animals - mean 2.3 log$_{10}$
  - 4/8 mice had sustained HBsAg loss with anti-HBs, i.e. achieved functional cure

Mueller H, et al. AASLD 2019; #704
Ways to activate Antiviral Immunity against HBV

1. Stimulate Antiviral Effector Cells
   - TLR-7, TLR-8, RLRs, CLR, NLRs
   - DNA sensors

2. Generate New T cells
   - Therapeutic vaccines

3. “Rescue” Exhausted T cells
   - Reduce viral antigens
   - Modulate immune receptors (PD-1)
   - Relieve suppression of T cells
   - Inhibit T regs
TLR-7 agonist RO7020531

- Liver targeting specific TLR-7
  - 150 mg QOD dosing for 6 weeks in NUC-suppressed CHB patients at AASLD 2018

PD activity in patients with flu-like symptoms

![Graphs showing Serum IFNα and Serum IP-10 activity over study days 0 to 42.]

Relationship between exposure and PD activity (maximum fold of change in individual patients)

<table>
<thead>
<tr>
<th>Peptidoglycan Activity</th>
<th>Fraction responding</th>
<th>Geometric mean fold change (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neopterin</td>
<td>6/8</td>
<td>3.13 (1.86–6.08)</td>
</tr>
<tr>
<td>IP-10</td>
<td>7/8</td>
<td>3.55 (1.37–36.43)</td>
</tr>
<tr>
<td>ISG15</td>
<td>8/8</td>
<td>11.21 (2.31–270.26)</td>
</tr>
<tr>
<td>OAS-1</td>
<td>8/8</td>
<td>4.85 (1.71–41.45)</td>
</tr>
<tr>
<td>MX1</td>
<td>8/8</td>
<td>6.78 (2.16–87.43)</td>
</tr>
<tr>
<td>TLR7</td>
<td>7/8</td>
<td>3.46 (2.04–6.84)</td>
</tr>
</tbody>
</table>

- At AASLD this year, additional 150 and 170 mg cohorts (Yuen #692)
  - full virologic results including HBsAg to be presented
  - Next year planned Phase II platform studies with other agents

Gane E, et al. AASLD 2018, San Francisco, USA. #LB-33
Yuen M-F, et al. AASLD 2019, Boston, USA. #692
TLR-8 agonist GS-9688

- EASL 2019: Phase 1b: 4 weekly doses in NUC suppressed CHB

**Serum IL-12p40 changes**

**Serum IL-RA changes**

- At this meeting, results of Phase II study in NUC suppressed CHB (Gane #697)
  - 24 HBeAg pos and 24 HBeAg neg CHB patients on NUCs
  - Safe and well tolerated
  - HBsAg loss (Week 24)
TLR-8 agonist GS-9688

- EASL 2019: Phase 1b: 4 weekly doses in NUC suppressed CHB

**Serum IL-12p40 changes**

**Serum IL-RA changes**

- **Dose-related PD without tachyphylaxis**
- **Activated mDCs, NK, MAIT, CD4, CD8 T cells**
- **safe and well tolerated, no systemic IFN-α**
- **NO change in HBsAg after 4 weeks**

- At this meeting, results of Phase II study in NUC suppressed CHB (Gane #697)
  - 24 HBeAg pos and 24 HBeAg neg CHB patients on NUCs
  - Safe and well tolerated
  - HBsAg loss (Week 24)
PD1/L1 blockade

- CHB characterised by immune exhaustion
- PDL1 blockade should restore effective intra-hepatic HBV-specific T-cell responses

- Single dose IV nivolumab 0.3mg/kg in CHB
  - 20/22 had reduction in HBsAg
  - One functional cure
  - Overall effect was small

- Dose will be limited by IR-AEs which can be prolonged and life-threatening
  - ACTG study exploring repeated doses
  - Need new approaches to PD1/L1 blockade

PD1/L1 blockade: new approaches at AALSD 2019

- Inhibition of PD-L1 synthesis by LNA (Abstract #691)
  - GalNAc-conjugated LNA ASO directed against PD-L1
    - Mice received 5 weekly subcut doses 5 mg/kg
      - 50% reduction in PD-L1 maintained for 8 weeks
      - 40-fold increase in liver HBV specific IFN-γ cells
      - 2.4 log reduction in HBsAg which was sustained

  Luangsay S et al. #691

- Inactivation of PD-L1 by small molecule inhibitors
  - Several small molecules can bind to and dimerise PD-L1 and inactivate the receptor
    - short lived PD effect improving safety if IR-AEs develop

HBV CURE Combination Studies

Replication inhibition ± Antigen reduction ± Immune stimulation

- RNAi
  - RNA destabiliser
  - PD1/L1 inhibitor
  - RNAi
  - PD1/L1 inhibitor
  - RNAi
  - TLR Agonist
  - RNAi
  - TLR Agonist

- CAM
  - CAM
  - Th. vaccine
  - CAM
  - TLR Agonist
  - CAM
  - Th Vaccine
  - CAM

- RNAi
  - CAM
  - RNAi
  - PD1/L1 inhibitor
  - RNAi
  - PD1/L1 inhibitor
  - RNAi
  - TLR Agonist

- CAM
  - CAM
  - CAM
  - New DNA inhibitor
  - New DNA inhibitor
  - New DNA inhibitor
  - New DNA inhibitor
HBV CURE Combination Studies

Triple therapy: siRNA plus CAM plus NUC (Yuen #LP4)

- 12 eAg+/eAg- CHB patients in open label POC study
  1. JNJ-3989 200 mg subcut on Days 1, 28 and 56
  2. JNJ-6379 250mg OD for 12 weeks
  3. ETV/ TDV OD

- Well tolerated, few Gr1 ALT increases
- Robust antiviral activity
  - HBsAg decline 1.8 log by Day 111
  - Robust declines in other viral parameters
AASLD 2019 Conclusions

- Several promising candidates already in Phase II
  1. Will CAMs + NUC be enough to clear HBsAg?
  2. Will siRNAs achieve off-treatment HBsAg loss?
  3. Will reports of ALT elevations with some CAMs and siRNAs be deemed agent specific or become a class dose-limiting effect?
  4. How should the immunomodulators be used?
  5. Will PD1 blockade be safe at the dose needed to clear HBsAg?
  6. Which combinations should be prioritised in Platform studies and in which patient populations?
Class of 2019: who is most likely to succeed?

Class of 1974
Riverside High School Reunion

Most unlikely to succeed
Bill Gates
Class Nerd of 1974

"Whoa! We sure blew that prediction!"
Special thanks to

- Dr Anuj Gaggar, Audrey Lau, Gilead Sciences
- Dr Anna Maria Geretti, Cynthia Wat, Roche
- Dr Anna Bakardjieva, VIR Technology
- Uri Lopatin, Rich Colonno, Assembly Bio
- Bruce Given, Arrowhead Pharmaceuticals