A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (Trial H2: VIR-7831 (GSK4182136))

Version 1.0
20 November 2020

NCT05780281

Appendix H2: VIR-7831 (GSK4182136) – version 1.0 (20 November 2020)

The content of this appendix is confidential and should only be viewed by persons covered by the CDA entered between GSK-Vir and NIAID in relation to the ACTIV-3 study.

This appendix provides detailed information pertaining to the study of this investigational agent. If not stated otherwise, the text in the master protocol gives the approach that will be taken to study this agent.

H.2.1. Introduction and rationale for studying the agent

VIR-7831 is a fully human neutralizing immunoglobulin G (IgG)-1 kappa monoclonal antibody (mAb) derived from antibody S309 (1) from a survivor of SARS-CoV-1. Vir-7831 targets a highly conserved epitope on the spike protein of SARS-CoV-1 and SARS-CoV-2, and potently neutralizes SARS-CoV-2 in live virus assays, preventing subsequent viral entry into human cells and viral replication. VIR-7831 also contains a 2 amino acid Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life. VIR-7831 is expected to decrease viral replication, mitigating the severity of disease in patients in whom ongoing viral replication is an important driver of COVID-19 pathophysiology.

Whereas one antiviral agent (remdesivir) has been demonstrated to have clinical benefit in the target population for this trial and is now part of standard-of-care (see Appendix I), it is plausible that additional antiviral effects from VIR-7831 in combination with remdesivir may provide additive, if not synergistic, antiviral effects and hence contribute to improvement in time to sustained recovery.

VIR-7831 is being developed for treatment of COVID-19, by Vir Biotechnology, Inc. (Vir) and GlaxoSmithKline (GSK). Vir is a company that discovers and makes medicines. GSK is a global healthcare company that discovers and makes vaccines, medicines, and other health products. In April 2020, GSK and Vir entered into a collaboration to develop, register and commercialize VIR-7831. Under the terms of the collaboration Vir will be the sponsor of the clinical studies. GSK will, however, be the applicant and subsequent marketing authorization holder in all countries where a marketing authorization is sought including the USA.

GSK-VIR is conducting a randomized, double-blind, multi-center, placebo-controlled trial of VIR-7831 (Study VIR-7831-5001)(IND 149315) (2), which aims to demonstrate the prevention of progression of mild/moderate COVID-19 to severe/critical disease in adult participants without need for hospitalization for acute care at time of enrolment. Participants with early, mild/moderate COVID-19 who are at high risk for progression of their COVID-19 disease will be randomized 1:1 to receive a single, intravenous infusion of either VIR-7831 or placebo. The Lead-In phase of study VIR-7831-5001 will serve as the first-in-human assessment and will include 20 non-hospitalized participants who have early, mild/moderate COVID-19 and are at high risk of disease progression. These participants will be given a single intravenous infusion of VIR-7831 (500 mg) and confined for 7 days for safety

monitoring. Following a safety assessment of unblinded data through 14 days (Day 15) of follow-up by the study independent data monitoring committee (IDMC; comparable with the DSMB for the TICO master protocol), the expansion phase of Study VIR-7831-5001 will progress, where additional participants with early, mild/moderate COVID-19 who are at high risk of disease progression will be enrolled.

Relevant blinded data from the first 21 participants in the trial referred to above (VIR-7831-5001) is summarized below (section H2.1.1) and included in the ACTIV-3 informed consent relating to the investigation of VIR-7831 in ACTIV-3.

H2.1.1 *Potential risk and benefits from VIR-7831*

VIR-7831 targets a highly conserved protein/glycan epitope on the SARS-CoV-2 SB domain, distinct from the receptor-binding motif. VIR-7831 has been demonstrated in vitro to be a highly potent fully human IgG neutralizing SARS-CoV-2 antibody which has the potential to be an effective therapeutic in severe to critically ill patients with COVID-19 (1).

The anticipated safety risk is considered low, based on the known mechanism of action for human derived neutralizing antibodies in acute viral disease states. VIR-7831 is a highly specific mAb directed at foreign (non-human) epitope(s). The complementarity determining regions (CDRs) of VIR-7831 are identical - except for one amino acid substitution (N55Q) introduced to aid antibody developability - to the parent mAb (S309) derived from B lymphocytes of a naturally convalescent SARS-CoV-1-infected patient. The Fc domain of VIR-7831 also contains a two amino acid modification (LS) in order to increase lung tissue bioavailability (3) and extend half-life (4). Hence, VIR-7831 has undergone natural positive and negative selection pressures in vivo, unlike humanized antibodies generated in mice. Therefore, off-target binding and tissue cross-reactivity are considered unlikely, which is further supported by the absence of binding to membranes of human tissue in a tissue cross-reactivity study. In addition, there were no VIR-7831-related safety findings identified in a GLP cynomolgus monkey 2-week repeat-dose IV infusion toxicology study up to 500 mg/kg, the no-observed-adverse-effect-level (NOAEL) and highest dose tested. The study is currently in the 105-day (approximately 5 half-lives) recovery phase (IB Section 4.3, (5)).

Potential risks associated with the infusion of an IgG1 mAb directed toward a microbial pathogen are primarily infusion-related immediate and non-immediate hypersensitivity reactions. *In vitro* studies in which cells (moDC, PBMC and U937) infected with SAR-CoV-2 were exposed to VIR-7831, did not reveal release of cytokines or chemokines (IB Section 4.1.2, (5)). Signs and symptoms of infusion-related immediate hypersensitivity reactions may include, but are not limited to: anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticaria, tachycardia, and throat irritation or chest tightness.

The VIR-7831-5001 IDMC has reviewed unblinded data through Day 15 of follow-up from the Lead-In cohort of 21 participants and no serious adverse events or significant safety signals emerged to effect the risk:benefit profile of VIR-7831. A review of blinded data by the protocol team demonstrated that participants experienced only mild adverse events of

grade 1 and maximally grade 2 (using the DAIDS adverse event scale), and this included dehydration and feeling cold.

There is a theoretical risk that VIR-7831 may cause antibody-dependent enhancement (ADE) of viral replication or disease. Antibody-dependent enhancement (ADE) of disease theoretically can occur via one of three previously described mechanisms:

1. By facilitating viral entry into host cells and enhancing viral replication in these cells;
2. By increasing viral fusion with target host cells, enhancing viral replication in these cells.
3. By enhancing disease pathology from viral antigen-antibody related immune complex deposition or complement activation and immune cell recruitment in target organs;

The first two mechanisms are hypothesized to occur at sub-neutralizing antibody concentrations (6) and have been observed with some monoclonal antibody therapies used in other unrelated viral diseases such as Dengue and Zika virus infections. Unlike ADE associated with Dengue and Zika virus infections, this phenomenon has not been clearly established for coronavirus infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and has not been reported to date with SARS-CoV-2. This study will include participant follow-up for 18 months to assess for the potential of enhanced disease in the context of waning VIR-7831 levels, which may manifest as an increased incidence of re-infection or increased severity of re-infections after recovery from initial illness. The third mechanism is hypothesized to occur at high levels of antigen (i.e., viral load) and antibody potentially leading to immune complex deposition and complement activation or FcγR activation in tissue sites of high viral replication. This may manifest as acute deterioration temporally associated with VIR-7831 infusion or as increased severity or duration of illness in VIR-7831-treated participants vs. placebo-treated participants. Limited experience with the use of convalescent serum as a treatment for patients with severe COVID-19 has not indicated safety concerns related to this type of ADE (7). VIR-7831 will be administered to patients at sufficiently high dose levels to neutralize SARS-CoV-2 and avoid sub-neutralizing concentrations in the presence of virus that are typically associated with ADE. Furthermore, no evidence of ADE of infection was observed at sub-neutralizing concentrations of VIR-7831 in several *in vitro* assays. Specifically, there was no increase in internalization of SARS-CoV-2 and no increased replication of SARS-CoV-2 in VeroE6 control cells, monocyte-derived dendritic cells, peripheral blood mononuclear cells, or the monocytic cell line U937 in the presence of VIR-7831 (IB Section 4.1.2, (5)). If ADE occurs, it will likely manifest clinically as an imbalance in the severity or duration of illness in the VIR-7831 arm compared with the placebo arm.

A Vir-mAb targeting Influenza A (VIR-2482) with the same LS modification as 7831 has been trialled in healthy volunteers. Injection site reactions (erythema, pain, swelling and bruising) were uncommon, all were mild and generally resolved within 48 hours. There were no treatment-related discontinuations and no SAEs (unpublished data) (8).

Another NIH/NIAID mAb (VRC01LS) with the LS modification targeting HIV is in development and was administered to 70 healthy volunteers in a phase 1 study (9). There were no SAEs in this study. Post administration symptoms were mild or moderate for both objective local and systemic reactions. Six AEs were assessed as possibly related to VRC01LS administration and all were mild in severity. Two reports of diarrhoea, one in

group 1 (5 mg/kg IV) and one in group 5 (5 mg/kg subcut), occurred on the day of VRC01LS administration and resolved the same day. One group 2 volunteer experienced light-headedness on the day following administration, and symptoms resolved within 24 hours. One AE in group 5 pertained to an injection site reaction with hyperpigmentation that resolved 14 days post administration. Two AEs in group 5 were due to elevated alanine aminotransferase levels (56 and 69 IU/L) on day 14 post injection and both resolved within 15 days after onset.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of VIR-7831 may be found in the Investigator's Brochure (14) and Participant Information Leaflet.

Given the safety profile of VIR 7831 in the nonclinical studies and the well-established safety profile of human-derived monoclonal antibodies with similar Fc modifications, and the limited disease directed therapeutic options for patients with COVID-19 illness, the overall benefit-risk assessment of this study is considered favorable.

H2.1.2 *Motivation for agent selection by the ACTIV Trial Oversight Committee (TOC)*
The ACTIV-2/3 Agent Selection Committee (ASC) reviewed the GSK-Vir SARS-CoV-2 neutralizing antibody voted in favor of the agent proceeding into ACTIV-3, and the TOC endorsed that recommendation. GSK-Vir's Vir-7831 antibody was supported because GSK-Vir presented strong preclinical data for viral neutralization, including studies on the chance of viral resistance and how to counter act that issue. Live virus neutralization using the parent antibody Vir-7831 against SARS-CoV-2 strain USA-WA1/2020 yielded a mean IC_{50} of 79 ng/mL (Diamond Laboratory). VIR-7831 was found to neutralize USA-WA1/2020 with a mean IC_{50} and IC_{90} of 100 ng/ml and 186 ng/ml, respectively (VIR Biotechnology). VIR-7831 binds to recombinant SARS-CoV-2-RBD protein with an equilibrium constant (KD) of 0.21 nM as determined by Surface Plasmon Resonance. Passaging of SARS-CoV-2 for >1 month in the presence of fixed concentrations of antibody demonstrated no emergence of viral escape mutants even at the minimum antibody concentration tested (10x IC_{50}), indicating the potential for this antibody to have a high barrier to resistance.

GSK-Vir also provided a strong rationale for their choice of dosing for their agent which was strongly supported by their preclinical dose finding studies. The ASC also noted that the proposed LS mutation clearly increases the plasma half-life of mAbs, data to support an effect of the LS mutation on tissue distribution (and specifically lung distribution) of infused mAbs are more nascent. In addition, GSK-Vir was the first company to perform *in vitro* testing of their candidate mAb with remdesivir, giving consideration to their desired entry to ACTIV-3 inpatient study and the expectation that remdesivir will be the standard of care for in-patient study participants. Finally, the ASC found the manufacturing and scalability strategy for GSK-Vir sufficient for the full trial and beyond.

GSK/Vir statement regarding plans for licensure: GSK is a global pharmaceutical company and attempts to bring important medical breakthroughs to as many patients in as many countries as possible. It would therefore be their general intent to pursue licensure in countries where the trial is being conducted. In the case of the COVID-19 pandemic, the actual decision to pursue licensure will be impacted by other factors which may include:

status of the COVID-19 pandemic in the country and medical need, availability of other therapies including vaccines, available drug supply and other supply feasibility issues, and other regulatory considerations.

H2.1.3 Justification for dose chosen for VIR-7831

A single dose of 500 mg was selected for the study based on in vitro neutralization data, in vitro resistance data, expected human PK extrapolated from a study in cynomolgus monkeys, and the results of the GLP monkey toxicology study.

VIR-7831 neutralized SARS-CoV-2 live virus with an average EC_{90} value of 186.3 ng/mL (range: 125.8 – 329.5 ng/mL) (IB Section 4.1.1.2, (5)). In resistance analyses, no viral breakthrough was observed through 10 passages at fixed concentrations of antibody even at the lowest dose tested (~10x EC_{50}), indicating the potential for VIR-7831 to have a high barrier to resistance (IB Section 4.1.1.4, (5)).

Using an increasing concentration selection method to force resistance emergence, modest fold changes in EC_{50} were observed during viral selection (5-to 6-fold change in EC_{50}) for some passages (IB Section 4.1.1.4, (5)). Sequencing and testing of spike variants from these passages using a pseudotyped virus system did not identify causal variants for this modest shift in potency. One passage of virus did demonstrate a >10-fold shift in EC_{50} which correlated with an E340A mutation. Further assessment has identified E340A to be a monoclonal antibody-resistant mutant (MARM) that confers a >100-fold reduction in susceptibility to VIR-7831. Notably, E340 is 100% conserved among available SARS-CoV-2 sequences (IB Section 1.3.2, (5)). Due to the binary nature of the resistance selection results, a specific inhibitory quotient (IQ) was not informed by the resistance profiling. However, as our understanding of the biology of SARS-CoV-2 is currently still limited and very few strains are available to directly assess breadth of coverage, a conservative IQ (>10) is appropriate in this case.

The cynomolgus monkey PK study (single IV dose, 5 mg/kg, IB section 4.2, (14)) was fit to a 2 compartment PK model. Human PK parameters were scaled from the cynomolgus monkey using an allometric scaling approach for fully human IgGs (allometric coefficient of 0.85 and 1 for CL and V, respectively; 10). The predicted serum clearance of VIR-7831 in humans is estimated to be 141 mL/day and estimated volume of distribution is 6500 mL (~93 mL/kg) assuming human weight of 70 kg. The projected human terminal elimination half-life is approximately 32 days.

In order to reduce risk to patients (treatment failure, emergence of viral resistance), a single therapeutic dose was selected that ensures VIR-7831 concentrations in the lung are maintained far above levels anticipated to be protective for SARS-CoV-2 infection for the duration of the 28-day treatment window and beyond. A dose of 500 mg is expected to maintain serum levels at or above 38.5 µg/mL for the duration of the 28-day treatment period. Based on a conservative EC_{90} (0.33 µg/mL) from the highest end of the EC_{90} range (IB Section 4.2.7, (5)), and accounting for the lung:serum ratio for IgG (assumed conservative value of 0.25; reported range 0.25-0.68 for whole lung and interstitial fluid, respectively; (11-14)) the serum trough concentration following a 500 mg dose is expected to result in lung concentrations associated with maximal (> 99%) antiviral activity; > 29 x tissue-adjusted EC_{90} for the duration of the 28 day treatment period. This conservative inhibitory quotient (29-fold) in lung is believed to be appropriate to increase potential for treatment success and reduce risk for resistance.

Additionally, a 500 mg dose is anticipated to result in protective levels of VIR-7831 in nasopharyngeal secretions (>5 x tissue adjusted EC_{90} assuming NPS:serum ratio of 0.05, 12) which could potentially reduce transmission.

The NOAEL for VIR-7831 was 500 mg/kg, the highest dose tested, when VIR-7831 was administered via IV infusion once a week for 2 weeks in cynomolgus monkeys (IB Section 4.3, (5)). At this NOAEL, preliminary C_{max} and area-under-the-curve $(AUC)_{0\text{-}t}$ (AUC from time 0 to 168hr post-end of infusion following the 2nd dose) were 13500 µg/mL and 48200 µg•day/mL, respectively. The human equivalent dose (HED) (HED calculated via direct mg/kg conversion according to FDA guidance on proteins administered intravascularly with Mr > 100,000 daltons; (15)) is 500 mg/kg or a 30,000 mg fixed dose (using human body weight of 60 kg). Using a safety factor of 10, the maximum recommended starting dose in humans is approximately 50 mg/kg or a 3,000 mg fixed dose. Based on the proposed 500 mg human dose, the margins based on the HED, C_{max}, and AUC (conservative AUC margin based on partial $AUC_{0\text{-}t}$ from TX-7831-0102 and expected AUC_{inf} in humans) are 60-, 87-, and 13.6-fold, respectively, supporting the proposed clinical dose of 500 mg.

H2.2. Agent specific eligibility criteria

In addition to the inclusion and exclusion criteria outlined in the master protocol, the following patients will be excluded: 1) pregnant women; and 2) nursing mothers. In addition, prior to the initial futility assessment which is performed when approximately 150 participants have been enrolled on VIR-7831 and 150 on placebo, patients on high-flow oxygen or non-invasive ventilation (category 5 of the pulmonary ordinal outcome) will be excluded. These patients may be eligible for the trial if the initial futility assessment is passed by this agent.

H2.3. Description of investigational agent

H2.3.1. Administration and duration

A single infusion will be administered over a one-hour period. Please refer to the pharmacy procedures for details about the infusion rate. Study participants will be monitored closely, and, per discretion of the physician supervising the infusion, adjustments in the infusion rate will be made and/or the infusion paused or stopped. Physician supervising the infusion may use supportive measures per local practice, if indicated.

See the PIM and Pharmacy Procedures for further details. See also section H2.5 below for guidance on the clinical management of the infusion, including infusion-related reactions.

H2.3.2. Formulation and preparation

VIR-7831 is provided in vials of 10 ml solution containing 250 mg antibody each. VIR-7831 must be stored between 2ºC and 8ºC.

A total of 2 vials are required for dosing of the agent at 500 mg (see Table H2.1). The agent will be administered at a concentration of 1 mg/ml to 10 mg/ml. Placebo is normal

saline from local supply. Detailed instructions for preparing the infusion bag for the investigational agent and matching placebo are described in the pharmacy procedures for this agent.

The master protocol and general procedures described in the PIM for preparing the infusion bag by the unblinded pharmacist will be followed.

Table H2.1. Study medication overview.

Intervention Name	**Placebo**	**VIR-7831**
Dose Formulation	Sterile 0.9% (w/v) sodium chloride solution	Solution in single-use vial (250 mg/ 10 mL)
Dosage Level (mg)	Not applicable	500 mg
Dose Volume (mL)	Refer to pharmacy manual	Refer to pharmacy manual
Route of administration	IV infusion	IV infusion
Use	Placebo	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Saline for placebo will be provided locally by the site.	VIR-7831 will be provided centrally by the Sponsor.
Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study intervention will be provided in single-use vials, individually packaged in a carton, and labelled appropriately
Current/Former Name(s) or Alias(es)	Not applicable	VIR-7831, GSK4182136

H2.3.3 Supply, distribution, and accountability
Procedures for ordering and accepting drug, for maintaining inventory of VIR-7831, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

H2.3.4. Contraindicated medications
No medication is known to be contraindicated in patients receiving the investigational agent. Whenever a concomitant medication or the study agent is initiated or a dose changed, investigators must review the concomitant medication's prescribing information and the relevant protocol appendix/appendices, as well as the most recent package insert, Investigator's Brochure, or updated information from DCR, NIAID to obtain the most current information on drug interactions, contraindications, and precautions.

H2.3.5. Precautionary medications
The clinical site should have necessary equipment and medications for the management of any infusion reaction (see section H2.5 below).

Premedication for infusions is not planned.

If an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from premedication, the study investigator(s) should determine the appropriate premedication.

The investigators and sponsor may decide to recommend premedication, if the frequency of infusion reactions among participants warrants it. If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants. The decision to implement premedication for infusions in subsequent participants will be made by the investigator and sponsor and recorded in the study documentation. Any pre-medications given will be documented as a concomitant therapy.

H2.4. Clinical and laboratory evaluations

H2.4.1 Timing of Assessments

Appendix B outlines the clinical and laboratory monitoring of the master protocol. Assessment and reporting of AEs (section 10.1.1), SAEs (section 10.1.2) and unanticipated problems (section 10.1.3) and their severity, causality (section 10.1.5) and expectedness (section 10.1.6) is performed as outlined in the relevant section of the master protocol.

H2.4.2 Immunogenicity Assessments

At the visits specified in the master protocol (Days 0, 28, and 90) venous blood samples will be collected to determine antibody production against VIR-7831. Immunogenicity may be assessed by a validated assay designed to detect ADAs in the presence of VIR-7831. Antibodies may be further characterized for their ability to neutralize the activity of VIR-7831. Remaining volume from the PK sample may also be used for immunogenicity assessments as needed.

H2.4.3. Pharmacokinetic Assessments

At the visits specified in the master protocol (Days 0, 1, 5, 28, and 90) venous blood samples will be collected to determine VIR-7831 serum concentration for pharmacokinetic assessment. The PK/Immunogenicity assessment will require 2 mL of the serum collected, as described in the Master Protocol Appendix B as “Research Sample Storage”. PK samples may be assessed by a validated assay at a bioanalytical lab. The PK assessment will use the same 2 ml serum specified for the Immunogenicity assessment (see section H2.4.2). Analysis of samples from placebo-treated subjects is not planned. Remaining sample used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate. Samples maybe shipped to the lab for analyses in batches as the substudy is unfolding. Results from such analyses will be returned to the trial central database. This data and all other data on the participants will remain in the trial central database until the trial is unblinded.

H2.5. Clinical management issues

All participants should be monitored closely for 2 hours after the infusion, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

H2.5.1. Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction, include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

H2.5.2. Site Needs

The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion reaction, which may include, but is not limited to, oxygen, IV fluid, epinephrine (/adrenaline), acetaminophen (/paracetamol) and antihistamine.

Pharmacy procedures in the PIM outlines needs of the study site pharmacy and/or local site pharmacy.

H2.5.3. Management of Infusion Reactions including Discontinuation

If the participant experiences an infusion reaction, then supportive care should be used in accordance with the signs and symptoms. If a severe and potentially life-threatening infusion reaction occurs with VIR-7831/placebo, its use should be permanently discontinued.

If a participant is not infused with VIR-7831/placebo or the complete infusion is not given, all follow-up procedures and reporting's outlined in the master protocol (Appendix B for overview), should be adhered to as indicated.

H2.5.4. Adverse Events of Special Interest (AESI)

The following are AESIs for the agent VIR-7831 or placebo for VIR-7831:

- Infusion-related reactions
- Allergic/hypersensitivity reactions

H2.6. References

1. Pinto et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature 2020;583(7815):290-295
2. https://clinicaltrials.gov/ct2/show/NCT04545060
3. Hope. Multiscale imaging of therapeutic antibody distribution and localisation. Presented at 2019 HIV & HBV Cure Forum; Jul 20-21; Mexico City, Mexico,
4. Ko et al. Enhanced Fc receptor function improves protection against primate SHIV infection. Nature 2014;514(7524):642-5.
5. VIR-7831 Investigator's Brochure, Edition 1, 28 July 2020.

6. Arvin AM, Fink K, Schmid MA, Cathcart A, Spreadfico R, Havenar-Daughton C, Lanzavecchia A, Corti D, Virgin HW. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature. https://doi.org/10.1038/s41586-020-2538-8 (2020).

7. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020;117(17):9490-6.

8. https://clinicaltrials.gov/ct2/show/NCT04033406?term=VIR-2482&draw=2&rank=1 (VIR-2482 against influenza)

9. Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: A Phase 1 open-label clinical trial in healthy adults. Gaudinski M et al. Plos Medicine; 2018 https://doi.org/10.1371/journal.pmed.1002493

10. Deng R, Iyer S, Theil FP, Mortensen DL, Fielder PJ, Prabhu S. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned? MAbs. 2011 Jan-Feb;3(1):61-6. doi: 10.4161/mabs.3.1.13799. Epub 2011 Jan 1. PMID: 20962582; PMCID: PMC3038012.

11. Baxter LT, Zhu H, Mackensen DG, Jain RK. Physiologically based pharmacokinetic model for specific and nonspecific monoclonal antibodies and fragments in normal tissues and human tumour xenografts in nude mice. Cancer Res. 1994 Mar 15; 54(6): 1517–1528.

12. Covell DG, Barbet J, Holton OD, Black CD, Parker RJ, Weinstein JN. Pharmacokinetics of monoclonal immunoglobulin G1, F(ab')2, and Fab' in mice. Cancer Res.1986 Aug;46(8):3969-78.

13. Datta-Mannan A. Mechanisms Influencing the Pharmacokinetics and Disposition of Monoclonal Antibodies and Peptides. Drug Metab Dispos. 2019 Oct;47(10):1100-1110.

14. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci. 2004 Nov;93(11):2645-68.

15. Lim JJ, Derby MA, Zhang Y, Deng R, Larouche R, Anderson M, Maia M, Carrier S, Pelletier I, Girard J, Kulkarni P, Newton E, Tavel JA. A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose Study To Investigate the Safety, Tolerability, and Pharmacokinetics of an Anti-Influenza B Virus Monoclonal Antibody, MHAB5553A, in Healthy Volunteers. Antimicrob Agents Chemother. 2017 Jul 25;61(8):e00279-17. doi: 10.1128/AAC.00279-17. PMID: 28559255; PMCID: PMC5527589.