EASL 2019 Review

Conference call and Webcast
April 15, 2019
Cautionary Note Regarding Forward-Looking Statements

The information in this presentation contains forward-looking statements regarding future events, including statements about the clinical and therapeutic potential of Assembly Biosciences’ core protein inhibitors, including ABI-H0731, ABI-H2158 and ABI-H3733, the initiation, timing, progress and results of nonclinical studies and clinical studies for our HBV-cure program, our regulatory strategies for our core inhibitors, and the strength of our capital position. Certain forward-looking statements may be identified by reference to a future period or periods or by use of forward-looking terminology such as “anticipated,” “expected,” “likely,” “may,” “potential,” or “predictive.” Such forward-looking statements, which are intended to be covered by the safe harbor provisions contained in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, are just predictions and are subject to risks and uncertainties that could cause the actual events or results to differ materially. These risks and uncertainties include, among others: outcomes of clinical studies are uncertain; and results of earlier preclinical and nonclinical studies may not be predictive of future clinical studies results; the components, timing, patient enrollment and completion rates, cost and results of clinical trials and other development activities involving our product candidates; the duration and results of regulatory review of our product candidates by the FDA and foreign regulatory authorities; our estimates regarding our capital requirements, and our need for future capital; and the possible impairment of, or inability to obtain or protect, intellectual property rights and the costs of obtaining and protecting such rights. These and other potential risks and uncertainties that could cause actual results to differ from the results predicted are more fully detailed under the heading “Risk Factors” in Assembly Biosciences’ Annual Report on Form 10-K for the year ended December 31, 2018 filed with the Securities and Exchange Commission (the “SEC”) and any additional reports filed with the SEC following the date of this presentation. It is not possible for Assembly Biosciences management to predict all risks nor can it assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this presentation may not occur and actual results could differ materially and adversely from those anticipated. Any forward-looking statement speaks only as of the date on which it is made, and no obligation to update or revise any forward-looking statement is assumed, whether as a result of new information, future events or otherwise, except as required by law.
Developing a Potential Cure for Hepatitis B (HBV)

Cure is achievable but currently at very low rates

Core Inhibitors

We believe backbone of curative therapy

Novel mechanism designed to break the HBV life cycle

Assembly Biosciences has a deep pipeline of potent core inhibitors
ASMB Presented Two Oral and Two Poster Presentations at EASL

• **ABI-H0731 Phase 2a Interim Results: Late Breaker Oral Presentation**, Dr. Jay Lalezari, Quest Clinical Research, San Francisco
  – *Interim Safety and Efficacy Results of the ABI-H0731 Phase 2a Program Exploring the Combination of ABI-H0731 with Nuc Therapy in Treatment-Naïve and Treatment-Suppressed Chronic Hepatitis B Patients*
  – “Best of ILC”

• **ABI-H2158 Phase 1a Results: Late Breaker Poster Presentation**
  – *Phase 1a Study of the Safety, Tolerability and Pharmacokinetics of ABI-H2158, a Novel Second-Generation HBV Core Inhibitor, In Healthy Volunteers*

• **ABI-H3733 Preclinical Profile: Oral Presentation**, Richard Colonno, SVP & CSO Virology Operations, ASMB
  – *Preclinical Profile of HBV Core Protein Inhibitor, ABI-H3733, a Potent Inhibitor of cccDNA Generation in HBV Infected Cells*

• **cccDNA Turnover Study: Poster Presentation**, Qi Huang, VP Virology Discovery, CSO Assembly China
  – *Rapid Turnover of HBV cccDNA in Nucleoside-Treated Chronic Hepatitis B Patients During Drug Resistance Emergence and Breakthrough*
ASMB HBV Core Inhibitor Program Portfolio

- Focused on identifying increasingly potent CIs while maintaining favorable drug-like properties
- Established pipeline of novel molecules with distinct chemical scaffolds

<table>
<thead>
<tr>
<th>Drug Candidate</th>
<th>Discovery &amp; Optimization</th>
<th>IND Enabling</th>
<th>Phase 1a</th>
<th>Phase 1b</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>NDA Filing</th>
<th>Worldwide Rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI-H0731</td>
<td>Fast Track Designation, “Best of AASLD ‘18” “Best of ILC ‘19”</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase 2a Studies EASL Oral LB-06</td>
<td></td>
</tr>
<tr>
<td>ABI-H2158</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase 1a Study EASL LB-12 Poster</td>
<td></td>
</tr>
<tr>
<td>ABI-H3733</td>
<td>Preclinical Profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EASL Oral PS-073</td>
<td></td>
</tr>
<tr>
<td>CI Discovery Program</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EASL Oral PS-073</td>
<td></td>
</tr>
</tbody>
</table>
Proof of Concept for CI combination therapy is two-fold:

1. **POC Antiviral Superiority** – Elimination of viremia via DNA and RNA declines
2. **POC Cure** – Declines in viral antigens and no relapse on therapy

EASL Overview

Richard Colonno, PhD – EVP & CSO Virology Operations
New Therapies are Needed to Increase Cure Rates in CHB

Nucleos(t)ide Pol Inhibitors (Nuc)
- Current “Standard of Care” for HBV
- Safe, well tolerated, with minimal resistance
- Reduce HBV DNA

But Fail to ……
- Eliminate virus
- Prevent new cccDNA formation
- Indefinite treatment

Cure is not possible without elimination of residual virus
Prolonged Nuc Therapy Fails to Eliminate Viral Replication

- PCR-detectable HBV DNA persists in 70-80% of patients despite TDF treatment for 5 years\(^1\)

- Detected DNA represents *infectious virus*!

  *EASL 2019 (PS-150) – “Evidence for the presence of infectious virus in the serum from chronic hepatitis B patients suppressed on nucleos(t)ide therapy with detectable but not quantifiable HBV DNA” Burdette et al.*

- Residual viremia refractory to elimination by Nuc therapy

- Likely accounts for poor cure rates

\(^1\)Marcellin, et al, AASLD 2014, Poster 1861
CIs Block Viral Replication and cccDNA Establishment

Core Protein Inhibitors (CIs)

- Inhibit multiple steps in viral replication cycle
- Achieve deeper levels of viral inhibition than Nucs alone

AND

- Can block the formation of cccDNA

Goal is to use combination therapy to increase cure rates with finite treatment duration
ABI-H0731: Interim Results from Ongoing Phase 2a Studies
HBV Core Inhibitor ABI-H0731

- Discovered and developed at ASMB
- Novel proprietary chemical class - DBAA (dibenzothiazepinecarboxamides)
- Well tolerated in Phase 1 studies
- Efficacious in a Phase 1b 28-day monotherapy study\(^1\)
  - HBeAg pos patients (300 mg QD) exhibited
    - Mean DNA reduction = \(2.9 \log_{10} \text{ IU/mL}\)
    - Mean RNA reduction = \(2.0 \log_{10} \text{ copies/mL}\)

Phase 2 program explores critical steps needed to achieve higher cure rates
1. Faster and deeper elimination of viremia
2. Prevention of new cccDNA generation
3. Decay of existing cccDNA and infected cells
4. Demonstrate viral suppression sustained off therapy

\(^{\text{1}}\)Yuen et al, AASLD 2018
Interim Review of ABI-H0731 Phase 2a Studies

**Study 201**
47 HBeAg+ / 26 HBeAg-
Patients on SOC Nuc therapy

- **3:2**
  - Nuc + 731 (300 mg)
  - Nuc + PBO

**Primary efficacy endpoints**
- Wk 24 Log$_{10}$ decline in HBsAg or HBeAg

**Study 202**
25 HBeAg+ Tx Naïve Viremic Patients

- **1:1**
  - ETV + 731 (300 mg)
  - ETV + PBO

**Primary efficacy endpoints**
- Wk 12 and 24 Log$_{10}$ decline in HBV DNA

**Study 211**
Nuc + 731
≤1 Yr Open Label Extension

---

**# Subjects**

<table>
<thead>
<tr>
<th>Study 201</th>
<th>Study 202</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>Wk 12</td>
</tr>
<tr>
<td>73</td>
<td>65</td>
</tr>
<tr>
<td>25</td>
<td>24</td>
</tr>
</tbody>
</table>

ETV: Entecavir; PBO: Placebo
Blinded, Pooled Safety Summary: Well Tolerated with Favorable Safety Profile

Summary of TEAEs (Studies 201 and 202)

- No SAEs or treatment related discontinuations or interruptions
- Adverse events were mostly mild, infrequent, and considered unrelated to study drug
- No Flares on treatment
- No clinical AE > grade 2
- 3 patients with rash considered “possibly related” (2x grade 1, 1x grade 2); none associated with systemic findings
- Only 1 patient in each study has had a grade 2 AE considered possibly related to study drug
  - Macular/maculopapular rash–resolved on antihistamine (Study 201)
  - ALT increase–resolved with continued treatment (Study 202)
Study 202
Interim Antiviral Efficacy

Highly Viremic Subjects
Study 202: Superior DNA Reductions with 731 Combination

**Mean Log_{10} HBV DNA Decline**

<table>
<thead>
<tr>
<th>Week</th>
<th>ETV</th>
<th>ETV + 731</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>3.29</td>
<td>4.54</td>
<td>&lt;.011</td>
</tr>
<tr>
<td>24</td>
<td>3.99</td>
<td>5.94</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

HBV DNA assessed by Roche Cobas qPCR; LOQ = 20 IU

- Significantly **faster** and **deeper** reductions in HBV DNA levels, as early as Week 2 (P=.03)
- Among subjects with abnormal ALT at entry, more rapid ALT normalization seen in combination arm
  - 5/7 vs. 0/5 by Week 4 (P <.05)
  - 7/7 vs. 2/5 by Week 12 (P <.05)
Study 202: Superior RNA Reductions with 731 Combination

**HBV RNA Declines**

<table>
<thead>
<tr>
<th>Week</th>
<th>ETV</th>
<th>731 + ETV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0.44</td>
<td>2.27</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>24</td>
<td>0.61</td>
<td>2.54</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

HBV RNA assessed by RT qPCR; LOQ = 200 copies/mL

- All patients on combination achieved a rapid decline in RNA levels
Study 201
Interim Antiviral Efficacy

HBV DNA “Nuc Suppressed” Subjects
Elimination of Residual Viremia is an Important Unmet Medical Need

- Nucs do not eliminate HBV viremia even after years on treatment\(^1\)
- Detected DNA represents “infectious virus”
  - ILC2019, PS-150: “Evidence for the presence of infectious virus in the serum from chronic hepatitis B patients suppressed on nucleos(t)ide therapy with detectable but not quantifiable HBV DNA”

- A highly sensitive semi-quantitative PCR assay was developed at ASMB to detect viral DNA levels to 2-5 IU/mL to monitor loss of residual virus

\(^1\) Marcellin, et al, AASLD 2014, P1861
Study 201: Elimination of Detectable Virus Only on Combination

At Week 24, longitudinal serum samples were assayed for detectable virus

### Nuc Monotherapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment Week</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuc</td>
<td>M</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>1 TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 TAF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 731 Combo Therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment Week</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuc</td>
<td>M</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HBV DNA PCR Assay To Quantitate Low Level Viremia**

- DNA purified from longitudinal serum samples (0 – 24 Wk)
- PCR amplification (40-45 cycles) using individually optimized primers

**Residual viremia is not eliminated by Nuc therapy**

**Elimination of detectable virus ONLY observed on combination**
HBeAg Positive Patients with RNA >LOQ at Baseline (N = 37)

- All subjects on combination arm achieved rapid RNA declines
- Of subjects with detectable baseline RNA, 60% of 731 combo subjects achieved RNA <LOQ (200 copies/mL) by Week 16 vs. 0% on Nuc arm

### Mean Log_{10} HBV RNA Decline

<table>
<thead>
<tr>
<th>Week</th>
<th>Nuc</th>
<th>731 + Nuc</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0.05</td>
<td>2.34</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>24</td>
<td>0.15</td>
<td>2.20</td>
<td>.012</td>
</tr>
</tbody>
</table>
Study 201: Antigen Declines at Interim Analysis

- Antigen declines anticipated to follow elimination of residual viremia
- Study subjects continue to be treated and followed in open label Study 211
- Safety, viremia and viral antigens continue to be monitored over time

<table>
<thead>
<tr>
<th>Patients Treated 24 Weeks*</th>
<th>Treatment</th>
<th>Nuc</th>
<th>731 + Nuc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DNA (TND&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>0/4 (0%)</td>
<td>5/6 (83%)</td>
</tr>
<tr>
<td></td>
<td>RNA (&lt;200 Copies/mL)</td>
<td>0/3 (0%)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3/6 (50%)</td>
</tr>
<tr>
<td></td>
<td>HBeAg ≥ 0.5 Log&lt;sub&gt;10&lt;/sub&gt; Decline</td>
<td>0/3 (0%)</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td></td>
<td>HBsAg ≥ 0.5 Log&lt;sub&gt;10&lt;/sub&gt; Decline</td>
<td>0/4 (0%)</td>
<td>0/6 (0%)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Target not detected by ASMB semi-quantitative PCR
<sup>2</sup> a 4<sup>th</sup> subject on Nuc was BLQ at baseline

*Subjects with available data
Summary of Interim Data for Phase 2a Studies on ABI-H0731

Favorable safety and tolerability profile
- AEs and lab abnormalities were generally considered unrelated, grade 1 and transient

Combination of 731+Nuc demonstrated superior antiviral activity vs. Nuc alone
- In treatment naïve patients, faster and deeper declines in HBV DNA observed starting at Week 2
- In Nuc “suppressed” patients, HBV DNA reductions to below limits of high-sensitivity PCR assay
- In both studies, significant HBV RNA declines

Elimination of residual viremia will likely be required to prevent new cccDNA formation and increase cure rates
- HBeAg and HBsAg decline are anticipated to follow elimination of viremia

Ongoing Studies to Define Timelines to cccDNA Loss, Sustained Suppression & Potential Cure

- Faster/Deeper Decline DNA & RNA (<BLQ)
- Elimination of DNA & RNA (TND)
- Decay of cccDNA
- Declines of HBeAg & HBsAg
Next Steps & Upcoming Milestones
EASL Highlights and Next Steps

- Nucs are effective, but do not eliminate residual HBV DNA and HBV RNA
- Combination of 731+ Nuc demonstrated potential to eliminate residual HBV DNA
- Core Inhibitors have the potential to be the backbone of future HBV regimens
  - We believe that elimination of residual viremia will likely be a critical milestone required to increase rates of cure
- 2158 currently in dose finding Phase 1b study and Phase 2a studies expected to follow immediately
- 3733 expected to initiate Phase 1a study in early 2020
- Initiating discussions with global regulatory bodies regarding design of next studies and pathways to approval for 731 + Nuc combination
Strong Trajectory in 2019: Upcoming Milestones

**HBV**

- **ABI-H0731**
  - Phase 2a (Viral antigen POC)
  - Study 201
  - Extension study

- **ABI-H2158**
  - Phase 1a
  - Phase 1b
  - Phase 2a

- **ABI-H3733**
  - IND enabling
  - Phase 1a

**KEY HBV MEETINGS**

**STRONG BALANCE SHEET:** ~$218M in cash (as of 12/31/2018)
Q&A
EASL Highlights and Next Steps

- Nucs are effective, but do not eliminate residual HBV DNA and HBV RNA
- Combination of 731+ Nuc demonstrated potential to eliminate residual HBV DNA
- Core Inhibitors have the potential to be the backbone of future HBV regimens
  - We believe that elimination of residual viremia will likely be a critical milestone required to increase rates of cure
- 2158 currently in dose finding Phase 1b study and Phase 2a studies expected to follow immediately
- 3733 expected to initiate Phase 1a study in early 2020
- Initiating discussions with global regulatory bodies regarding design of next studies and pathways to approval for 731 + Nuc combination
Thank You!
Appendix
ABI-H0731: Study 201 – Actual RNA Levels

Nuc

Nuc+731
ABI-H2158: Second Generation Core Protein Inhibitor

Phase 1a Safety, Tolerability and PK in 48 Healthy Volunteers

• No dose dependent TEAEs, pattern of clinical safety or laboratory abnormalities observed
• Exposures increased in a roughly dose-proportional fashion
• Steady-state concentrations achieved quickly in the MAD cohort, with accumulation of \( \approx 1.5 \)-fold at steady state
• No significant food effect observed

Trough liver concentrations are projected to exceed the \textit{in vitro} EC\(_{90}\) (334 nM) for inhibition of cccDNA establishment with QD dosing of 100 mg and higher

Phase 1b ongoing….
ABI-H3733: Relative Potency in Blocking cccDNA Generation

HBV Infection of HepG2-NTCP Cells

<table>
<thead>
<tr>
<th>Southern Blots</th>
<th>Control</th>
<th>1,000 nM ETV</th>
<th>41</th>
<th>123</th>
<th>370</th>
<th>1,111</th>
<th>3,333</th>
<th>10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsid Melting (Readout = rcDNA)</td>
<td>ABI-H3733</td>
<td><img src="image1" alt="image" /></td>
<td><img src="image2" alt="image" /></td>
<td><img src="image3" alt="image" /></td>
<td><img src="image4" alt="image" /></td>
<td><img src="image5" alt="image" /></td>
<td><img src="image6" alt="image" /></td>
<td><img src="image7" alt="image" /></td>
</tr>
<tr>
<td>ABI-H2158</td>
<td><img src="image8" alt="image" /></td>
<td><img src="image9" alt="image" /></td>
<td><img src="image10" alt="image" /></td>
<td><img src="image11" alt="image" /></td>
<td><img src="image12" alt="image" /></td>
<td><img src="image13" alt="image" /></td>
<td><img src="image14" alt="image" /></td>
<td><img src="image15" alt="image" /></td>
</tr>
<tr>
<td>ABI-H0731</td>
<td><img src="image16" alt="image" /></td>
<td><img src="image17" alt="image" /></td>
<td><img src="image18" alt="image" /></td>
<td><img src="image19" alt="image" /></td>
<td><img src="image20" alt="image" /></td>
<td><img src="image21" alt="image" /></td>
<td><img src="image22" alt="image" /></td>
<td><img src="image23" alt="image" /></td>
</tr>
</tbody>
</table>

| cccDNA Inhibition (Readout = cccDNA) | ABI-H3733 | ![image](image24) | ![image](image25) | ![image](image26) | ![image](image27) | ![image](image28) |
| ABI-H2158 | ![image](image29) | ![image](image30) | ![image](image31) | ![image](image32) | ![image](image33) |
| ABI-H0731 | ![image](image34) | ![image](image35) | ![image](image36) | ![image](image37) | ![image](image38) |

**EC$_{50}$ (nM)**
- ABI-H3733: 133
- ABI-H2158: 565
- ABI-H0731: 4,565

**Inhibition of cccDNA Establishment**

- 3733
- 2158
- 731

**Concentration (nM)**

**Percent of Control**

- 100
- 80
- 60
- 40
- 20
- 0

- 10
- 100
- 1000
- 10000
Summary Results From Expanded cccDNA Biosynthesis Study

- Genetic source of resistance shown to be cccDNA
- pgRNA closely reflects genetic composition of cccDNA pools
- Turnover of cccDNA from sensitive to resistant and from resistant to sensitive occurs in 12-16 weeks
- Suggests relatively rapid biologic turnover of both pgRNA and cccDNA pools and/or infected cells
- No evidence to support existence of inactive subpopulation of cccDNA, as genetic changes are observed in the entire population of cccDNA

Results indicate that existing cccDNA has a limited half-life, suggesting that therapies inhibiting establishment of new cccDNA may lead to higher cure rates for patients with HBV