VIR-3434, an investigational monoclonal antibody neutralizing Hepatitis B virus and facilitating FcγR-mediated elimination of HBsAg
– Preclinical Studies

Michael A. Schmid, PhD, Vir Biotechnology

The HBV Forum – Webinar on January 18th 2022
Forward-Looking Statements

Statements in this presentation that are not statements of historical fact are forward-looking statements. Such forward-looking statements include, without limitation, statements regarding the near-term financial performance of Vir Biotechnology, Inc. (the “Company”), the timing and expected number of therapeutic doses that the Company will be able to supply to patients, the expected success, cost, and timing of the Company’s research and clinical development plans and clinical trials, the Company’s goals with respect to the prophylaxis or treatment of COVID-19, HBV, influenza A and HIV, the Company’s objectives, strategy, technology platform and clinical trial designs, the potential benefits of the Company’s collaborations, and the Company’s ability to complete certain milestones. Words such as “believe,” “anticipate,” “plan,” “expect,” “intend,” “will,” “may,” “goal,” “potential” and similar expressions are intended to identify forward-looking statements, though not all forward-looking statements necessarily contain these identifying words. These forward-looking statements are based on the beliefs of the management of the Company as well as assumptions made by and information currently available to the Company. Such statements reflect the current views of the Company with respect to future events and are subject to known and unknown risks, including business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company, including, without limitation, risks inherent in developing the Company’s products and technologies, future results from the Company’s ongoing and planned clinical trials such as unexpected data or clinical site activation rates or clinical trial enrollment rates that are lower than expected, difficulties arising from the Company’s collaborations, challenges in accessing adequate manufacturing capacity, the Company’s ability to obtain adequate financing to fund its planned clinical trials and other expenses, statements related to regulatory authorizations and approvals, trends in the industry, changes in the competitive landscape, delays or disruptions due to the COVID-19 pandemic, including supply chain disruptions, the legal and regulatory framework for the industry, unexpected litigation or disputes and future expenditures. In light of these risks and uncertainties, the events or circumstances referred to in the forward-looking statements may not occur. The actual results may vary from the anticipated results and the variations may be material. Other factors that may cause the Company’s actual results to differ from current expectations are discussed in the Company’s filings with the U.S. Securities and Exchange Commission, including the section titled “Risk Factors” contained therein. These forward-looking statements should not be taken as forecasts or promises nor should they be taken as implying any indication, assurance or guarantee that the assumptions on which such forward-looking statements have been made are correct or exhaustive or, in the case of the assumptions, fully stated in this presentation. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date this presentation is given. Except as required by law, the Company undertakes no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise. The Company claims the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 for all forward-looking statements.

This presentation discusses product candidates that are under clinical study, and which have not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of these product candidates for the use for which such product candidates are being studied.

The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products.
Acknowledgements

at Vir Biotechnology & Humabs Biomed

Andreas Schulze, Stephan Urban at Molecular Virology, University Hospital Heidelberg & German Center for Infection Research, Heidelberg

Kosh Agarwal at Kings College Hospital, London, United Kingdom
Man-Fung Yuen at Queen Mary Hospital, University of Hong Kong
Heiner Wedemeyer at Hannover Medical School, Germany
Edward Gane at University of Auckland, Auckland, New Zealand
VIR-3434: an Fc-engineered human antibody against HBsAg with multiple potential mechanisms of action

1. Inhibition of viral entry (binding HBsAg antigenic loop, pan-genotypic neutralization)

2. Clearance of HBsAg and delivery to dendritic cells

3. Presentation to and stimulation of T cells (vaccinal effect)


Vaccinal Effect: VIR-3434, an Fc-engineered antibody as a potential therapeutic vaccine against HBV

Fc engineered (GAALIE) to increase binding to FcgRs IIA & IIIA (activating) and to decrease binding to FcgRIIB (inhibitory)

Durable HBV-specific immunity, potential functional cure


GAALIE mutation: Bournazos et al. 2020; CD, cluster of differentiation; DC, dendritic cell; FcR, fragment crystallizable receptor; Teff, effector T cell; WT, wild-type
Fc engineering & the vaccinal effect protect during cancer cell & influenza virus infection studies

7E3-GAALIE (anti-sLeA carbohydrate) reduced lung metastatic foci of B16 tumor cells compared to 7E3-WT

FY1-GAALIE (anti-HA stem mAb) induced a CD8+ T cell-mediated vaccinal effect and better protected huFcgR mice from infection with influenza virus

FcγR signaling inducing effector functions that could mediate HBsAg elimination and potentially lead to functional cure

GAALIE-Fc mutation & mAb:HBsAg ratios are crucial

VIR-3434 promotes FcγR-mediated association of HBsAg to immune cells in whole blood from HBV+ donors

Methods

- Whole blood from HBV+ donor (9,400 IU/mL HBsAg) with 50 µg/mL VIR-3434 for 2 hours at 37°C
- Flow cytometry: HBsAg stained with anti-HBs mAb that is not competing with VIR-3434

Additional Data & Conclusions

- GAALIE-Fc is essential to mediate HBsAg binding to immune cells
- HBsAg binding is in line with FcgRIIIa (CD16) expression
Vaccinal effect: VIR-3434 in complex with HBsAg activates moDCs and stimulates antigen-specific reporter CD4+ T cells.

HBsAg:mAb 50 µg/ml VIR-3434

IL4+GMCSF 6 days
Treat APOs with antigen

Coculture APC with transgenic TCR T cell line (HLA matched)

moDC activation marker CD83, similar for CD86 and cytokines in supernatant

TCR-transgenic Jurkat reporter cells as model for CD4+ T cells

Clinical data, phase 1: single dose of VIR-3434: preliminary HBsAg change from baseline

- Virally suppressed participants with **chronic HBV infection** and HBsAg < 3,000 IU/mL
- **Single doses** of 6, 18, or 75 mg of VIR-3434 were generally well tolerated; all AEs were grade 1-2
- Rapid decline in HBsAg $\geq 1 \log_{10}$ IU/mL within 7 days
- The largest ($> 2 \log_{10}$) reductions in HBsAg were observed for 75 mg
- Full analysis of VIR-3434 PK and HBsAg:VIR-3434 complex disposition is ongoing

Note: HBsAg measured with Abbott ARCHITECT®. 1, 2 Two participants in the 18 mg cohort had undetectable or lower-than-expected free PK and $< 0.5 \log_{10}$ IU/mL reductions in HBsAg

Conclusions

- VIR-3434 targets the conserved antigenic loop within HBsAg and mediates pan-genotypic neutralization of HBV in vitro.

- In vitro, Fc-engineered VIR-3434 bound and activated FcγRIIa and IIIa more efficiently compared to the mAb with wild-type Fc.

- VIR-3434 mediated the association of HBsAg to immune cells (neutrophils, monocytes, and NK cells) in whole blood of patients with CHB.

- VIR-3434 in complex with HBsAg activated moDCs more efficiently and induced CD4+ reporter T cell responses, in vitro. These results are a first step towards potential long-term immunity and functional cure via a vaccinal effect.

- In patients with CHB, a single low dose of 6, 18 or 75 mg of VIR-3434 resulted in rapid reductions in HBsAg within 1 week.