25 August 2021

Information Processing Unit, Area 6
Medicines and Healthcare products Regulatory Agency
10th Floor, 10 South Colonnade
Canary Wharf
London E14 4PU
UK

Re: **Initial Clinical Trial Application**

Study Drugs:	IMPs: • Selgantolimod (SLGN; GS-9688), • Opdivo® (Nivolumab) • VIR-2218 Non-IMPs: Vemlidy® (tenofovir alafenamide (TAF)) – authorised auxiliary medicinal product
Protocol number:	GS-US-465-4439
EudraCT number:	2021-000672-11
Protocol Title:	A Phase 2a, Open-Label Study to Evaluate the Safety and Efficacy of Selgantolimod (SLGN)-Containing Combination Therapies for the Treatment of Chronic Hepatitis B (CHB)

Gilead Submission No: 9688-21-14588
Gilead PO No: 200017076

Dear Sir/Madam,

Please find enclosed the necessary documentation supporting an initial Clinical Trial Application to the clinical trial detailed above, along with rationale and details presented below.

Study Rationale and Design

The proposed Phase 2 Study, GS-US-465-4439, is a multicenter, open-label study to evaluate the safety and efficacy of combination treatment with 2 immunomodulatory agents, a toll-like receptor 8 (TLR8) agonist, SLGN, and a programmed cell death protein

Gilead Sciences Ltd 280 High Holborn, WC1V 7EE, London, United Kingdom
Tel +44 (0)2036 814 500 | Fax +44 (0)2036 814 699

1 (PD-1) checkpoint inhibitor, nivolumab, with and/or without short interfering RNA (siRNA), VIR-2218, in both virally suppressed and viremic patients with chronic hepatitis B. The study will consist of 3 cohorts (Cohorts 1, 2, and 3).

Cohort 1 includes virally suppressed patients and the aim of the cohort is to evaluate the hypothesis that maximum viral and antigen reduction before immunomodulation therapy will improve HBV specific immune response to combination treatment.

Cohort 2 and 3 includes viremic CHB-infected patients and the aim of the viremic cohorts is to evaluate the hypothesis that immune modulation in the presence of active liver inflammation caused by HBV infection will improve HBV-specific immune response to treatment.

It is planned to conduct the trial at approximately 30 centers globally. Cohorts 1-3 will enroll approximately 120 male and nonpregnant female subjects, ages 18 to 65 years, inclusive, with CHB infection without presence of cirrhosis, and who are viremic or virally suppressed on NUC for at least 6 months.

Out of approximately 120 subjects mentioned above, approximately 40 NUC-suppressed and 80 viremic CHB-infected subjects, will be enrolled and assigned into a cohort described below. Each cohort will enroll an approximate (±10%) equal number of HBeAg-positive and HBeAg-negative subjects; and up to 20% of subjects can have HBsAg ≤ 100 IU/mL.

Cohort 1 (NUC-Suppressed Cohort): Subjects will receive CCI mg TAF tablet administered orally, CCI and CCI mg VIR-2218 administered CCI . CCI SLGN** mg (CCI mg tablets) CCI and CCI mg/kg nivolumab CCI .

Cohort 2: Subjects will be randomized 2:1 into Cohort 2 (Groups A and B) and stratified by HBsAg > or ≤ 3 log10 IU/mL.

Group A: Subjects will receive CCI mg VIR-2218 CCI CCI , SLGN** mg (CCI mg CCI and CCI mg/kg nivolumab CCI .

Group B: Subjects will receive SLGN** mg (CCI mg tablets) CCI and CCI mg/kg nivolumab CCI

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Cohort 3 will be initiated at the discretion of the sponsor after Cohort 2 has completed enrollment. Subjects will receive CCI mg VIR-2218 CCI SLGN mg (CCI mg tablets) CCI and CCI mg/kg nivolumab CCI .

At the end of treatment, all subjects will enter the FU (Follow-Up) period per protocol section 3.5.

Scientific Advice: Scientific advice has not been given for this study.

Paediatric Investigation Plan: This study is not part of a PIP.

Investigational Medicinal Products
There are four study drugs in this trial: Selgantolimod (SLGN; GS-9688), Nivolumab and VIR- 2218 are investigational medicinal products, tenofovir alafenamide (TAF) is an authorised auxiliary medicinal product.

Selgantolimod (SLGN; (GS-9688) is a Toll-like receptor 8 (TLR8) agonist). Selgantolimod has demonstrated in healthy volunteers and CHB patients' evidence of biological activity with dose dependent induction of IL-12p40 and IL-1RA and preliminary PK data shows a similar profile in patients compared to healthy volunteers in the first-in-human study, with minimal to no accumulation over time.

Nivolumab (Opdivo®, BMS), an anti-PD-1 immunoglobulin (Ig)G4 monoclonal antibody, is approved (FDA approval from December 2014, granted Marketing Authorization by EMA from July 2015) for the treatment of metastatic melanoma and is under development for other malignancies including lung cancer and hepatocellular carcinoma.

TAF (Vemlidy®) is a novel oral prodrug of tenofovir (TFV), a nucleotide analogue that inhibits HIV-1 reverse transcription. Patients randomized in Cohort 1 will be receiving TAF CCI mg orally. Vemlidy is approved for the treatment of HBV in the United States, the European Union, and other countries worldwide.

VIR-2218 is a novel synthetic ribonucleic acid interference (RNAi) therapeutic that is being developed for the treatment of chronic hepatitis B virus (HBV) infection. VIR-2218 is a short interfering RNA (siRNA) that targets a region of the HBV genome that is common to all HBV viral transcripts. VIR-2218 is pharmacologically active against HBV genotypes A through J. The use of siRNA offers a novel strategy for the treatment of chronic HBV infection.

Risk-Benefit Assessment: Based on available information, the benefit/risk balance for this study is considered positive. The reference safety assessment for this study is included in the Section 1.5 of the study protocol.

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Reference safety information (RSI): For the reference safety information of Selgantolimod please refer to section 8.1 of Investigator's Brochure for SLGN, Edition 5, dated 26 October 2020.

For the reference safety information of VIR-2218 please refer to Appendix 1 of Investigator's Brochure for VIR-2218, Edition 3, dated 17 February 2021.

There are two IMPDs included in this submission: IMPD for SLGN and VIR-2218 IMPD. Information on manufacturers can be found in a table 2.1.P.3-1 of each IMPD.

Since Vemlidy® (TAF) and Opdivo® have Marketing Authorizations in the European Union and ICH country, for information, please refer to Summaries of Product Characteristics (SmPC). For this study, Opdivo® is being used as investigational product while Vemlidy® is being used as an auxiliary medicinal product. Vemlidy® is being dosed according to the approved product marketed labels. Opdivo® is being dosed as described in section 1.4.2. Rationale for Dose Selection of Nivolumab of the study protocol.

Gilead also confirms that the study is being supplied by centrally distributed Vemlidy and Opdivo marketed products. These marketed products are similar to country's locally available commercial product.

DSMB/Data and Safety monitoring: This is an open-label study, has a small study population (n=20-60 per cohort), and evaluates investigational agents which have demonstrated safety in prior studies. Study is designed to closely and routinely monitor each patient for adverse events AEs (including serious adverse events [SAEs], serious adverse drug reactions [SADRs], suspected unexpected serious adverse reactions [SUSARs]), laboratory abnormalities, ophthalmologic examinations, and vital sign changes. Specific parameters are included in the protocol to allow for dose modification, interruption, and early discontinuation of patients. Dose modification and discontinuation criteria for subjects with ALT elevations or flare by treatment and cohort are assessed according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities. Increased virtual or in-clinic visits can be established based on the investigator's discretion to further monitor patient safety. Stopping rules are also provided in the protocol to allow for cohort/study discontinuation. The sponsor and assigned medical monitor will review safety data from all patients throughout the study and during follow-up to identify potential safety signals. Should significant findings be identified during ongoing safety monitoring that may impact an Investigator's treatment decisions or toxicity management of patients, information will be provided to investigators through formal communication (e.g. letter, email). All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug.

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Good Laboratory Practice (GLP): Where applicable, studies have been conducted in accordance with Good Laboratory Practice (GLP) requirements and standards. Study details are provided in Appendix 8.2 of Investigator Brochure for SLGN and Appendix 2 of Investigator Brochure for VIR-2218.

In support of this application, please find below a tabulated list of documentation below.

Submission components:

General information	Version/Date
Cover Letter	25 August 2021
MHRA Application Form (IRAS) PDF	25 August 2021
MHRA Application Form (IRAS) XML	25 August 2021
EudraCT number confirmation email	08 February 2021
UK Legal Representation Declaration	21 October 2020
UK Local Applicant letter	21 October 2020
List of NCAs to which the application has been submitted and details of decision	N/A
Outline of all active trials with the same IMPs	June 2021
Study Protocol-related	
Protocol GS-US-465-4439	Original, 04 March 2021
IMP-related	
GS-9688 (Selgantolimod) Tablets IMPD	Version 2.3, July 2021
VIR-2218 (ALN-HBV-02) IMPD	Version 1.0, June 2021
Nivolumab (Opdivo) sIMPD	Version 1.0, June 2021
TAF (Vemlidy) sIMPD	Version 3.1, June 2021
TSE statement for Selgantolimod	15 June 2021
TSE statement for Vemlidy	15 June 2021
TSE statement for VIR-2218	15 June 2021
Local approved product label for Opdivo®	26 July 2021
Local approved product label for Vemlidy®	01 January 2021
IMP label for Selgantolimod	01 February 2021
IMP label for VIR-2218 (Vial)	12 March 2021
IMP label for VIR-2218 (Carton)	05 March 2021
IMP label for Nivolumab (Vial)	10 March 2021
IMP label for Nivolumab (Carton)	05 March 2021
IMP label for Tenofovir	19 February 2021
Investigator's Brochure for Selgantolimod	Edition 5, 26 October 2020
Investigator's Brochure for VIR-2218	Edition 3, 17 February 2021
QP Declaration for Selgantolimod	17 June 2021
QP Declaration for Nivolumab	17 June 2021
QP Declaration for Vemlidy	17 June 2021
QP Declaration for VIR-2218	06 September 2021
MA-IMP [redacted]	25 May 2021

Gilead Sciences Ltd 280 High Holborn, WC1V 7EE, London, United Kingdom
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MA-IMP CCI [redacted]	05 March 2021

I trust this is in order, please do not hesitate to contact me should you have any questions.

Yours faithfully,

PPD

PPD
Manager, Regulatory Affairs Associate (UK & Ireland) – Gilead Sciences Ltd
Telephone: PPD
Email: PPD

Gilead Sciences Ltd 280 High Holborn, WC1V 7EE, London, United Kingdom
Tel +44 (0)2036 814 500 | Fax +44 (0)2036 814 699