A PHASE 2A SINGLE-ARM, PROSPECTIVE, OPEN-LABEL PILOT STUDY TO EVALUATE THE SAFETY AND EFFICACY OF DUAL COSTIMULATION BLOCKADE WITH VIB4920 AND BELATACEPT FOR PROPHYLAXIS OF ALLOGRAFT REJECTION IN ADULTS RECEIVING A KIDNEY TRANSPLANT

Sponsor Protocol Number: VIB4920.P2.S1

Application Number: IND 141544

Investigational Product: VIB4920

Sponsor: Viela Bio, Inc.

Medical Monitor: PPD

Contract Research Organization: CTI Clinical Trial & Consulting Services

Protocol Version number: Final Protocol v4.0

Date: 23 Jul 2021

Protocol History: Protocol v1.0; Amendment 1, v2.0, Amendment 2 v3.0

Summary of Changes

Protocol Number: VIB4920.P2.S1
Application Number: IND 141544
Investigational Product: VIB4920
Protocol Version Number: Final Protocol v4.0
Protocol Version History: Protocol v1.0; Amendment 1, v2.0; Amendment 2, v3.0

Section, Page	Protocol v3.0 Text	Modified Text	Rationale for Change
Synopsis, Methodology, Page 11	Subjects who are unwilling to comply with study schedule after early discontinuation of treatment should undergo End-of-Treatment/End-of-Study visit at time of discontinuation and undergo complete safety follow up at 4, 8, and 12-weeks after end treatment visit.	Subjects who are unwilling to comply with study schedule after early discontinuation of treatment should undergo End-of-Treatment/End-of-Study visit at time of discontinuation and undergo complete safety follow up at 4, 8, and 12-weeks after End-of-Treatment visit.	Correct error in previous protocol terminology.
Section 7.1, Overall Study Design, Page 32	The study will be conducted at two centers in the United States in a total of approximately 20 patients meeting all inclusion and exclusion criteria.	The study will be conducted at approximately four centers in the United States in a total of approximately 20 patients meeting all inclusion and exclusion criteria.	Update to reflect current number of sites expected to participate.
Table 2, Schedule of Assessments – Screening Period, Footnote o, Page 37	Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study.	Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study. Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia- related medications, electrolytes and intravenous fluids, do not need to be collected. Any transplant related medications, such as immunosuppressive drugs, administered during this period should be collected.	Clarify the concomitant medications that are to be collected and excluding perioperative, standard of care medications.

Section, Page	Protocol v3.0 Text	Modified Text	Rationale for Change
Table 3, Schedule of Assessments – Treatment Period (Day 0 to Week 24), Footnote t, Page 39	CCI , frozen, CCI , when feasible, with CCI	CCI , frozen, CCI with CCI	CCI will only occur in CCI
Table 3, Schedule of Assessments – Treatment Period (Day 0 to Week 24), Footnote v, Page 39	Surveillance renal biopsies following reperfusion of the allograft on Day 0 and again at the end of Week 24.	Surveillance renal biopsies following reperfusion of the allograft on Day 0 and again at the end of Week 24. Where necessary to minimize any potential risk associated with the biopsy, a CT guided biopsy may be performed at the investigator's discretion in consultation with the medical monitor.	Allow for CT guided biopsy in subjects if deemed necessary by the investigator.
Table 3, Schedule of Assessments – Treatment Period (Day 0 to Week 24), Footnote w, Page 39	Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study.	Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study. Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia- related medications, electrolytes and intravenous fluids, do not need to be collected. Any transplant related medications, such as immunosuppressive drugs, administered during this period should be collected.	Update for consistency with revisions throughout the protocol.
Table 4, Schedule of Assessments – Treatment Period (Week 28 to Week 48) and Post-Treatment Safety Follow-up, Footnote q, Page 41	Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study.	Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study. Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia- related medications, electrolytes and intravenous fluids, do not need to be collected. Any transplant related medications, such as immunosuppressive drugs,	Update for consistency with revisions throughout the protocol.

Section, Page	Protocol v3.0 Text	Modified Text	Rationale for Change
		administered during this period should be collected.	
Section 8.4.1, Biological Samples, Page 45	If consent is withdrawn, any samples collected prior to that time may still be given to and used by the Sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.	If consent is withdrawn, any samples collected prior to that time may still be given to and used by the Sponsor but no new samples will be collected unless specifically required to monitor safety of the subject.	Clarify data may still be collected from subjects who withdraw consent based on previously provided samples; however, no additional samples will be collected.
Section 9.2, Concomitant Medications, Page 49	Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study.	Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study. Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia- related medications, electrolytes and intravenous fluids, do not need to be collected. Any transplant related medications, such as immunosuppressive drugs, administered during this period should be collected.	Update for consistency with revisions throughout the protocol.
Section 10.1.3, VIB4920 Inspection, Page 50	Refer to the Product Complaint section for further instructions (Section 11.1.7).	Refer to the Product Complaint section for further instructions (Section 10.1.7).	Correct error in the referenced section of the protocol.
Section 10.1.7, Reporting Product Complaints, Page 52	Email: Productcomplaints @VielaBio.com Phone: +1 (240) 575-6744 +1 (240) 329-0283 +1 (240) 920-0066 Mail: Viela Bio, Inc. Attn: Quality Assurance and Compliance One MedImmune Way, Gaithersburg, MD USA 20878	Email: ClinicalProductComplaints @horizontherapeutics.com Phone: 1-866-479-6742	Update to reflect current product complaint report contacts.
Section 11.1.12, CCI [redacted], Page 58	CCI [redacted] will be	CCI [redacted] will be collected from CCI [redacted]	Update for consistency with

Section, Page	Protocol v3.0 Text	Modified Text	Rationale for Change
	collected from CCI as designated in Table 3 and Table 4. The CCI that may include, but is not limited to, CCI Details on drawing, handling, and shipping CCI will be detailed in the study Lab Manual.	CCI . The CCI that may include, but is not limited to, CCI . Details on drawing, handling, and shipping CCI will be detailed in the study Lab Manual.	revisions throughout the protocol.
Section 11.1.20, Prior and Concomitant Medications, Page 60	N/A	Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia- related medications, do not need to be collected. Any transplant related medications, such as immunosuppressive drugs, administered during this period should be collected.	Update for consistency with revisions throughout the protocol.
Section 11.1.24 Surveillance Biopsy, Page 61	N/A	A surveillance renal biopsy will performed following reperfusion of the allograft on Day 0 and again at the end of Week 24, as specified in the Schedule of Assessments (Table 3). Where necessary to minimize any potential risk associated with the biopsy, a CT guided biopsy may be performed at the investigator's discretion in consultation with the medical monitor. A CT scan utilizes ionizing radiation to provide imaging to guide the biopsy collection. There can be risks of radiation from the CT scan. The cumulative radiation exposure from this test is considered small.	Allow for CT guided biopsy in subjects if deemed necessary by the investigator and outline the associated risks.

Section, Page	Protocol v3.0 Text	Modified Text	Rationale for Change
Section 13.2.1.3. Adverse Events of Special Interest (AESIs), Page 65	Hepatic function abnormality (meeting the definition of Hy's Law)	Hepatic function abnormality (meeting the definition of Hy's Law, Appendix 4)	Include reference to supporting appendix.
Section 13.2.1.3. Adverse Events of Special Interest (AESIs), Page 65	Anaphylaxis and clinically significant (CTCAE Grade 3 or higher) hypersensitivity reactions.	Anaphylaxis and clinically significant (CTCAE Grade 3 or higher) hypersensitivity reactions (Appendix 2)	Include reference to supporting appendix.
Section 13.2.1.3. Adverse Events of Special Interest (AESIs), Page 65	Severe Infusion-related reactions (CTCAE Grade 3 or higher).	Severe Infusion-related reactions (CTCAE Grade 3 or higher, Appendix 3)	Include reference to supporting appendix.
Section 13.5.1, Assessment of Severity, Page 67	Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 14.2.1.2.	Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.2.1.2.	Correct error in the referenced section of the protocol.
Section 13.6 Reporting Serious Adverse Events, Page 68	All SAEs (related and unrelated) will be recorded from written informed consent signature up to the end of the safety follow-up, whether or not they are related to the study.	All SAEs/AESIs (related and unrelated) will be recorded from written informed consent signature up to the end of the safety follow-up, whether or not they are related to the study.	Clarify AESIs require reporting according to SAE timelines.
Section 13.6 Reporting Serious Adverse Events, Page 68	Any SAEs considered related to the investigational product and discovered by the investigator at any time after the study should be reported.	Any SAEs/AESIs considered related to the investigational product and discovered by the investigator at any time after the study should be reported.	Update for consistency with revisions throughout the protocol.
Section 13.6 Reporting Serious Adverse Events, Page 68	All SAEs must be reported within 24 hours by submitting a SAE/AESI Report Form by email to:	All SAEs/AESIs must be reported within 24 hours by submitting a SAE/AESI Report Form by email to:	Update for consistency with revisions throughout the protocol.
Section 13.6 Reporting Serious Adverse Events, Page 68	Additional follow-up information, if required or available, should all be reported within one business day of receipt, should be completed on a follow-up SAE form, placed with the original SAE information and kept with the appropriate	Additional follow-up information, if required or available, should all be reported within one business day of receipt, should be completed on a follow-up SAE/AESI form, placed with the original SAE/AESI information and kept with the	Update for consistency with revisions throughout the protocol.

Section, Page	Protocol v3.0 Text	Modified Text	Rationale for Change
	section of the eCRF and/or study file.	appropriate section of the eCRF and/or study file.	
Section 13.6 Reporting Serious Adverse Events, Page 68	Viela Bio, Inc. or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the IRB or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site.	Viela Bio, Inc. or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the IRB or Independent Ethics Committee (IEC) of all SAEs/AESIs that occur at his or her site.	Update for consistency with revisions throughout the protocol.
Section 13.6 Reporting Serious Adverse Events, Page 68	Each site is responsible for notifying its IRB or IEC of these additional SAEs.	Each site is responsible for notifying its IRB or IEC of these additional SAEs/AESIs.	Update for consistency with revisions throughout the protocol
Section 14.2.1.1 Primary Efficacy Endpoint, Page 69	For the primary analysis the acute rejection rating will be based on the consensus of the pathologists at the two participating sites.	For the primary analysis the acute rejection rating will be based on the consensus of the pathologists at the initial two participating sites.	Update for consistency with revisions throughout the protocol.

2. SYNOPSIS

Name of Sponsor/Company:
Viela Bio, Inc.

Name of Investigational Product:
VIB4920

Title of Study:
A Phase 2a Single-arm, Prospective, Open-label Pilot Study to Evaluate the Safety and Efficacy of Dual Costimulation Blockade with VIB4920 and belatacept for Prophylaxis of Allograft Rejection in Adults Receiving a Kidney Transplant

No. of centers: Approximately four

Country: USA

Phase of development: 2a

Objectives:

Primary:

1. To demonstrate that when added to standard-of-care induction regimen that includes Thymoglobulin® (anti-thymocyte globulin [rabbit]) and corticosteroids, dual costimulation blockade with multiple doses of VIB4920 + belatacept, started at the time of kidney transplant surgery and repeated every 2-4 weeks post-transplantation, prevents composite efficacy failure (tBPAR of grade 1A or higher, graft loss or death) at Week 24 post-transplantation in the majority of subjects (≥ 17/20).

Secondary:

1. To evaluate individual components (and combinations of the individual components) of the composite efficacy endpoint at Weeks 12, 24 and 48 post-transplantation.
2. To evaluate safety and tolerability of dual costimulation blockade with VIB4920 + belatacept in subjects receiving a kidney transplant.
3. To evaluate the pharmacokinetics and immunogenicity (anti-drug antibodies - ADA) of VIB4920.

Exploratory:

1. Evaluate CCI at Weeks 4, 12, 24 and 48 post-transplantation using CCI in subjects receiving a kidney transplant.
2. To understand changes in CCI and CCI in blood related to pharmacology of VIB4920.
3. To evaluate the CCI of CCI on CCI.

Methodology:

This is a Phase 2a, prospective single-arm, open-label pilot study to evaluate the efficacy, safety and tolerability of dual costimulation blockade with VIB4920 + belatacept in adult male or female

recipients of a renal allograft from a deceased, living unrelated or human leukocyte antigen (HLA) non-identical living related donor.

The study will be conducted at approximately four centers in the United States in a total of approximately 20 patients meeting all inclusion and exclusion criteria. Eligible patients are males or females, aged 18-70, who are low immunologic risk candidates (no donor-specific antibodies and a negative cross-match testing by T- and B- cell flow or by virtual cross-match) undergoing a first renal transplantation from a standard criteria deceased donor, living unrelated or HLA non-identical living related donor.

Immunosuppression will be achieved by administration of VIB4920 + belatacept (with Thymoglobulin and corticosteroids) according to the following regimen:

- Thymoglobulin 1.5 mg/kg by intravenous (IV) infusion prior to reperfusion of the allograft on the day of transplantation surgery (Day 0), prior to VIB4920+belatacept infusion on post-op Day 1, on post-op Day 2, and prior to VIB4920+belatacept infusion on post-op Day 3 or 4. Adjustments in the total dose of 6 mg/kg or frequency of delivery are allowed for clinical cause (i.e., thrombocytopenia). Reasons for adjustments should be clearly stated in the medical record and appropriate case report form.
- Methylprednisolone by IV infusion (500, 250, 125 and 60 mg on Days 0, 1, 2 and 3, respectively) followed by oral administration of prednisone 30 mg per day on Days 4, 5, 6 and 7. Subjects may be tapered to at least 20 mg per day on Day 8, to at least 10 mg per day on Day 15, and to at least 5 mg per day on Day 22. Discontinuation of prednisone should occur following the post-op Day 28 visit.
- VIB4920 1500 mg by IV infusion on post-op Day 1, repeated on post-op Day 3 or 4 (timing is at investigator's discretion), Week 2, and at the end of Weeks 4, 6, 8 and 10; then 1500 mg every four weeks from Week 12 to Week 48.
- Belatacept 10 mg/kg by IV infusion on post-op Day 1, repeated on post-op Day 3 or 4 (timing is at investigator's discretion), and at the end of Weeks 2, 4, 8 and 12; then 5 mg/kg IV every four weeks from Week 16 to Week 48.

Subjects with evidence of renal allograft dysfunction (rising serum creatinine not attributable to technical complications) and/or evidence of cell-mediated or antibody mediated rejection on biopsy will be treated with additional immunosuppression, as clinically indicated and according to standard care at each participating clinical site. Whether to continue VIB4920 + belatacept will be determined based on the histologic grade of the rejection and the clinical response to immunosuppressive therapy.

Patients may be screened between Day -28 and Day -1 prior to transplantation, with eligibility reconfirmed on Day 0 prior to induction of anesthesia for transplant surgery and prior to administration of Thymoglobulin or methylprednisolone. Subjects will be admitted to the transplant center for administration of VIB4920 and belatacept, observation and assessment of safety/tolerability and may be discharged after administration of VIB4920+belatacept on Day 3 or 4 (at the discretion of the investigator) following completion of all scheduled Visit 4 assessments. Subjects will return to the study center for safety monitoring on Day 7 and for administration of study medication(s) and safety monitoring on Week 2; then every 2 weeks for 5 visits (at the end of Weeks 4, 6, 8, 10 and 12), and then monthly for 9 visits (at the end of Weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48). All subjects will be followed on study through Week 48 for acute rejection, graft survival and patient survival. Subjects

who prematurely discontinue treatment with VIB4920 and/or belatacept will undergo an End-of-Treatment visit at time of discontinuation and follow Schedule of Assessments through Week 48 and at least three months after last dose with VIB4920 and/or belatacept completing the study with End of Study visit. Subjects who are unwilling to comply with study schedule after early discontinuation of treatment should undergo End-of-Treatment/End-of-Study visit at time of discontinuation and undergo complete safety follow up at 4, 8, and 12-weeks after End-of-Treatment visit. Subjects who wish to prematurely discontinue study participation should be asked to undergo an End-of-Study visit assessment before withdrawing consent.

Number of patients (planned): Eligible patients (i.e., meeting all inclusion and exclusion criteria) will be included in the study until a total of 20 patients undergo the scheduled kidney transplant surgery with intention -to-treat with the revised "full-dose" regimen of Thymoglobulin, extended steroids, and an additional dose of VIB4920 on Day 3 or 4, *and* receive at least one dose of VIB4920.

Inclusion criteria:

1. Written informed consent and any locally required authorization (e.g., data privacy) obtained from the patient prior to performing any protocol-related procedures, including screening evaluations.
2. Male or female recipients aged 18-70.
3. Recipients of a first renal transplant from a standard criteria deceased donor, living unrelated or HLA non-identical living related donor.
4. Recipients who are at low immunologic risk:
    a. No donor specific antibodies (DSA), and
    b. Negative cross-match testing (by T- and B- cell flow or by virtual cross-match).
5. Recipients with up to date vaccination as per local immunization schedules.
6. A female subject is eligible if she is:
    a. Not pregnant or nursing.
    b. Of non-childbearing potential (i.e., post-menopausal defined as having been amenorrheic for at least 1 year prior to screening, has had a bilateral tubal ligation at least 6 months prior to screening, or has had a bilateral oophorectomy or hysterectomy).
    c. Of childbearing potential, must have a negative serum pregnancy test within 48 hours prior to surgery and be using an effective method of contraception (per site specific recommendations) which must be continued for at least 6 months after the final dose of investigational product.
7. Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide from Day 0 through to the end of the study and must agree to continue using such precautions for at least 6 months after the final dose of investigational product.

Exclusion Criteria

1. Patients receiving an allograft from an ABO-incompatible donor.
2. Patients treated with systemic immunosuppressive drug therapy for more than a total of 2 weeks within 24 weeks prior to ICF signature.
3. Patients who have undergone lymphodepleting therapy (e.g., Thymoglobulin, alemtuzumab).

4. Patients with known immunodeficiency.
5. Patients with medical history of confirmed venous thromboembolism, arterial thrombosis, coagulopathy or known platelet disorders.
6. Patients with risk factors for venous thromboembolism or arterial thrombosis (e.g., immobilization or major surgery within 12 weeks before screening), prothrombotic status (including but not limited to congenital or inherited deficiency of antithrombin III, protein C, protein S, or confirmed diagnosis of antiphospholipid syndrome).
7. Patients requiring treatment with antithrombotic drugs (clopidogrel, prasugrel, warfarin, others). Low-dose aspirin treatment (up to 100 mg/day) is allowed.
8. Patients requiring long-term systemic anticoagulation after transplantation, which would interfere with obtaining biopsies.
9. Patients with poor vascular access such that IV administration of the study medications may be compromised.
10. Patients with any contraindication to kidney biopsy.
11. CMV-seronegative recipients of a CMV-seropositive donor kidney, or unknown CMV serostatus.
12. EBV-seronegative or with unknown EBV serostatus.
13. Receipt of live (attenuated) vaccine within the 4 weeks before screening.
14. Patients with high potential of graft loss due to recurrence of underlying kidney disease.
15. Prior solid organ transplant or potential to require a concurrent organ or cell transplant.
16. Previous treatment with belatacept.
17. Previous treatment with CD40 or anti-CD40L agents.
18. Use of B cell depleting therapy (e.g., rituximab), non-depleting B cell directed therapy (e.g., belimumab) or abatacept within 1 year prior to enrollment.
19. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
20. At screening blood tests, any of the following:
    a. Aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN)
    b. Alanine aminotransferase (ALT) > 2.5 × ULN
    c. Alkaline phosphatase (ALP) > 2.5 × ULN
    d. Total bilirubin (TBL) > 2 × ULN
    e. Hemoglobin < 75 g/L
    f. Neutrophils < 1.5×10^9/L
    g. Platelets < 100×10^9/L
21. Patients with severe systemic infections, current or within the 2 weeks prior to transplant surgery.
22. Positive test for chronic hepatitis B infection at screening or within the last 12 months, defined as either (1) positive hepatitis B surface antigen [HBsAg] or (2) a positive hepatitis B core antibody [anti-HBc] PLUS negative hepatitis B surface antibody [anti-HBs]. Note that subjects with a positive anti-HBs ONLY or a positive anti-HBc PLUS positive anti-HBs AND negative HBsAg are eligible to enroll.
23. Positive test for hepatitis C virus antibody at screening or within the last 12 months.
24. Positive test for HIV antibody at screening or within the last 12 months.
25. History of or active tuberculosis (TB), or a positive QuantiFERON®-TB Gold test (for recipients of living donor kidneys) at screening, unless previously treated for latent tuberculosis. Subjects with an indeterminate QuantiFERON®-TB Gold test result can repeat the

test, but if the repeat test is also indeterminate, they are excluded. Other standard of care methods performed for determining the TB status (e.g., chest X-rays) are permitted.

26. History of cancer, except as follows:
    a. In situ carcinoma of the cervix treated with apparent success with curative therapy > 12 months prior to screening; or
    b. Cutaneous basal cell or squamous cell carcinoma treated with apparent success with curative therapy
27. Any severe cardiovascular, respiratory, endocrine, gastrointestinal, hematological, neurological, psychiatric, or systemic disorder that could impact the evaluation of safety and efficacy assessments or affect the subject's ability to participate in the study or the subject's safety.
28. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.
29. Lactating or pregnant females or females who intend to become pregnant anytime from signing the informed consent form (ICF) through 6 months after receiving the last dose of investigational product
30. Known history of severe allergy or reaction to any component of the investigational product formulation or to any other biologic therapy.
31. Unwilling or unable to comply with the protocol, complete study assessments, and complete the study period.

Expected duration of study participation:

The total duration of subject participation in the study may be up to approximately 64 weeks (4 weeks of screening period + 48 weeks of treatment period + 12 weeks of safety follow-up).

Reference therapy, dosage and mode of administration:

Not applicable

Criteria for evaluation:

Efficacy:

Primary

The primary efficacy endpoint is the incidence of efficacy failure, defined as treated biopsy-proven acute rejection (tBPAR) of grade 1A or higher, graft loss or death, at Week 24 post-transplantation. For the primary analysis the acute rejection rating will be based on the consensus of the pathologists at the initial two participating sites.

Secondary

In addition to Week 24, the incidence of efficacy failure as defined in the primary efficacy endpoint will be analyzed at Week 12 and Week 48.

The following secondary variables will also be analyzed at Weeks 12, 24 and 48:

- Incidence of tBPAR, graft loss, death or loss to follow-up (LTFU)
- Incidence of antibody-mediated rejection
- Incidence of tBPAR
- Incidence of BPAR
- Incidence of treated acute rejections
- Proportion of subjects with de novo donor-specific antibodies (dnDSA)

Safety:

Safety endpoints will include:

- Treatment emergent adverse events and serious adverse events
- Treatment-emergent adverse events of special interest
  - Thrombotic and embolic events
  - Hepatic function abnormality (meeting the definition of Hy's Law, Appendix 4)
  - Anaphylaxis and clinically significant (CTCAE Grade 3 or higher) hypersensitivity reactions (Appendix 2)
  - Immune complex disease
  - Severe infusion-related reactions (CTCAE Grade 3 or higher, Appendix 3)
  - Malignant neoplasm
  - Infections:
    - Clinically significant (CTCAE Grade 3 or higher) infections
    - Opportunistic infections associated with immunosuppression including but not limited to reactivation of latent viral infection [varicella zoster virus (VZV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), JC virus (JCV), cytomegalovirus (CMV), BK polyoma virus], fungal infections and tuberculosis
- Laboratory data (laboratory variables by visit, change from baseline of laboratory variables by visit)
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and body weight) by visit
- ECG by visit

Pharmacokinetics

VIB4920 plasma concentration over visits. Individual and mean plasma concentration-time profiles of VIB4920 will be generated.

When possible, the following PK parameters will be accessed for VIB4920 concentration: maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), systemic clearance (CL), and terminal elimination half-life ($t_{1/2}$). Additional PK parameters may be determined and reported as appropriate.

Immunogenicity

The number and percentage of subjects who develop detectable ADA will be summarized. The impact of ADA on PK and the association with AEs and SAEs will be assessed.

Exploratory:

- Proportion of subjects with CCI [redacted] at Weeks 12, 24 and 48
- Changes in CCI [redacted] between Week 4 and Week 24; Week 4 to Week 48; Week 24 and Week 48
- Changes over time in CCI [redacted] related to VIB4920 pharmacology
- Changes over time in the CCI [redacted] and CCI [redacted]

Statistical methods:

The primary and secondary efficacy endpoints will be analyzed descriptively by calculating the proportion of incidence and the corresponding 80% exact confidence interval. The safety endpoints will be summarized descriptively as well. The number and percentage of subjects reporting treatment emergent- AEs will be summarized by system organ class and preferred terms, by severity, and by relationship to the investigational product. The number and percentage of subjects reporting SAEs and AESIs will be summarized. Laboratory, vital sign, and ECG measurements, as well as their changes from baseline, at each visit and shift from baseline, if applicable, will be summarized descriptively.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
AST	Aspartate aminotransferase
BCR	B Cell Receptor
BPAR	Biopsy proven acute rejection
CD	Cluster of differentiation
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CRF	Case report form
D5W	5% dextrose in water
DGF	Delayed graft function
dnDSA	De novo donor-specific antibodies
DSA	Donor specific antibodies
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FTIH	First-time-in-human
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
hCGβ	Serum human chorionic gonadotrophin beta
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus

Abbreviation or Specialist Term	Explanation
HLA	Human leukocyte antigen
HSA	Human serum albumin
HSV	Herpes simplex virus
ICF	Informed consent form
ICH	International Council for Harmonization
IV	Intravenous
IEC	Independent Ethics Committee
IRB	Institutional Review Board
JCV	JC virus
mAb	Monoclonal antibody
MAD	Multiple-ascending dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
mTOR Inhibitor	Mammalian target of rapamycin
NHP	Non-human primates
NS	Sodium chloride
NOAEL	No observed adverse effects level
OAE	Other adverse event
PBMC	Peripheral blood mononuclear cells
PI	Principal Investigator The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PK	Pharmacokinetics
PRA	Panel Reactive Antibody test
RA	Rheumatoid arthritis
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse event
SAD	Single-ascending dose
SC	Subcutaneous
SID	Subject identifier

Abbreviation or Specialist Term	Explanation
SWFI	Sterile water for injection
TAC	Tacrolimus
TB	Tuberculosis
TBL	Total bilirubin
tBPAR	Treated biopsy-proven acute rejection
TCR	T-cell receptor
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
USP	United States Pharmacopeia
VZV	Varicella zoster virus

5. INTRODUCTION

5.1. Background

Post transplantation immunosuppressive management has reduced rates of acute rejection and improved 1-year outcomes; however, all-cause graft failure at 5 years is still approximately 28% for deceased donor and 16% for living donor transplants (Wang, Skeans et al. 2016). Calcineurin inhibitors (CNIs) and corticosteroids, often used as maintenance immunosuppression in kidney transplant patients, are associated with toxicities and side effects that contribute to decreased renal function and increased morbidity and mortality (Naesens, Kuypers et al. 2009). These long-term outcomes indicate a need for selective immunomodulators which may improve long-term patient and allograft survival by avoiding the chronic toxicities of nonselective immunosuppressive therapies.

Rejection of organ allografts is mediated by interactions of both innate and adaptive immune systems, with T cells having a central role mainly due to their ability to recognize foreign antigen fragments resulting in T cell activation, clonal expansion, differentiation into effector cells, and destruction of the transplanted organ. Another important mechanism is T cell-dependent B cell activation and differentiation that leads to production of alloantibodies and alloantibody mediated rejection. For optimal activation, T cells require simultaneous engagement of the high-affinity antigen-specific T-cell receptor (TCR) and signaling through costimulatory molecules (Zhang, Pierson et al. 2015). The cluster of differentiation (CD)28-CD80/86 and CD40-CD40L pathways are two of the most important pathways shown to have a pivotal role in transplantation (Adams, Ford et al. 2016).

Targeting CD40L for the prevention of transplant rejection has been considered since the mid-1990s. In a landmark study, an anti-CD40L monoclonal antibody induced markedly prolonged survival of fully disparate murine cardiac allografts in both naive and sensitized hosts (Larsen, Alexander et al. 1996). Further studies confirmed a beneficial effect of anti-CD40L on graft survival using various rodent models: recurrence of diabetes in islet isografts in rats with autoimmune diabetes (Kover, Geng et al. 2000), corneal transplants in mice (Qian, Boisgerault et al. 2001) and limb allografts in mice (Tung, Mackinnon et al. 2003).

A number of studies in non-human primates (NHP) have also established the utility of anti-CD40L monoclonal antibodies in prevention of transplant rejection for kidney (Kirk, Harlan et al. 1997, Kirk, Burkly et al. 1999), (Preston, Xu et al. 2005), (Kanmaz, Fechner et al. 2004, Schuler, Bigaud et al. 2004), (Pearson, Trambley et al. 2002), skin (Elster, Xu et al. 2001) and (Xu, Montgomery et al. 2003), in islet transplant (Kenyon, Chatzipetrou et al. 1999, Kenyon, Fernandez et al. 1999) and heart transplant (Pierson, Chang et al. 1999). However, in many settings CD40L blockade alone was not uniformly sufficient to prevent acute or chronic rejection, suggesting that adjunct treatment may be required to fully control T cell recognition/activation. These observations led to the exploration of dual costimulatory blockade to prevent allograft rejection.

5.1.1. Dual co-stimulatory blockade in mice

In one of the very first publications describing the effect of dual costimulatory blockade in animals (Larsen, Elwood et al. 1996), mice receiving cardiac allografts were treated with CTLA4-Ig or anti-CD40L antibody alone or in combination. Anti-CD40L alone prolonged

cardiac allograft survival but only the combination of CTLA4-Ig and anti-CD40L prevented allograft loss during the observation period. Animals treated with the combination of CTLA4-Ig and anti-CD40L had no chronic vascular rejection and were histologically free of lymphocytic infiltration, fibrosis and had no coronary arterial intimal lesions. No adverse events (AEs) were reported with the dual costimulatory blockade in this study (Larsen, Elwood et al. 1996). In a similar murine cardiac allograft model, (Shirasugi, Adams et al. 2002) dual costimulatory blockade with CTLA4-Ig and anti-CD40L resulted in long-term acceptance of cardiac allografts. No AEs were reported other than the transplant rejection.

5.1.2. Dual co-stimulatory blockade in NHP

Dual co-stimulatory blockade with CTLA4-Ig and anti-CD40 ligand has been tested in NHPs. In a kidney transplant model, a brief perioperative treatment of donor kidney sensitized animals with CTLA4-Ig or anti-CD40 ligand (5C8) alone led to rejection-free survival of 20–98 days compared to 5-8 days in control animals (Kirk, Harlan et al. 1997). Two animals received a combination regimen, one rejected at 32 days and the second at 100 days post transplantation. Retreatment of the latter animal with the same regimen fully reversed rejection. Extending the treatment period from 14 to 28-days post-transplantation extended renal allograft survival for up to 9 months without any further intervention (Knechtle, Kirk et al. 1999) demonstrating that the combination of CTLA4-Ig and anti-CD40L is more effective than either agent alone in preserving renal allograft survival without the need for chronic immunosuppression.

In another study of kidney transplant in rhesus monkeys, dual costimulatory blockade with CTLA4-Ig and anti-CD40L or anti-CD40 improved allograft survival compared to CTLA4-Ig alone with the two longest allograft survivals observed in animals receiving CTLA4-Ig plus anti-CD40L (Pearson, Trambley et al. 2002). Dual costimulatory blockade, but not CTLA4-Ig monotherapy, also prevented the development of donor-specific antibodies in recipient monkeys.

5.1.3. Costimulatory blockade in human kidney transplantation

5.1.3.1. Blocking the CD28-CD80/86 pathway

Belatacept (Nulojix®) is a fusion protein of human IgG1 linked to the extracellular domain of CTLA-4 that blocks costimulation and inhibits T-cell activation. It is U.S. Food and Drug Administration-approved for prophylaxis of organ rejection in adult patients receiving a kidney transplant for use in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids (Food and Drug Administration 2017). The pivotal phase III clinical trial (The Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial [BENEFIT]) found that compared to cyclosporine, belatacept was associated with superior renal function and similar patient/graft survival at 1 year after kidney transplantation, despite a higher rate (approximately 17%) of early acute rejection (Vincenti, Charpentier et al. 2010). In addition to the higher rate of acute rejection, the histologic severity of the rejections appeared to be greater; antibody mediated rejection was also reported. Despite belatacept's improved long-term efficacy in preserving renal function compared to CNIs, the high rate of acute kidney rejections has limited its use.

Early biopsy proven acute rejection (BPAR) was reduced following T cell depleting induction therapy followed by CNI-free and steroid-free maintenance with belatacept and sirolimus or everolimus. Ferguson et al compared two belatacept-based regimens (belatacept + MMF and

belatacept + sirolimus) to tacrolimus + MMF. All subject received Thymoglobulin (6 mg/kg) and a 4-day course of corticosteroids as induction therapy (Ferguson, Grinyo et al. 2011). Eighty-nine patients were randomized and transplanted. At month 6, acute rejection occurred in 4 patients in the belatacept-MMF, 1 in the belatacept-sirolimus group and 1 in the tacrolimus-MMF group. Most acute rejections occurred in the first 3 months. More than two-thirds of patients in the belatacept groups remained on CNI- and steroid-free regimens at 12 months and the estimated glomerular filtration rate was 8–10 mL/min higher with either belatacept regimen than with tacrolimus-MMF. Overall safety was comparable between groups (Ferguson, Grinyo et al. 2011).

Wojciechowski et al reported low acute rejection rate (comparable to that seen in patients receiving calcineurin inhibitor-based regimens) with belatacept and everolimus maintenance following induction with a reduced dose Thymoglobulin (3 mg/kg) regimen. Graft function remained excellent at 1 year (Wojciechowski, Chandran et al. 2017).

Importantly, in both studies approximately 38% of patients receiving sirolimus or everolimus did not tolerate their mTOR inhibitor and had to be converted to another immunosuppressant.

Kirk et al investigated a belatacept-based regimen without CNIs or steroids using alemtuzumab induction, monthly belatacept and daily sirolimus (Kirk, Guasch et al. 2014). The regimen was successful in preventing clinical allograft rejection; none of the 20 patients experienced BPAR, nor did any patient develop donor specific antibodies (DSA) within the first year. Subclinical rejection was detected on surveillance biopsy in the first year in 3 patients. All maintained stable function, remained on protocol therapy, and resolved their histological findings on subsequent surveillance biopsies. Ten patients elected oral immunosuppressant weaning, seven of whom were maintained rejection-free on monotherapy belatacept. All three patients who failed weaning responded to conventional treatment and achieved stable allograft function (Kirk, Guasch et al. 2014).

5.1.3.2. Blocking the CD40-CD40L pathway

The experience with blocking the CD40-CD40L ligand pathway in human transplantation is limited. Preliminary results with BG9588 (hu5C8, a humanized anti-CD40L monoclonal antibody [mAb]) in combination with MMF in kidney transplantation showed mild, steroid-sensitive acute rejection early in the post-transplant period in 5/7 patients, including two who received hu5C8 as monotherapy. These mild rejection episodes have been easily reversed with steroids and long-term good renal function was achieved in all patients (Kirk, Knechtle et al. 2001). The study drug was well tolerated during the infusion but thromboembolic events in this study and other studies with hu5C8 in non-transplant indications led to discontinuation of hu5C8 development.

Recently, CFZ533 a fully human, Fc-silenced, nondepleting, IgG1 mAb against CD40 was compared to tacrolimus following basiliximab induction in patients receiving kidney transplants. Six-month interim results demonstrated comparable efficacy on the composite endpoint of treated biopsy-proven acute rejection, graft loss, or death (21.2 vs. 22.2%) and better renal function (55.8 vs. 45.5 mL/min) with CFZ533 vs. tacrolimus, respectively, with fewer infectious complications in the CFZ533 group (Nashan, Tedesco et al. 2018).

These studies demonstrate that combining belatacept with an mTOR inhibitor effectively prevents kidney allograft rejection without CNIs or steroids when used following T cell depleting induction with alemtuzumab or Thymoglobulin and that selected, immunologically low-risk patients can be maintained safely on once monthly intravenous (IV) belatacept. Experience with blocking the CD40-CD40L pathway in human kidney transplant is limited but early results show promising efficacy. These data together with the existing preclinical evidence supporting the synergistic effect of simultaneously blocking the CD28-CD80/86 and CD40-CD40L pathways provide the scientific and clinical foundation for the rationale of combining belatacept and VIB4920 to prevent allograft rejection and preserve renal function without the use of conventional immunosuppression.

5.2. Safety experience

5.2.1. Belatacept

Belatacept (Nulojix) is approved for prophylaxis of organ rejection in adult patients receiving a kidney transplant. The use of belatacept is contraindicated in transplant recipients who are Epstein-Barr virus (EBV)-seronegative or with unknown serostatus due to the increased risk of developing posttransplant lymphoproliferative disorders, predominantly involving the central nervous system. As with all immunosuppressants there is an increased risk of infections, including serious and opportunistic infections with belatacept. However, in clinical trials the rate of infections was not higher than in the control arm receiving cyclosporine (Food and Drug Administration 2017). In a long term, 7-year follow up of the BENEFIT study, the most common AEs in each of the groups were serious infections with cumulative incidence rates of 10.7% for belatacept, and 13.3% cyclosporine (Vincenti 2016).

In the pivotal clinical trials belatacept was used after induction therapy with basiliximab. Recent exploratory studies used induction therapy with the T cell depleting agents alemtuzumab or Thymoglobulin, at standard (6 mg/kg) or reduced (3 mg/kg) doses. Although the studies were limited in size and were not designed to formally assess safety, no unanticipated toxicity was observed in any of these studies (Kirk, Guasch et al. 2014, Grinyo, Del Carmen Rial et al. 2017, Wojciechowski, Chandran et al. 2017).

5.2.2. VIB4920

Several repeat-dose studies (maximum weekly dosing duration of 6 months) and one single dose study were conducted in cynomolgus monkeys to evaluate the safety, pharmacokinetics, and pharmacodynamics of CD40L inhibition by IV or subcutaneous (SC) administration of VIB4920 (formerly MEDI4920) or its parent molecule. The no observed adverse effect levels (NOAELs) for repeat-dose studies were the highest doses tested for most of the studies: 150 mg/kg weekly IV or SC and 300 mg/kg weekly IV for the 5-week studies; 250 mg/kg weekly SC for the 6-month study. The NOAEL for the single-dose study was 600 mg/kg IV. Weekly IV administration of 150 or 300 mg/kg VIB4920 for 6 months resulted in early euthanasia of one animal at 150 mg/kg/dose on Day 92 associated with declining clinical condition, adverse clinical pathology changes, and microscopic evidence of inflammatory cell infiltrates in multiple tissues. In addition, one animal dosed at 300 mg/kg/dose had enlarged spleen with nodular and abnormal appearance at scheduled necropsy on Day 192. Microscopically, increased amounts of inflammatory cell infiltrates in multiple organs and tissues were present in this animal and a

systemic opportunistic fungal infection was detected; this was considered secondary to the pharmacology of VIB4920. Therefore, no NOAEL was established for IV dosing in the 6-month study. However, the NOAEL for the SC cohort in the 6-month study was 250 mg/kg weekly.

The safety of VIB4920 was evaluated in single ascending dose clinical study in healthy subjects and in a multiple ascending dose study in patients with active rheumatoid arthritis (RA). Overall, VIB4920 was well tolerated with a balanced distribution of treatment-emergent adverse events (TEAEs) observed between placebo and the active dose groups in both studies. There were no infusion-related reactions, severe infections or deaths (Albulescu, Müller-Ladner et al. 2018).

The most common TEAEs reported in the multiple-ascending dose (MAD) study in RA were diarrhea, hyperhidrosis, upper respiratory tract infection and urinary tract infection, each occurring in 3 patients (7.1%). One grade 4 serious adverse event (SAE) of encephalitis was reported in the 1500 mg VIB4920 dose group, occurring after 6 doses of study drug. No etiological infectious agent was identified, and the event was considered unrelated to VIB4920. Several months after discontinuing VIB4920 similar symptoms recurred and patient was subsequently diagnosed with metastatic melanoma of the brain. Notably, no clinically significant coagulation or platelet function abnormalities were observed following treatment with VIB4920 in either study.

Previous human studies with anti-CD40L monoclonal antibodies identified an increased risk of thromboembolic events linked to concurrent antibody-mediated binding to both CD40L and FcgRIIa on adjacent platelets resulting in thrombosis (Kawai, Andrews et al. 2000). To avoid the safety complications associated with mAb based targeting of CD40L, VIB4920 was developed by an alternate approach using a non-antibody based structure that does not contain an Fc region, and therefore is unlikely to induce adverse platelet responses. Accordingly, no thromboembolic events or clinically important abnormal platelet or coagulation parameters were noticed in any of the NHP or human studies with VIB4920 (see VIB4920 Investigators Brochure for additional details).

5.2.3. Dual co-stimulatory blockade

There is no clinical experience with dual co-stimulatory blockade in humans.

No serious toxicity signal was reported from murine studies spanning various organ transplantation models. Several studies tested simultaneous blockade of the CD28-CD80/86 and CD40-CD40L pathways in NHP. In a kidney transplant model, the combination of CTLA4-Ig and anti-CD40 ligand (5C8) was well tolerated with no increase in opportunistic infections or lymphoproliferative diseases. One animal treated with combination costimulatory blockers developed shigella and campylobacter enterocolitis. This pathogen is common in rhesus monkeys and untreated animals from the same colony were also infected with the same pathogens (Kirk, Harlan et al. 1997). Importantly, neither drug affected peripheral T cell or B cell counts and no T cell activation or cytokine release occurred, and no clinically important alterations in peripheral blood were noted. Additionally, the dual costimulatory blockade did not alter in vitro T cell responsiveness, as they exhibited strong reaction to donor and third party cells but without allograft rejection (Pearson, Trambley et al. 2002, Xu, Montgomery et al. 2003).

In another study of kidney transplant in rhesus monkeys, dual costimulatory blockade with CTLA4-Ig and anti-CD40L or anti-CD40 significantly improved allograft survival compared to CTLA4-Ig (Pearson, Trambley et al. 2002). In this study all three cytomegalovirus (CMV) negative recipients receiving kidneys from CMV positive donors developed CMV infection. One of these monkeys were treated with anti-CD40 monotherapy and two with the combination of CTLA4-Ig and anti-CD40L. None of the CMV positive recipients in any treatment group had CMV infection post-transplant. No other toxicity was reported from this study (Thompson, Cardona et al. 2011).

5.3. Rationale for the Study

This is the first evaluation of the efficacy and safety of VIB4920 + belatacept in its target indication: prevention of allograft rejection in solid organ transplantation. This study will allow to assess the potential of VIB4920 + belatacept to replace standard immunosuppression with a CNI, MMF and corticosteroids in terms of anti-rejection efficacy, while preserving renal function with an acceptable safety and tolerability profile. Results of this study will be used to inform the dose and regimen selection for investigation in later phases of clinical development.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and all applicable regulatory requirements.

5.4. Rationale for Endpoints

The primary and secondary efficacy endpoints are consistent with well-established precedents by global health authorities for clinical development of immunosuppressive regimens in de novo kidney transplantation.

5.5. Rationale for Dose(s) Selected

In this study, we propose to use T cell depleting induction therapy followed by a combination of belatacept (blocking the CD28-CD80/86 pathway) and VIB4920 (blocking CD40 ligand). T cell depletion will be used to reduce the acute T cell mediated response and protect against acute rejection in the immediate post-transplant period. Thymoglobulin will be administered at its approved dosing regimen for prophylaxis of acute rejection in patients receiving a kidney transplant. Following induction, belatacept will be combined with VIB4920 starting on Day 1 post-transplant to maximize the impact of dual costimulatory blockade on the alloimmune response against the graft. Belatacept will be administered at its approved dosing regimen. VIB4920 will initially be given at the highest dose and frequency used in the Phase 1b rheumatoid arthritis study (1500 mg IV every 2 weeks) with an additional dose administered at Day 3 or Day 4. The initial higher dose of VIB4920 and the additional dose at Day 3 or 4 is chosen because the early postoperative period in kidney transplant is characterized by a hyperacute inflammatory environment with upregulation of both cell-bound and soluble CD40L and more frequent administration of VIB4920 may be required to achieve the necessary CD40L blockade. In addition, administering the VIB4920 and belatacept on the same schedule maximizes the dual co-stimulatory blockade. Moreover, the first three months post-transplant is also the period when most acute rejections occurred in the belatacept studies, therefore it is prudent to provide higher doses during this period. After 12 weeks the dosing frequency will be changed to every 4 weeks. This dosing regimen is expected to provide VIB4920 concentrations

above IC67 during the first 12 weeks and between IC50 and IC67 between Week 12 and 48. The prolonged duration of clinical and biomarker responses in RA at these drug levels further support the less intensive administration regimen after Week 12.

5.6. Rationale for Study Population

The study population is low immunological risk adult recipients of a first kidney allograft from a standard criteria deceased donor, living unrelated or human leukocyte antigen (HLA) non-identical living related donor, typical for early development studies of new immunosuppression regimens in kidney transplantation.

This is a single-arm, open-label exploratory study without a concurrent control group. The results of this study will be interpreted in the context of efficacy results from patients in randomized, controlled trials treated with a Food and Drug Administration (FDA)-approved standard-of-care composed of tacrolimus (TAC), MMF and corticosteroids and outcomes of standard of care therapies in current clinical practice. Results of this study will be used to inform the dose and regimen selection for investigation in later phases of clinical development.

6. STUDY HYPOTHESES AND OBJECTIVES

6.1. Primary Hypothesis

Blockade of the CD40/CD40L pathway with VIB4920, and blockade of the CD28-CD80/86 pathway with belatacept, will prevent renal allograft rejection (treated biopsy-proven acute rejection (tBPAR)) without traditional maintenance immunosuppression.

6.2. Secondary Hypothesis

Dual costimulation blockade with multiple doses of VIB4920 + belatacept is well tolerated and has an acceptable safety profile.

6.3. Primary Objective

The primary objective is to demonstrate that when added to standard-of-care induction regimen that includes Thymoglobulin® (anti-thymocyte globulin [rabbit]) and corticosteroids, dual costimulation blockade with multiple doses of VIB4920 + belatacept, started at the time of kidney transplant surgery and repeated every 2-4 weeks post-transplantation, prevents composite efficacy failure (tBPAR of grade 1A or higher, graft loss or death) at Week 24 post-transplantation in the majority of subjects (≥ 17/20).

6.4. Secondary Objectives

The secondary study objectives are to:

1. Evaluate individual components (and combinations of the individual components) of the composite efficacy endpoint at Weeks 12, 24 and 48 post-transplantation.

2. Evaluate safety and tolerability of dual costimulation blockade with VIB4920 + belatacept in subjects receiving a kidney transplant.
3. Evaluate the pharmacokinetics and immunogenicity (ADA) of VIB4920.

6.5. Exploratory Objectives

The exploratory study objectives are to:

1. Evaluate renal function at Weeks 4, 12, 24 and 48 post-transplantation using estimated glomerular filtration rate (eGFR) by MDRD formula ($eGFR_{MDRD}$) in subjects receiving a kidney transplant.
2. Understand changes in CCI and CCI in blood related to pharmacology of VIB4920.
3. Evaluate the CCI of CCI on CCI.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 2a, single-arm, open-label pilot study to evaluate the efficacy, safety and tolerability of dual costimulation blockade with VIB4920 + belatacept in adult male or female recipients of a renal allograft from a deceased, living unrelated or HLA non-identical living related donor. The basic scheme is presented in Figure 1.

The study will be conducted at approximately four centers in the United States in a total of approximately 20 patients meeting all inclusion and exclusion criteria. Eligible patients are males or females, aged 18-70, who are low immunologic risk candidates (no donor-specific antibodies and a negative cross-match testing by T- and B- cell flow or by virtual cross-match) undergoing a first renal transplantation from a standard criteria deceased donor, or HLA non-identical living related donor.

Immunosuppression will be achieved by administration of VIB4920 + belatacept (with Thymoglobulin and corticosteroids) according to the following regimen:

- Thymoglobulin 1.5 mg/kg by IV infusion prior to reperfusion of the allograft on the day of transplantation surgery (Day 0) , prior to VIB4920+belatacept infusion on post-op Day 1, on post-op Day 2, and prior to VIB4920+belatacept infusion on post-op Day 3 or 4. Adjustments in the total dose of 6 mg/kg or frequency of delivery are allowed for clinical cause (i.e., thrombocytopenia). Reasons for adjustments should be clearly stated in the medical record and appropriate case report form.
- Methylprednisolone by IV infusion (500, 250, 125 and 60 mg on Days 0, 1, 2 and 3, respectively) followed by oral administration of prednisone 30 mg per day on Days 4, 5, 6 and 7. Subjects may be tapered to at least 20 mg per day on Day 8, to at least 10 mg per day on Day 15, and to at least 5 mg per day on Day 22. Discontinuation of prednisone should occur following the post-op Day 28 visit.

- VIB4920 1500 mg by IV infusion on post-op Day 1, repeated on post-op Day 3 or 4 (timing is at investigator's discretion), Week 2, and at the end of Weeks 4, 6, 8 and 10; then 1500 mg every four weeks from Week 12 to Week 48.
- Belatacept 10 mg/kg by IV infusion on post-op Day 1, repeated on post-op Day 3 or 4 (timing is at investigator's discretion), and at the end of Weeks 2, 4, 8 and 12; then 5 mg/kg IV every four weeks from Week 16 to Week 48.

Subjects with evidence of renal allograft dysfunction (rising serum creatinine not attributable to technical complications) and/or evidence of cell-mediated or antibody mediated rejection on biopsy will be treated with additional immunosuppression, as clinically indicated and according to standard care at each participating clinical site. Whether to continue VIB4920+belatacept will be determined based on the histologic grade of the rejection and the clinical response to immunosuppressive therapy, as defined below.

Written informed consent and any locally required authorization (e.g., data privacy) will be obtained from the subject prior to performing any protocol-related procedures, including screening evaluations. Patients may be screened between Day -28 and Day -1 prior to transplantation, with eligibility reconfirmed on Day 0 prior to induction of anesthesia for transplant surgery and prior to administration of Thymoglobulin or methylprednisolone. Subjects will be admitted to the transplant center for administration of VIB4920 and belatacept, observation and assessment of safety/tolerability and may be discharged after administration of belatacept+VIB4920 on Day 3 or 4 (at the discretion of the investigator) following completion of all scheduled Visit 4 assessments. Subjects will return to the study center for safety monitoring on Day 7 and for administration of study medication(s) and safety monitoring on Week 2; then every 2 weeks for 5 visits (at the end of Weeks 4, 6, 8, 10 and 12), and then monthly for 9 visits (at the end of Weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48). All subjects will be followed on study through Week 48 for acute rejection, graft survival and patient survival. Subjects who prematurely discontinue treatment with VIB4920 and/or belatacept will undergo an End-of-Treatment visit at time of discontinuation and follow Schedule of Assessments through Week 48 and at least three months after last dose with VIB4920 and/or belatacept completing the study with End of Study visit. Subjects who are unwilling to comply with study schedule after early discontinuation of treatment should undergo End-of-Treatment/End-of-Study visit at time of discontinuation and undergo complete safety follow up at 4, 8, and 12-weeks after end treatment visit. Subjects who wish to prematurely discontinue study participation should be asked to undergo an End-of-Study visit assessment before withdrawing consent.

A graft core biopsy must be performed within 48 hours for all cases of suspected acute rejection (based on the investigator's clinical judgment), regardless of initiation of anti-rejection treatment. Biopsies will be read by local pathologist according to Banff criteria 2017 (Haas, Loupy et al. 2018) and will be used to guide patient management. In addition, all subjects will undergo surveillance renal biopsies following reperfusion of the allograft on Day 0 and again at the end of Week 24.

- Subjects with mild cellular rejection (Banff Grade 1A or 1B) will be treated with corticosteroids and continue treatment with VIB4920 + belatacept.
- Subjects with Banff Grade 2A lesions will be treated with corticosteroids, then re-biopsied (at investigator's discretion), and will continue treatment with VIB4920 +

belatacept if the repeat biopsy shows resolution of acute rejection or transitioned to standard of care immunosuppression for persistent or worsening lesions.

- Subjects with BPAR of Banff Grade ≥ 2B, or any antibody mediated rejection, must discontinue treatment with VIB4920, with subsequent management at the discretion of the investigator.

Following completion of all required evaluations at the Week 48 visit, subjects will be followed for an additional 12 weeks for safety while receiving standard of care management at the investigator's discretion.

7.2. Number of Subjects

Eligible patients (i.e., meeting all inclusion and exclusion criteria) will be included in the study until a total of 20 patients undergo the scheduled kidney transplant surgery with intention to treat with the revised "full-dose" regimen of Thymoglobulin, extended steroids, and an additional dose of VIB4920 on Day 3 or 4, *and* receive at least one dose of VIB4920.

7.3. Treatment Assignment

This is a single-arm, open-label exploratory study. All eligible patients will be treated with the same VIB4920/belatacept/Thymoglobulin/corticosteroids regimen detailed in Section 9.1.

7.4. Dose Adjustment Criteria

Not applicable.

7.5. Criteria for Study Termination

Periodic reviews of all available safety data will be conducted by the Sponsor. The Sponsor reserves the right to temporarily suspend or permanently terminate this study at any time. The reasons for temporarily suspending or permanently terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
2. Subject enrollment is unsatisfactory.
3. Non-compliance that might significantly jeopardize the validity or integrity of the study.
4. Sponsor decision to terminate development of the investigational product for this indication.

A decision to terminate may also be made by health authorities, regulatory bodies, or a specific Institutional Review Board (IRB) or ethics committee.

Figure 1: Study Design

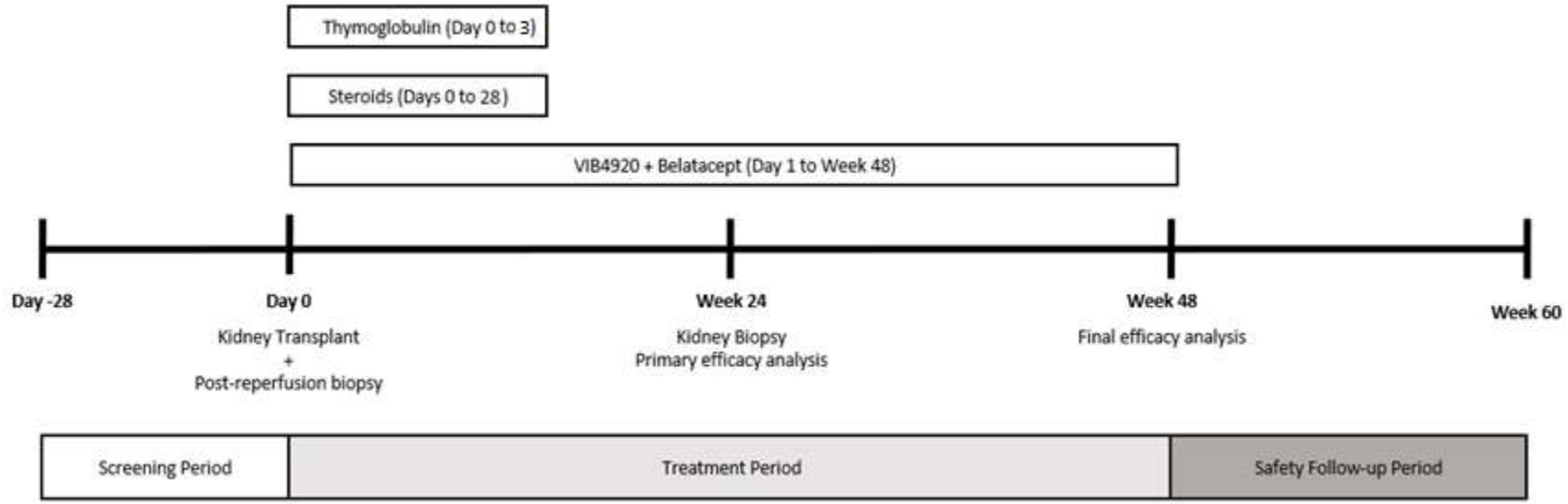

Table 2: Schedule of Assessments - Screening Period

Study Period	Screening Period
Visit Number	**V1**
Procedure / Study Day or Week	**Day -28 to -1**
Screening log	X
Informed consent/Assign SID number	X
Inclusion/exclusion criteria	X
Demographics[a]	X
Background – recipient[b]	X
Background – donor[c]	X
Medical history[d]	X
Viral serology – recipient[e]	X
Viral serology – donor[e]	X
QuantiFERON®-TB Gold[f]	X
Pregnancy test[g]	X
Vital signs[h]	X
Symptom-directed physical examination[i]	X
12-lead ECG	X
Hematology[j]	X
Blood chemistry[k]	X
Coagulation parameters[l]	X
CCI	[redacted]
[redacted] – [redacted]	X
CCI	X
Prior and concomitant meds[o]	X
Adverse Events[p]	X

[a] Date of birth, sex, race and ethnicity.

[b] The following recipient background information should be collected: end-stage renal disease leading to transplantation, current dialysis (none, hemodialysis, peritoneal dialysis) and dialysis start date, highest PRA, most recent PRA and HLA type.

[c] The following should be collected from donors: sex, race, ethnicity, transplant donor type (living related, living unrelated, deceased heart beating, deceased non-heart beating).

[d] Medical history includes all ongoing conditions and relevant/significant medical history (including all major hospitalizations and surgeries), as determined by the Investigator.

[e] Screening viral serology includes: CMV, EBV, HCV, HBsAg, HIV.

[f] The history of or active tuberculosis (TB) should be recorded. For recipients of living donor kidneys, a QuantiFERON®-TB Gold test should be performed at screening, unless previously treated for latent tuberculosis. Subjects with an indeterminate QuantiFERON®-TB Gold test result can repeat the test, but if the repeat test is also indeterminate, they are excluded. Other standard of care methods performed for determining the TB status (e.g., chest X-rays) are permitted.

[g] Serum hCGβ (females of childbearing potential only).

[h] Vital signs will include blood pressure, heart (pulse) rate, respiratory rate, and body temperature.

[i] At screening, a symptom-directed physical examination will be completed. Abnormalities will be recorded on the medical history eCRF page.

[j] The hematology panel will include a complete blood count, with differential (including basophils, eosinophils, lymphocytes, monocytes, and neutrophils), hemoglobin, hematocrit, platelets and white blood cell count.

[k] Chemistry and renal profile will include creatinine, blood urea nitrogen, fasting glucose, total protein and electrolytes (including sodium, potassium, chloride, calcium, bicarbonate and phosphorus). Hepatic profile will include albumin, total bilirubin, indirect bilirubin, AST, ALT, ALP and gamma glutamyl transferase.

[l] Coagulation parameters will include prothrombin time and partial thromboplastin time.

[m] [redacted]

[o] Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study. Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia-related medications, electrolytes and intravenous fluids, do not need to be collected. Any transplant related medications, such as immunosuppressive drugs, administered during this period should be collected.

[p] All AEs that occur between written informed consent signature and the end of the safety follow-up, whether or not related to the study drug, must be recorded in the eCRF. Note: allograft rejection is a primary study endpoint to be reported as a study outcome, not as an adverse event. Instances of acute rejection that meet serious criteria should be captured on the Suspected Acute Rejection and Kidney Allograft Biopsy eCRFs as outlined in Section 12.2. Non-serious electrolyte abnormalities requiring an intervention observed within 30 days of transplantation need not be recorded as adverse events. If the electrolyte abnormality or the therapeutic intervention to correct it meets criteria for a serious adverse event it must be reported as an SAE during the entire study.

Table 3: Schedule of Assessments – Treatment period (Day 0 to Week 24)

Study Period		Treatment Period (Day 0 to Week 24)											
Visit Number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Procedure [a]/ Study Day or Week	**Day 0**	**Day 1**	**Day 3 or 4**	**Day 7**	**Week 2 ± 1 day**	**Week 4 ± 2 days**	**Week 6 ± 2 days**	**Week 8 ± 2 days**	**Week 10 ± 2 days**	**Week 12 + 2 days**	**Week 16 ± 3 days**	**Week 20 ± 3 days**	**Week 24 + 3 days**
Inclusion/exclusion criteria	X[b]												
Thymoglobulin	**Day 0 to Day 3**												
Corticosteroids	**Day 0 to Day 28**												
VIB4920 administration[c]		X	X[e]		X	X	X	X	X	X	X	X	X
Belatacept administration		X[d]	X[e]		X	X		X		X	X	X	X
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[g]	X					X				X			X
12-lead ECG	X	X				X				X			X
Hematology[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunoglobulins[j]	X					X				X			X
Coagulation parameters[k]	X	X			X	X		X		X	X	X	X
Pregnancy test[l]	X					X		X		X	X	X	X
Urinalysis[m]		X				X		X		X			X
Spot UPCR[n]		X		X	X	X		X		X	X	X	X
BK polyoma viral load		X			X	X	X	X	X	X	X	X	X
CMV, EBV viral load		X				X		X		X			X
CCI [redacted]	X					X				X			X
CCI [redacted] – [redacted]	X				X	X				X			X
CCI [redacted]	X					X				X			X
Pharmacokinetics		X[q]	X[q]	X	X	X		X	X[q]	X	X		X
Immunogenicity[r]		X				X				X			X
CCI [redacted]	X	X	X	X	X	X		X	X	X	X		X
CCI [redacted]	X					X			X	X			X

CCI [redacted]	X					X				X			X
CCI [redacted]	X		X		X	X		X		X			X
Surveillance biopsy[v]	X												X
Prior and concomitant meds[w]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[x]	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Unless otherwise noted, blood collections to be drawn prior to therapeutic administration. Site staff will administer all study medications intravenously at the study center, except for prednisone (which will be self-administered by the subject at Day 4 through Day 28).

[b] Subject's eligibility to be reconfirmed prior to administration of Thymoglobulin and induction of anesthesia for transplant surgery on Day 0.

[c] Each subject must receive the entire volume of investigational product solution in the IV bag over 90 minutes (approximately 2.8 mL/min). VIB4920 should be administered prior to belatacept.

[d] First dose of belatacept on Day 1 to be given no sooner than 12 hours after the end of Thymoglobulin infusion.

[e] Second dose of belatacept+VIB4920 may be administered on Day 3 (instead of Day 4) to facilitate early hospital discharge, at investigator's discretion.

[f] Vital signs (BP, heart [pulse] rate, respiratory rate, and body temperature) will be obtained prior to the start of each VIB4920 infusion.

[g] A complete physical examination will include general appearance, skin, HEENT (head, ears, eyes, nose, throat), cardiovascular, pulmonary, abdomen, neurological, lymph nodes, spine and extremities (skeletal). As part of the physical examination, a clinical assessment will be performed and will include the evaluation of the subject for clinical signs of infection, allograft rejection, AEs, and change in renal function. Any abnormalities will be recorded on the Case Report Form (CRF). Clinically significant changes from baseline physical examination that are detected during follow-up will be recorded as an AE on the appropriate eCRF pages.

[h] Complete blood count, with differential (including basophils, eosinophils, lymphocytes, monocytes and neutrophils, hemoglobin, hematocrit, platelets and white blood cell count.

[i] Chemistry and renal profile (creatinine, blood urea nitrogen, fasting glucose, total protein and electrolytes [including sodium, potassium, chloride, calcium, bicarbonate, and phosphorus]). Hepatic profile will include albumin, total bilirubin, indirect bilirubin, AST, ALT, ALP and gamma glutamyl transferase.

[j] Total immunoglobulins, IgA, IgG and IgM.

[k] Coagulation parameters will include prothrombin time and partial thromboplastin time.

[l] Serum or urine hCGβ (females of childbearing potential only).

[m] Protein, glucose, blood, ketones, leukocytes, and pH by dipstick analysis. Microscopy (crystals, casts, white blood cells, red blood cells) will be performed if any abnormalities are observed.

[n] UPCR - quantitation of proteinuria and urine protein:creatinine ratio by spot urine.

[o] Blood CCI [redacted].

[p] Blood CCI [redacted]

[q] At V3, V4, V10, plasma samples for PK of VIB4920 to be taken predose and within 10 minutes after the end of infusion.

[r] Plasma samples for immunogenicity to be taken prior to administration of drug.

[s] Plasma and serum samples for CCI [redacted] Assessments include changes in CCI [redacted] and CCI [redacted].

[t] CCI [redacted], frozen, CCI [redacted].

[u] Blood CCI [redacted].

[v] Surveillance renal biopsies following reperfusion of the allograft on Day 0 and again at the end of Week 24. Where necessary to minimize any potential risk associated with the biopsy, a CT guided biopsy may be performed at the investigator's discretion in consultation with the medical monitor.

[w] Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study. Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia-related medications, electrolytes, and intravenous fluids,do not need to be collected. Any transplant related medications, such as immunosuppressive drugs, administered during this period should be collected.

[x] All SAEs that occur between written informed consent signature and the end of the safety follow-up, whether or not they are related to the study, must be recorded in the eCRF. Note: allograft rejection is a primary study endpoint to be reported as a study outcome, not as an adverse event. Instances of acute rejection that meet serious criteria should be captured on the Suspected Acute Rejection and Kidney Allograft Biopsy eCRFs as outlined in Section 12.2. Non-serious electrolyte abnormalities requiring an intervention observed within 30 days of transplantation need not be recorded as adverse events. If the electrolyte abnormality or the therapeutic intervention to correct it meets criteria for a serious adverse event it must be reported as an SAE during the entire study.

Table 4: Schedule of Assessments – Treatment period (Week 28 to Week 48) and Post-treatment Safety Follow-up

Study Period	Treatment Period (Week 28 to Week 48)							Post-treatment Safety Follow-up		
Visit Number	V15	V16	V17	V18	V19	V20	EOT	FU1	FU2	FU3/EOS
Procedure / Study Day or Week	Week 28 ± 3 days	Week 32 ± 3 days	Week 36 ± 3 days	Week 40 ± 3 days	Week 44 ± 3 days	Week 48 + 3 days		End of Treatment + 4 weeks (± 5 days)	End of Treatment + 8 weeks (± 5 days)	End of Treatment + 12 weeks (± 5 days)
Study drug administration[a]	X	X	X	X	X	X				
Vital signs[b]	X	X	X	X	X	X	X	X	X	X
Physical examination[c]	X		X			X	X	X		X
12-lead ECG	X		X			X	X			X
Hematology[d]	X	X	X	X	X	X	X	X	X	X
Blood chemistry[e]	X	X	X	X	X	X	X	X	X	X
Immunoglobulins[f]						X				X
Coagulation parameters[g]	X	X	X	X	X	X	X	X	X	X
Pregnancy test[h]	X	X	X	X	X	X	X			X
Urinalysis[i]		X				X	X	X	X	X
Spot UPCR[j]	X	X	X	X	X	X	X	X	X	X
BK polyoma viral load	X	X	X	X	X	X	X	X	X	X
CMV, EBV viral load			X			X	X			X
CCI [redacted]			X			X	X			X
CCI [redacted]			X			X	X		X	X
CCI [redacted]						X	X			X
Pharmacokinetics[m]	X		X	X		X	X		X	X
Immunogenicity[m]			X			X	X			X
CCI [redacted]	X		X	X		X	X		X	X
CCI [redacted]			X			X	X			X

CCI [redacted]			X			X	X			X
CCI [redacted]			X			X	X			X
Prior and concomitant meds[q]	X	X	X	X	X	X	X	X	X	X
Adverse events[r]	X	X	X	X	X	X	X	X	X	X

[a] Study drug during Week 28 to Week 48 refers to dual treatment with VIB4920 + belatacept.

[b] Vital signs (BP, heart [pulse] rate, respiratory rate, and body temperature) will be obtained prior to the start of each VIB4920 infusion.

[c] A complete physical examination will include general appearance, skin, HEENT (head, ears, eyes, nose, throat), cardiovascular, pulmonary, abdomen, neurological, lymph nodes, spine and extremities (skeletal). As part of the physical examination, a clinical assessment will be performed and will include the evaluation of the subject for clinical signs of infection, allograft rejection, AEs, and change in renal function. Any abnormalities will be recorded on the Case Report Form (CRF). Clinically significant changes from baseline physical examination that are detected during follow-up will be recorded as an AE on the appropriate eCRF pages.

[d] Complete blood count, with differential (including basophils, eosinophils, lymphocytes, monocytes and neutrophils, hemoglobin, hematocrit, platelets and white blood cell count

[e] Chemistry and renal profile (creatinine, blood urea nitrogen, fasting glucose, total protein and electrolytes [including sodium, potassium, chloride, calcium, bicarbonate, and phosphorus]). Hepatic profile will include albumin, total bilirubin, indirect bilirubin, AST, ALT, ALP and gamma glutamyl transferase.

[f] Total immunoglobulins, IgA, IgG and IgM

[g] Coagulation parameters will include prothrombin time and partial thromboplastin time.

[h] Serum or urine hCGβ (females of childbearing potential only).

[i] Protein, glucose, blood, ketones, leukocytes, and pH by dipstick analysis. Microscopy (crystals, casts, white blood cells, red blood cells) will be performed if any abnormalities are observed.

[j] UPCR - Quantitation of proteinuria and urine protein:creatinine ratio by spot urine.

[k] Blood draw into CytoChex tubes for flow cytometry on whole blood.

[l] Blood draw into EDTA tubes for flow cytometry on PBMCs.

[m] Plasma samples for PK and immunogenicity to be taken prior to administration of drug.

[n] Plasma and serum samples for CCI [redacted] Assessments include changes in CCI [redacted] and CCI [redacted] pathway.

[o] CCI [redacted], frozen, CCI [redacted], when feasible, with additional CCI [redacted].

[p] Blood CCI [redacted].

[q] Prior and concomitant meds will be recorded from 30 days prior to administration of VIB4920 and through the end of the study. Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia-related medications, electrolytes, and intravenous fluids, do not need to be collected. Any transplant related medications, such as immunosuppressive drugs, administered during this period should be collected.

[r] All AEs that occur between written informed consent signature and the end of the safety follow-up, whether or not they are related to the study, must be recorded in the eCRF. Note: allograft rejection is a primary study endpoint to be reported as a study outcome, not as an adverse event. Instances of acute rejection that meet serious criteria should be captured on the Suspected Acute Rejection and Kidney Allograft Biopsy eCRFs as outlined in Section 12.2. Non-serious electrolyte abnormalities requiring an intervention observed within 30 days of transplantation need not be recorded as adverse events. If the electrolyte abnormality or the therapeutic intervention to correct it meets criteria for a serious adverse event it must be reported as an SAE during the entire study.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study inclusion:

1. Written informed consent and any locally required authorization (e.g., data privacy) obtained from the patient prior to performing any protocol-related procedures, including screening evaluations.
2. Male or female recipients aged 18-70.
3. Recipients of a first renal transplant from a standard criteria deceased, living unrelated or HLA non-identical living related donor.
4. Recipients who are at low immunologic risk:
    a. No DSA, and
    b. Negative cross-match testing (by T- and B- cell flow or by virtual cross-match).
5. Recipients with up to date vaccination as per local immunization schedules.
6. A female subject is eligible if she is:
    a. Not pregnant or nursing.
    b. Of non-childbearing potential (i.e., post-menopausal defined as having been amenorrheic for at least 1 year prior to screening, or has had a bilateral tubal ligation at least 6 months prior to screening, or has had a bilateral oophorectomy or hysterectomy).
    c. Of childbearing potential, must have a negative serum pregnancy test within 48 hours prior to surgery and be using an effective method of contraception (per site specific recommendations) which must be continued for at least 6 months after the final dose of investigational product.
7. Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide from Day 0 through to the end of the study and must agree to continue using such precautions for at least 6 months after the final dose of investigational product.

8.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria will be considered ineligible for this study:

1. Patients receiving an allograft from an ABO-incompatible donor.
2. Patients treated with systemic immunosuppressive drug therapy for more than a total of 2 weeks within 24 weeks prior to ICF signature.
3. Patients who have undergone lymphodepleting therapy (e.g., Thymoglobulin, alemtuzumab).
4. Patients with known immunodeficiency.

5. Patients with medical history of confirmed venous thromboembolism, arterial thrombosis, coagulopathy or known platelet disorders.
6. Patients with risk factors for venous thromboembolism or arterial thrombosis (e.g., immobilization or major surgery within 12 weeks before screening), prothrombotic status (including but not limited to congenital or inherited deficiency of antithrombin III, protein C, protein S, or confirmed diagnosis of antiphospholipid syndrome).
7. Patients requiring treatment with antithrombotic drugs (clopidogrel, prasugrel, warfarin, others). Low-dose aspirin treatment (up to 100 mg/day) is allowed.
8. Patients requiring long-term systemic anticoagulation after transplantation, which would interfere with obtaining biopsies.
9. Patients with poor vascular access such that IV administration of the study medications may be compromised.
10. Patients with any contraindication to kidney biopsy.
11. CMV-seronegative recipients of a CMV-seropositive donor kidney, or unknown CMV serostatus.
12. EBV-seronegative or with unknown EBV serostatus.
13. Receipt of live (attenuated) vaccine within the 4 weeks before screening.
14. Patients with high potential of graft loss due to recurrence of underlying kidney disease.
15. Prior solid organ transplant or potential to require a concurrent organ or cell transplant.
16. Previous treatment with belatacept.
17. Previous treatment with CD40 or anti-CD40L agents.
18. Use of B depleting therapy (e.g., rituximab), non-depleting B cell directed therapy (e.g., belimumab) or abatacept within 1 year prior to enrollment.
19. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
20. At screening blood tests, any of the following:
    a. Aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN)
    b. Alanine aminotransferase (ALT) > 2.5 × ULN
    c. Alkaline phosphatase (ALP) > 2.5 × ULN
    d. Total bilirubin (TBL) > 2 × ULN
    e. Hemoglobin < 75 g/L
    f. Neutrophils < 1.5×10^9/L
    g. Platelets < 100×10^9/L
21. Patients with severe systemic infections, current or within the 2 weeks prior to transplant surgery.
22. Positive test for chronic hepatitis B infection at screening or within the last 12 months, defined as either (1) positive hepatitis B surface antigen [HBsAg] or (2) a positive hepatitis B core antibody [anti-HBc] PLUS negative hepatitis B surface antibody [anti-

HBs]. Note that subjects with a positive anti-HBs ONLY or a positive anti-HBc PLUS positive anti-HBs AND negative HBsAg are eligible to enroll.

23. Positive test for hepatitis C virus antibody at screening or within the last 12 months.
24. Positive test for HIV antibody at screening or within the last 12 months.
25. History of or active tuberculosis (TB), or a positive QuantiFERON®-TB Gold test at screening (for recipients of living donor kidneys), unless previously treated for latent tuberculosis. Subjects with an indeterminate QuantiFERON®-TB Gold test result can repeat the test, but if the repeat test is also indeterminate, they are excluded. Other standard of care methods performed for determining the TB status (e.g., chest X-rays) are permitted.
26. History of cancer, except as follows:
    a. In situ carcinoma of the cervix treated with apparent success with curative therapy > 12 months prior to screening; or
    b. Cutaneous basal cell or squamous cell carcinoma treated with apparent success with curative therapy
27. Any severe cardiovascular, respiratory, endocrine, gastrointestinal, hematological, neurological, psychiatric, or systemic disorder that could impact the evaluation of safety and efficacy assessments or affect the subject's ability to participate in the study or the subject's safety.
28. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.
29. Lactating or pregnant females or females who intend to become pregnant anytime from signing the informed consent form (ICF) through 6 months after receiving the last dose of investigational product
30. Known history of severe allergy or reaction to any component of the investigational product formulation or to any other biologic therapy.
31. Unwilling or unable to comply with the protocol, complete study assessments, and complete the study period.

8.3. Reasons for permanent study drug discontinuation

Study drug must be discontinued if the investigator determines that continuing it would result in a significant safety risk for that subject. Reasons for study drug discontinuation are or can be:

1. Failure to undergo the scheduled kidney transplant surgery.
2. Acute rejection of Banff Grade ≤ 2A that is not responsive to treatment with an adequate course of IV corticosteroids.
3. Any acute rejection of Banff Grade ≥ 2B or any antibody-mediated rejection.
4. Subjects with graft loss must discontinue treatment with VIB4920. The allograft will be presumed to be lost based on whichever of the following occurs first: the day the subject starts dialysis and is not able to subsequently be removed from dialysis (for a period of at

least 56 consecutive days), the day of nephrectomy, or the day reversible loss of graft perfusion is demonstrated by appropriate imaging techniques. Primary graft non-function is a subset of graft loss.

5. Withdrawal of consent from the study.
6. Withdrawal of consent from further treatment with investigational product.
7. AE or significant laboratory abnormality that, in the opinion of the investigator and/or the sponsor, warrants discontinuation of further dosing.
8. Pregnancy or a decision to become pregnant.
9. Hepatic function abnormality defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN related to VIB4920.
10. Anaphylaxis or a serious hypersensitivity reaction attributed to VIB4920.
11. Any life-threatening or serious infection or opportunistic infection.
12. Malignancy.

Subjects who prematurely discontinue study drug will undergo an EOT visit and all Week 48 safety assessments at the time of discontinuation. Subjects who discontinue study drug should NOT be considered withdrawn from the study until the Week 48 visit or until completion of the follow up period. A Study Drug Discontinuation form should be completed, giving the date and primary reason for stopping study treatment.

For subjects who withdraw prematurely from the study, the reason(s) for withdrawal must be recorded on the appropriate page of the eCRF. If possible, any subject who is withdrawn from the study will have, at the time of withdrawal, all exit procedures performed (i.e., Week 48 safety assessments). All clinically significant abnormalities will be followed-up, if possible, until resolved to the satisfaction of the Investigator.

Eligible subjects who fail to undergo the scheduled kidney transplant surgery and those who prematurely terminate study participation without receiving any dose of VIB4920 will be replaced. Subjects who prematurely terminate study participation for any other reason will not be replaced.

For subjects who are lost to follow-up (i.e. those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

8.4. Withdrawal of Informed Consent for Data and Biological Samples

8.4.1. Biological Samples

Study data are protected by the use of a SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject’s consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used

by the Sponsor but no new samples will be collected unless specifically required to monitor safety of the subject.

8.4.2. Samples Obtained for Future Research

Samples obtained for future research will be labeled with a sample identification number. If the subject withdraws consent for participating in future research, the sponsor will locate the subject's sample and destroy it.

If the subject consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drugs

All subjects will be treated with the same immunosuppression regimen consisting of:

- Thymoglobulin 1.5 mg/kg by IV infusion prior to reperfusion of the allograft on the day of transplantation surgery (Day 0), prior to VIB4920+belatacept infusion on post-op Day 1, on post-op Day 2, and prior to VIB4920+belatacept infusion on post-op Day 3 or 4. Adjustments in the total dose of 6 mg/kg or frequency of delivery are allowed for clinical cause (i.e., thrombocytopenia). Reasons for adjustments should be clearly stated in the medical record and appropriate case report form.
- Methylprednisolone by IV infusion (500, 250, 125 and 60 mg on Days 0, 1, 2 and 3, respectively) followed by oral administration of prednisone 30 mg per day on Days 4, 5, 6 and 7. Subjects may be tapered to at least 20 mg per day on Day 8, to at least 10 mg per day on Day 15, and to at least 5 mg per day on Day 22. Discontinuation of prednisone should occur following the post-op Day 28 visit.
- VIB4920 1500 mg by IV infusion on post-op Day 1, repeated on post-op Day 3 or 4 (timing is at investigator's discretion, Week 2, and at the end of Weeks 4, 6, 8 and 10; then 1500 mg every four weeks from Week 12 to Week 48.
- Belatacept 10 mg/kg by IV infusion on post-op Day 1 (1st dose ≥12 hours after Thymoglobulin infusion ends), repeated on post-op Day 3 or 4 (timing is at

investigator's discretion), and at the end of Weeks 2, 4, 8 and 12; then 5 mg/kg IV every four weeks from Week 16 to Week 48.

VIB4920 should be administered prior to belatacept. Timings of administration of each drug should be recorded.

The treatment schedule is represented in Table 5.

Table 5: Treatment Schedule

	D0 – Day of transplant	D1	D2	D3	D4	D5-D7	W2	W3	W4 ± 2 days	W6 ± 2 days	W8 ± 2 days	W10 ± 2 days
Thymoglobulin	1.5 mg/kg[a]	1.5 mg/kg[a]	1.5 mg/kg[a]	1.5 mg/kg[a]								
Methylprednisolone	500 mg	250 mg	125 mg	60 mg	30 mg[c]	30 mg[c]	20 mg[c]	10 mg[c]	5 mg[c]			
VIB4920		1500 mg		1500 mg[d]			1500 mg		1500 mg	1500 mg	1500 mg	1500 mg
Belatacept		10 mg/kg[b]		10 mg/kg[d]			10 mg/kg		10 mg/kg		10 mg/kg	

	W12 ± 2 days	W16 ± 3 days	W20 ± 3 days	W24 ± 3 days	W28 ± 3 days	W32 ± 3 days	W36 ± 3 days	W40 ± 3 days	W44 ± 3 days	W48 ± 3 days
Thymoglobulin										
Methylprednisolone										
VIB4920	1500 mg	1500 mg	1500 mg	1500 mg	1500 mg	1500 mg	1500 mg	1500 mg	1500 mg	1500 mg
Belatacept	10 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg

Site staff will administer all study medications intravenously at the study center except for prednisone (which will be self-administered by the subject at Day 4 through Day 28)

[a] Thymoglobulin daily dose of 1.5 mg/kg. Adjustments in the total dose of 6 mg/kg or frequency of delivery are allowed for clinical cause (i.e., thrombocytopenia). Reasons for adjustments should be clearly stated in the medical record and appropriate case report form.

[b] Belatacept 1st dose ≥12 hours after Thymoglobulin infusion ends

[c] Oral prednisone (self-administered by the subject) 30 mg/day on Day 4, 5, 6 and 7. Subjects may be tapered to at least 20 mg/day on Day 8, to at least 10 mg/day on Day 15, and to at least 5 mg/day on Day 22. Discontinuation of prednisone should occur following the post-op Day 28 visit.

[d] Belatacept+VIB4920 2nd dose on Day 3 or 4, at investigator's discretion

9.2. Concomitant Medications

Details regarding the name, medical indication, dose, route, and frequency of all prescription medications, over-the-counter medications, or alternative therapies taken within 30 days prior to administration of VIB4920 and through the end of the study will be recorded. Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia related medications, electrolytes, and intravenous fluids, do not need to be collected. Any transplant related medications, such as immunosuppressive drugs, administered during this period should be collected.

9.3. Prohibited Medications

The following concomitant medications are prohibited throughout the study:

- Non-protocol specified immunosuppressives such as tacrolimus, cyclosporine, sirolimus, everolimus, azathioprine, MMF, mycophenolic acid, basiliximab, alemtuzumab, intravenous immunoglobulins or any other immunosuppressive for the prophylaxis of acute rejection which is or may become available on the market during the course of the study. However, as specified in the protocol, patients who develop grades of acute cellular or antibody medicated rejection that require alternative treatment may be withdrawn from the study regimen and treated as necessary.
- Investigational drug therapy other than VIB4920.
- Live (attenuated) vaccine. Immunization with any live or live attenuated vaccine (i.e., measles, mumps, rubella and polio vaccine, Bacillus Calmette-Guerin, typhoid, yellow fever, cold adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) is specifically excluded during the treatment period.
- Biologics such as cytokine inhibitors, cytokine receptor inhibitors, B-cell depleting agents, etc.

Use of any prohibited medication during the study will be recorded in the eCRF. Additionally, administration or subsequent changes (increased or decreased in dose and/or frequency) in all medications will be recorded in the eCRF throughout the study.

9.4. Treatment Compliance

Site staff will administer all study medications intravenously at the study center, except for prednisone (which will be self-administered by the subject at Days 4, 5 and 6). The dose and date of administration of each study medication must be recorded in the subject's eCRF. Treatment compliance for IV infused medications will be assessed based on this information. For oral prednisone, compliance will be assessed based on drug accountability (subjects will be required to return any unused medication at the following visit).

9.5. Randomization and Blinding

This is a single-arm, open-label study. No randomization or blinding will be used.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. VIB4920

VIB4920 is a CD40L antagonist comprised of two identical Tn3 modules fused to human serum albumin (HSA). Each Tn3 is an engineered form of the third Fn3 protein domain of human Tenascin C. Polyglycine linkers join the two Tn3 domains, and the second Tn3 domain to the HSA protein. Each Tn3 binds specifically to human CD40L and inhibits its interaction with human CD40.

Each vial contains a nominal 500 mg of VIB4920. VIB4920 is formulated at 100 mg/mL in 10 mM sodium monobasic/dibasic phosphate buffer, 250 mM sucrose, and 0.02% (weight/volume [w/v]) poloxamer 188, pH 7.4.

10.1.1. VIB4920 Packaging and Labeling

The investigational product will be appropriately labeled in accordance with national laws and regulations.

VIB4920 is provided with three vials per kit.

10.1.2. VIB4920 Storage

All investigational product (VIB4920) supplied should not be shaken and requires no special biohazard handling. The investigational product must be stored at 2ºC to 8ºC (36ºF to 46ºF) in refrigerator with adequate temperature monitoring. Investigational product must not be frozen. It should be stored in the original outer package in a location with limited access.

10.1.3. VIB4920 Inspection

Each vial selected for dose preparation should be inspected. If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section for further instructions (Section 10.1.7).

10.1.4. VIB4920 Preparation

The investigational product is supplied as a sterile liquid in a 6R glass vial at a nominal fill volume of 5.0 mL, stoppered with siliconized 20 mm Teflon-coated elastomeric stopper, and sealed with flip-off cap overseal.

10.1.4.1. Dose Preparation Steps

No incompatibilities between VIB4920 and the components recommended for IV infusion (i.e., polyolefin IV bags for IV infusion, non-diethylhexyl phthalate infusion lines, and syringes used for dose preparation) have been observed.

VIB4920 does not contain preservatives and any unused portions must be discarded. Preparation of investigational product and IV bags is to be performed aseptically. Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE. If storage time exceeds these limits, a new dose must be prepared from new vials.

Three vials, one 250 mL IV bag containing 0.9% (w/v) saline (weight/volume [w/v]), and one IV infusion pump is required for administration of each 1500 mg dose of VIB4920.

The dose preparation steps are as follows:

1. For each 1500 mg IV dose, 15.0 mL of 0.9% saline should be removed from a prefilled 250 mL IV.
2. 15.0 mL of VIB4920 will be obtained from three (3) 500 mg vials by withdrawing 5.0 mL from each vial. Use a new needle for each withdrawal.
3. Investigational product should be added to the saline bag.
4. Gently mix the contents of the IV bag. The saline bag should then be inspected to ensure the solution is clear.

During preparation of the investigational product for infusion, the capacity of the tubing should be calculated in order to adjust the volume of investigational product solution needed to prime the IV tubing. This step is also necessary because the same volume of saline will be needed to flush the IV tubing at the completion of the infusion in order to deliver the complete volume of investigational product solution. Because the IV tubing contains investigational product solution, the saline flush must be infused using the same infusion rate as that used for the investigational product solution in the infusion bag.
For example, if the IV tubing capacity is 15 mL, the IV tubing should be primed with 15 mL of investigational product solution from the infusion bag before initiating the infusion. Once the infusion bag is empty, the IV tubing should be flushed with at least 15 mL of 0.9% saline (w/v) via the infusion pump at the same rate as dosing.

The start time of the infusion will be the time when infusion of the investigational product solution from the infusion bag (with IV tubing primed with investigational product solution) is started. The stop time of the infusion will be the time when the IV tubing has been flushed with a volume of 0.9% normal saline equivalent to IV tubing capacity (e.g., 15 mL for the example above) to administer the residual investigational product solution.

10.1.4.2. Intravenous administration

An experienced and qualified staff member will place the IV access.

VIB4920 will be infused using an IV infusion pump. Each subject must receive the entire volume of investigational product solution in the IV bag over at least 90 minutes (approximately 2.8 mL/min). Investigational product must be infused through a low-protein binding 0.2- or 0.22-μm in-line filter. Vital signs will be obtained prior to the start of each VIB4920 infusion.

A physician must be present at the site or immediately available to respond to emergencies during administration of investigational product. Fully functional resuscitation facilities should be available.

Further information on VIB4920 preparation and administration is provided in the IP Manual.

10.1.5. VIB4920 Accountability

Study site staff will maintain a record of the investigational product received, dispensed, administered and destroyed. All records will be maintained with controlled access. A study monitor will perform drug accountability and compliance monitoring during the study.

The Investigator will administer the study product only to subjects included in this study and according to the procedures established in this study protocol. Each administration of study product will be documented and transferred to the eCRF.

10.1.6. VIB4920 Handling and Disposal

The Investigator or designee must return any unused vials of VIB4920 to Viela Bio, Inc. or designee regardless of whether the study was completed or terminated prematurely. At the time of return, the Investigator must verify that unused or partially used study products have been returned and that no study products remain at the site. As an alternative to returning unused study product at the end of the study, the Investigator may destroy unused study medication on site with agreement from Viela Bio, Inc.

10.1.7. Reporting Product Complaints

Any defects with the investigational product must be reported immediately to the Viela Bio, Inc. Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to Viela Bio, Inc. and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

Viela Bio, Inc. contact information for reporting product complaints:

Email: ClinicalProductComplaints@horizontherapeutics.com

Phone: 1-866-479-6742

10.2. Belatacept

10.2.1. Supply

Belatacept (NULOJIX®) lyophilized powder for intravenous infusion will be dispensed by the site's hospital pharmacy. NULOJIX® is supplied as a single-use vial with a silicone-free disposable syringe in the following packaging configuration (Food and Drug Administration 2017):

Description		NDC Number
One 250-mg vial	One 12 mL Syringe	0003-0371-13

10.2.2. Storage/Handling

NULOJIX® must be stored refrigerated at 2°-8°C (36°-46°F). Protect NULOJIX® from light by storing in the original package until time of use.

The reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately. The NULOJIX® infusion must be completed within 24 hours of constitution of the NULOJIX® lyophilized powder. If not used immediately, the infusion solution may be stored under refrigeration conditions: 2°-8°C (36°-46°F) and protected from light for up to 24 hours (a maximum of 4 hours of the total 24 hours can be at room temperature: 20°-25°C [68°-77°F] and room light).

10.2.3. Preparation for Administration

If the silicone-free disposable syringe is dropped or becomes contaminated, use a new silicone-free disposable syringe from inventory.

1. Calculate the number of NULOJIX® vials required to provide the total infusion dose. Each vial contains 250 mg of belatacept lyophilized powder.
2. Reconstitute the contents of each vial of NULOJIX® with 10.5 mL of a suitable diluent using the silicone-free disposable syringe provided with each vial and an 18- to 21-gauge needle.

   Suitable diluents include: sterile water for injection (SWFI), 0.9% sodium chloride (NS), or 5% dextrose in water (D5W). Note: If the NULOJIX® powder is accidentally reconstituted using a different syringe than the one provided, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.
3. To reconstitute the NULOJIX® powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of diluent (10.5 mL of SWFI, NS, or D5W) to the glass wall of the vial.
4. To minimize foam formation, rotate the vial and invert with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. Do not shake.
5. The reconstituted solution contains a belatacept concentration of 25 mg/mL and should be clear to slightly opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.
6. Calculate the total volume of the reconstituted 25 mg/mL NULOJIX® solution required to provide the total infusion dose. Volume of 25 mg/mL NULOJIX® solution (in mL) = Prescribed Dose (in mg) ÷ 25 mg/mL
7. Prior to intravenous infusion, the required volume of the reconstituted NULOJIX® solution must be further diluted with a suitable infusion fluid (NS or D5W). NULOJIX® reconstituted with:
   - SWFI should be further diluted with either NS or D5W
   - NS should be further diluted with NS
   - D5W should be further diluted with D5W
8. From the appropriate size infusion bag or bottle, withdraw a volume of infusion fluid that is equal to the volume of the reconstituted NULOJIX® solution required to provide the prescribed dose. With the same silicone-free disposable syringe used for reconstitution,

withdraw the required amount of belatacept solution from the vial, inject it into the infusion bag or bottle, and gently rotate the infusion bag or bottle to ensure mixing.

The final belatacept concentration in the infusion bag or bottle should range from 2 mg/mL to 10 mg/mL. Typically, an infusion volume of 100 mL will be appropriate for most patients and doses, but total infusion volumes ranging from 50 mL to 250 mL may be used. Any unused solution remaining in the vials must be discarded.

9. Prior to administration, the NULOJIX® infusion should be inspected visually for particulate matter and discoloration. Discard the infusion if any particulate matter or discoloration is observed.
10. The entire NULOJIX® infusion should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2-1.2 μm).
    - The reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately. The NULOJIX® infusion must be completed within 24 hours of reconstitution of the NULOJIX® lyophilized powder. If not used immediately, the infusion solution may be stored under refrigeration conditions: 2°-8°C (36°-46°F) and protected from light for up to 24 hours (a maximum of 4 hours of the total 24 hours can be at room temperature: 20°-25°C [68°-77°F] and room light).
    - Infuse NULOJIX® in a separate line from other concomitantly infused agents. NULOJIX® should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of NULOJIX® with other agents.
    - VIB4920 should be administered prior to belatacept. Timings of administration of each drug should be recorded.

10.3. Thymoglobulin

10.3.1. Supply

Thymoglobulin will be dispensed by the site's hospital pharmacy. Thymoglobulin is supplied as a single-use clear glass 10 mL vial containing 25 mg of lyophilized (solid) Thymoglobulin. Each carton contains one Thymoglobulin vial (NDC 58468-0080-1) (Food and Drug Administration 2017).

10.3.2. Storage/Handling

- Store in refrigerator at 2°C to 8°C (36°F to 46°F).
- Protect from light.
- Do not freeze.
- Do not use after the expiration date indicated on the label.
- Reconstituted Thymoglobulin is physically and chemically stable for up to 24 hours at room temperature; however, room temperature storage is not recommended. As

Thymoglobulin contains no preservatives, reconstituted product should be used immediately.

- Infusion solutions of Thymoglobulin must be used immediately.
- Any unused drug remaining after infusion must be discarded.

10.3.3. Instructions for Dilution and Administration

10.3.3.1. Reconstitution

After calculating the number of vials needed, using aseptic technique, reconstitute each vial of Thymoglobulin with 5 mL of SWFI, USP.

1. Allow Thymoglobulin vials to reach room temperature before reconstituting the lyophilized product.
2. Aseptically remove caps to expose rubber stoppers.
3. Clean stoppers with germicidal or alcohol swab.
4. Aseptically reconstitute each vial of Thymoglobulin lyophilized powder with the 5 mL of SWFI.
5. Rotate vial gently until powder is completely dissolved. Each reconstituted vial contains 25 mg or 5 mg/mL of Thymoglobulin.
6. Inspect solution for particulate matter after reconstitution. Should some particulate matter remain, continue to gently rotate the vial until no particulate matter is visible. If particulate matter persists, discard this vial.

10.3.3.2. Dilution

1. Transfer the contents of the calculated number of Thymoglobulin vials into the bag of infusion solution (saline or dextrose). Recommended volume: per one vial of Thymoglobulin use 50 mL of infusion solution (total volume usually between 50 to 500 mL)
2. Mix the solution by inverting the bag gently only once or twice.

10.3.3.3. Infusion

Administer Thymoglobulin under strict medical supervision in a hospital setting, and carefully monitor patients during the infusion.

Thymoglobulin is less likely to produce side effects when administered at the recommended flow rate.

1. Follow the manufacturer’s instructions for the infusion administration set. Infuse through a 0.22 micrometer filter into a high-flow vein.
2. Set the flow rate to deliver the dose over a minimum of 6 hours for the single dose.

10.4. Corticosteroids

Corticosteroids (methylprednisolone and prednisone) will be dispensed by the hospital pharmacy and administered in the protocol-specified dose regimen.

11. STUDY ASSESSMENTS AND PROCEDURES

11.1.1. Informed Consent

All candidates for enrollment or legally authorized representative will sign an ICF prior to any screening activities. Informed consent must be obtained by the principal investigator or a designee, such as a sub-investigator, with IRB-approved qualifications.

Each patient must be given the opportunity to ask questions and to understand the details of study participation.

The consent process must be recorded in the subject's source documents and evidenced by the patient signing the ICF.

After signing the ICF, each subject will be assigned an identification number that will be used on all subject documentation. Numbers will be assigned in ascending sequential order. This number will also correspond to the subject number entered on test materials.

11.1.2. Demographic/Medical History

Demographic information to be collected includes date of birth, sex, race and ethnicity.

Medical history information to be collected includes all ongoing conditions and relevant/significant medical history (including all major hospitalizations and surgeries), as determined by the Investigator.

11.1.3. Background (donor and recipient)

The following background information should be collected from donors: sex, race, ethnicity, transplant donor type (living related, living unrelated, deceased heart beating, deceased non-heart beating).

The following recipient background information should be collected: end-stage renal disease leading to transplantation, current dialysis (none, hemodialysis, peritoneal dialysis) and dialysis start date, highest Panel Reactive Antibody (PRA) test, most recent PRA and HLA type.

11.1.4. Vital Signs

Vital signs including systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (RR) (breaths/min), body temperature (ºC) and body weight (kg) will be measured using clinically acceptable methods and devices as defined in the schedule of events and IP Administration manual.

11.1.5. Physical Examination

A complete physical examination will be completed at screening, while symptom-directed physical examinations will be performed thereafter, as specified in the Schedule of Assessments.

A complete physical examination will include the examination of the following body systems: general appearance, skin, HEENT (head, ears, eyes, nose, throat), cardiovascular, pulmonary, abdomen, neurological, lymph nodes, spine and extremities (skeletal). As part of the complete physical examination, a clinical assessment will be performed and will include the evaluation of the subject for clinical signs of infection, allograft rejection, AEs, and change in renal function. Any abnormalities will be recorded on the Case Report Form (CRF). At screening, abnormalities will be recorded on the medical history eCRF page. Clinically significant changes from baseline physical examination that are detected during follow-up will be recorded as an AE on the appropriate eCRF pages.

11.1.6. Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be performed. Each ECG will include ventricular heart rate and intervals (PR, QRS, QT, QTc). The PI will be responsible for providing an interpretation of the ECGs in terms of clinical significance to the subject (i.e., normal, abnormal but not clinically significant, abnormal and clinically significant.). Any abnormalities and clinical significance will be entered on the eCRF.

11.1.7. Laboratory Assessments

Blood and urine samples will be collected for laboratory safety tests as specified in the Schedule of Assessments. Laboratory testing is described below. For further details regarding laboratory assessments see the Study Laboratory Manual.

11.1.7.1 Hematology

The hematology panel will include a complete blood count, with differential (including basophils, eosinophils, lymphocytes, monocytes, and neutrophils), hemoglobin, hematocrit, platelets and white blood cell count.

11.1.7.2 Blood Chemistry

Chemistry and Renal Profile:

- Creatinine, blood urea nitrogen, fasting glucose, total protein and electrolytes (including sodium, potassium, chloride, calcium, bicarbonate, and phosphorus)

Hepatic Profile:

- Albumin, total bilirubin, indirect bilirubin, AST, ALT, alkaline phosphatase (ALP), and gamma glutamyl transferase.

11.1.7.3 Immunoglobulins

- Total immunoglobulins, IgA, IgG and IgM.

11.1.7.4. Coagulation Parameters

Prothrombin time and partial thromboplastin time will be assessed.

11.1.7.5. Urinalysis

The urinalysis will include protein, glucose, blood, ketones, leukocytes, and pH by dipstick analysis. Microscopy (crystals, casts, white blood cells, red blood cells) will also be performed if any abnormalities are observed.

11.1.8. Viral Serology

Serological tests for exposure to CMV, EBV, hepatitis C virus (HCV), HBsAg and HIV will be performed for recipient and donor at screening, if not conducted within the previous 12 months. Additionally, viral monitoring for BK polyoma virus, CMV and EBV will be conducted throughout the study, as specified in the Schedule of Assessments (Table 3 and

Table 4).

11.1.9. Pregnancy Screen

Serum human chorionic gonadotrophin beta (hCGβ) pregnancy test(s) will be completed for all females of childbearing potential during the screening period (before Day 0). Females screened within 1 week prior to Day 0 will not need to repeat the pregnancy test as part of the reconfirmation of eligibility. In the post-transplant period, serum or urine hCGβ pregnancy tests (at the investigator's discretion) will be performed as specified in the Schedule of Assessments (Table 3 and

Table 4).

11.1.10. Spot Urine Protein Creatinine Ratio

Quantitation of proteinuria and urine protein:creatinine ratio by spot urine sampling will be performed as specified in the Schedule of Assessments (Table 3 and

Table 4).

11.1.11. Renal Function

Renal function by CCI [redacted] will be assessed at each study visit.

11.1.12. CCI [redacted]

CCI [redacted] will be collected from CCI [redacted] as designated in CCI [redacted] and

CCI [redacted] may include, but is not limited to, CCI [redacted] Details on drawing, handling, and shipping CCI [redacted] will be detailed in the study Lab Manual.

11.1.13. Pharmacokinetics

Plasma samples to determine the concentration of VIB4920 will be taken according to the visits specified in the Schedule of Assessments (Table 3 and

Table 4) and measured using a validated immunoassay. Note: Samples for PK at V3, V4 and V10 are to be taken predose and within 10 minutes after the end of infusion.

11.1.14. CCI

CCI will be performed to CCI in CCI, as specified in the Schedule of Assessments (Table 2, Table 3, and

Table 4). Blood will be CCI for processing to CCI

11.1.15. CCI

CCI will be collected at the timepoints specified in the Schedule of Assessments (Table 2, Table 3, and

Table 4) for the CCI

11.1.16. Immunogenicity

Plasma samples for immunogenicity (anti-drug antibodies to VIB4920) will be taken prior to drug administration according to the visits specified in Table 3 and

Table 4 and assessed using a validated immunoassay.

11.1.17. CCI

Plasma, serum, and urine samples will be collected according to the visits specified in Table 3 and

Table 4. Assessments include changes in CCI and CCI

11.1.18. CCI

A blood sample will be collected CCI The CCI may be used for CCI and CCI, by tests including but not limited to CCI

11.1.19. Estimate of Blood Volume to be Collected Per Study Visit

The estimated volume of blood to be collected from each subject at each visit (and across all visits) from screening to the last visit of the Safety Follow-up (FU3) is presented in Table 6. If repeats of any blood tests are required, the volume of blood collection will increase accordingly.

Table 6: Estimate of Total Blood Volume to be collected per study visit

Study Period	Approximate Volume (mL)
Screening Period	42
Day 0	64
Day 1	43
Day 3 or 4	31
Day 7	23
Week 2 ± 1 day	40
Week 4 ± 2 days	82
Week 6 ± 2 days	12
Week 8 ± 2 days	45
Week 10 ± 2 days	29
Week 12 + 2 days	82
Week 16 ± 3 days	32
Week 20 ± 3 days	16
Week 24 +3 days	82
Week 28 ± 3 days	32
Week 32 ± 3 days	16
Week 36 ± 3 days	68
Week 40 ± 3 days	32
Week 44 ± 3 days	16
Week 48 +3 days	82
EOT	78
End of Treatment + 4 weeks	14
End of Treatment + 8 weeks	35
End of Treatment + 12 weeks	82
Total	995

The volume of blood was estimated assuming that a serum pregnancy test will be performed. Thus, the volume of blood to be collected may be less for subjects performing urine pregnancy tests.
Total may be less than indicated for subjects with available serological tests for exposure to CMV, EBV, HCV, HBsAg and HIV performed within the 12 months prior to screening and those who prematurely discontinue study treatment.
Total excludes the End-of-Treatment visit.

11.1.20. Prior & Concomitant Medications

Details regarding the name, medical indication, dose, route, and frequency of all prescription medications, over-the-counter medications, or alternative therapies taken within 30 days prior to administration of VIB4920 and through the end of the study will be recorded. Medications administered in the perioperative period solely for the conduct of surgery, such as anesthesia related medications, electrolytes, and intravenous fluids do not need to be collected. Any transplant related medications, such as immunosuppressive drugs, administered during this period should be collected.

11.1.21. Cytomegalovirus Prophylaxis

CMV pre-emptive therapy or prophylaxis is recommended for all cases in which either the donor or the recipient tests positive for CMV. It is recommended that CMV prophylaxis be administered for a minimum of 14 weeks after transplantation. Prophylaxis with IV ganciclovir or oral valganciclovir is recommended and will be administered according to local practice, taking into account dose adjustments based on renal function. Cases of CMV negative donor kidneys transplanted into CMV negative recipients will be treated according to local practice. CMV prophylaxis is also recommended following any AEs requiring antibody treatment of acute rejection episodes.

11.1.22. *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia prophylaxis

All subjects will be treated according to local standard of care. The same prophylaxis strategy should be applied for all subjects at a given site. Starting prophylaxis with trimethoprim-sulfamethoxazole when oral medication can be tolerated is recommended, continuing for the first 6 months after transplantation. Aerosolized pentamidine or dapsone may be administered to subjects unable to tolerate trimethoprim-sulfamethoxazole.

11.1.23. Prophylaxis and treatment of oral Candida

All subjects will be treated according to local standard of care. The same prophylaxis strategy should be applied for all subjects at a given site. Nystatin suspension in a swish and swallow regimen, oral fluconazole or clotrimazole troches are recommended for the prophylaxis or treatment of oral thrush (Candida).

11.1.24. Surveillance Biopsy

A surveillance renal biopsy will performed following reperfusion of the allograft on Day 0 and again at the end of Week 24, as specified in the Schedule of Assessments (Table 3). Where necessary to minimize any potential risk associated with the biopsy, a CT guided biopsy may be performed at the investigator's discretion in consultation with the medical monitor. A CT scan utilizes ionizing radiation to provide imaging to guide the biopsy collection. There can be risks of radiation from the CT scan. The cumulative radiation exposure from this test is considered small.

12. ASSESSMENT OF EFFICACY

Efficacy evaluation will be based on the assessment and recording of acute cellular rejection (tBPAR, BPAR, treated acute rejections) and antibody-mediated rejections, graft loss, death, de novo DSA and renal function throughout the study.

12.1. Histological Grading of Acute Allograft Rejection

Histological grading of acute allograft rejection from biopsy specimens and the diagnosis of antibody-mediated rejection will be based on Banff criteria 2017 (Haas, Loupy et al. 2018).

12.2. Handling of Acute Rejection Episodes

In all suspected acute rejection episodes, regardless of initiation of anti-rejection treatment, a graft core biopsy must be performed within 48 hours. Suspected rejections must be entered into in the corresponding eCRF pages (e.g., Suspected Acute Rejection eCRF, Kidney Allograft Biopsy eCRF, etc.) preferably within 24 hours.

Acute rejections should be treated with bolus methylprednisolone (other corticosteroids are acceptable at an equivalent dose) according to local practice. Recommended treatment is with at least 3 boluses of IV methylprednisolone with a minimal dose of 250 mg/bolus or at least 2 boluses of IV methylprednisolone with a minimal total dose of 750 mg.

- Subjects with mild cellular rejection (Banff Grade 1A or 1B) will be treated with corticosteroids and continue treatment with VIB4920 + belatacept.
- Subjects with Banff Grade 2A lesions will be treated with corticosteroids, then re-biopsied (at investigator's discretion), and will continue treatment with VIB4920 + belatacept if the repeat biopsy shows resolution of acute rejection or transitioned to standard of care immunosuppression for persistent or worsening lesions.
- Subjects with BPAR of Banff Grade ≥ 2B, or any antibody mediated rejection, must discontinue treatment with VIB4920, with subsequent management at the discretion of the investigator.

All medications used for the treatment of suspected or confirmed acute rejections must be recorded on the Immunosuppressive Therapies eCRF.

12.3. Allograft Loss

The allograft will be presumed to be lost based on whichever of the following occurs first: the day the subject starts dialysis and is not able to subsequently be removed from dialysis (for a period of at least 56 consecutive days), the day of nephrectomy, or the day reversible loss of graft perfusion is demonstrated by appropriate imaging techniques. Primary graft non-function is a subset of graft loss.

13. ASSESSMENT OF SAFETY

Safety assessments will consist of:

- Monitoring and recording all AEs and SAEs. Note: allograft rejection is a primary study endpoint to be reported as a study outcome, not as an adverse event.
- Regular monitoring of hematology, blood chemistry, immunoglobulins, coagulation parameters and urine results
- Regular monitoring of vital signs, body weight, physical condition, pregnancy (for females of childbearing potential) and concomitant medications
- Viral monitoring:
  - Every 2 weeks up to Week 12 for BK virus and monthly thereafter
  - Monthly for EBV and CMV viremia up to Week 12 and every 3 months thereafter

13.1. Delayed Graft Function

Subjects are considered to have delayed graft function (DGF) when:

- A dialysis is performed, where DGF is the reported reason (in this case, the end of DGF is considered the day the last dialysis session ends), and/or
- DGF is reported as an AE (in this case, the end of DGF is considered the day the reported AE ends, unless there is also dialysis reported which then defines the day the DGF ends).

In case a subject experiences DGF, the DGF is by definition starting at reperfusion after the transplantation procedure. If the graft dysfunction is starting later according to the investigator, then this condition is considered secondary graft dysfunction.

DGF must be reported as an AE for subjects who experience DGF without requiring dialysis. In case DGF is reported as an AE and dialysis is also reported, the end of DGF is considered the day the last dialysis session ends.

If Thymoglobulin or other prohibited medication is used to treat DGF, VIB4920 will be discontinued.

13.2. Adverse and Serious Adverse Events

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory

abnormality, the diagnosis or medical condition should be reported (e.g., renal failure, hematuria) not the laboratory abnormality (e.g., elevated creatinine, urine RBC increased).

Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

All AEs occurring between written informed consent signature and the end of the safety follow-up, whether or not they are related to the study, must be recorded in the eCRF.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or non-serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

Instances of acute rejection are anticipated on this study and have reporting guidelines referenced in Section 12.2. Acute rejection and manifestations of symptoms stemming from acute rejection are not reportable as serious adverse events.

Electrolyte abnormalities requiring an intervention are common during the peri-transplant period. Because they are expected they are not considered an untoward medical event. Therefore, non-serious electrolyte abnormalities requiring an intervention observed within 30 days of transplantation need not be recorded as adverse events. If the electrolyte abnormality or the therapeutic intervention to correct it meets criteria for a serious adverse event it must be reported as an SAE during the entire study.

13.2.1.2. Serious Adverse Event (SAE)

An SAE is an AE occurring during any study phase (i.e., screening period, treatment period, or safety follow-up), and at any dose of the investigational product, that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability/incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur between written informed consent signature and the end of the safety follow-up, whether or not they are related to the study, must be recorded in the eCRF. SAEs

identified at any time after the end of trial participation may be reported at the investigators' discretion.

Note: allograft rejection is a primary study endpoint to be reported as a study outcome, not as an adverse event. Instances of acute rejection that meet serious criteria should be captured on the Suspected Acute Rejection and Kidney Allograft Biopsy eCRFs as outlined in Section 12.2.

13.2.1.3. Adverse Events of Special Interest (AESIs)

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and collecting additional information by the investigator. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

The following AESIs will be particularly monitored in this study (see the Safety Handling Plan for instructions and timing on completing any additional information required for specific types of events related to the categories noted below):

- Thrombotic and embolic events
- Hepatic function abnormality (meeting the definition of Hy's Law, Appendix 4)
- Anaphylaxis and clinically significant (CTCAE Grade 3 or higher) hypersensitivity reactions (Appendix 2)
- Immune complex disease
- Severe Infusion-related reactions (CTCAE Grade 3 or higher, Appendix 3)
- Malignant neoplasm
- Infections:
  - Clinically significant (CTCAE Grade 3 or higher)
  - Opportunistic infections associated with immunosuppression including but not limited to reactivation of latent viral infection [VZV/HSV/EBV/JCV/CMV and BK polyoma virus], fungal infections and TB.

13.3. Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (e.g., the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (e.g., death as a passenger in an automobile accident)

- A clearly more likely alternative explanation for the event is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

13.4. Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes non-treatment-emergent SAEs (i.e., SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
- Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

13.5. Recording Adverse Events

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study. The AE term should be reported in standard medical terminology when possible.

13.5.1. Assessment of Severity

Severity will be assessed according to the following scale:

- Grade 1: An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2: An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

- Grade 3: A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5: Death (loss of life) as a result of an event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.2.1.2. An AE of severe intensity may not be considered serious.

13.5.2. Pregnancy

Should a pregnancy occur, it must be reported and recorded on a pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. Pregnancy outcomes for pregnant partners of male study participants must also be followed up and documented. When possible, the child's condition at birth should be recorded. No additional follow-up will be required.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

13.5.3. Time Period for Collection of Adverse Events

All AEs and SAEs occurring between written informed consent and the end of the safety follow-up will be collected.

13.5.4. Follow-up of Unresolved Adverse Events

Any non-serious AEs that are unresolved at the last visit of the safety follow-up period will be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. Information on SAEs has to be collected until they resolve or become permanent. Viela Bio retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

13.6. Reporting Serious Adverse Events

All SAEs/AESIs (related and unrelated) will be recorded from written informed consent signature up to the end of the safety follow-up, whether or not they are related to the study. Any SAEs/AESIs considered related to the investigational product and discovered by the investigator at any time after the study should be reported. Note: allograft rejection is a primary study endpoint to be reported as a study outcome, not as an adverse event. Instances of acute rejection

that meet serious criteria should be captured on the Suspected Acute Rejection and Kidney Allograft Biopsy eCRFs as outlined in Section 12.2.

All SAEs/AESIs must be reported within 24 hours by submitting a SAE/AESI Report Form by email to:

ICON Patient Safety
Email: icon-mads@iconplc.com

Alternatively, the SAE Report Form can be submitted by fax to:

ICON Patient Safety
Fax: 1-215-616-3096

Additional follow-up information, if required or available, should all be reported within one business day of receipt, should be completed on a follow-up SAE/AESI form, placed with the original SAE/AESI information and kept with the appropriate section of the eCRF and/or study file.

The designated sponsor representative (ICON) will work with the investigator to ensure that all the necessary information is provided within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs/AESIs.

Viela Bio, Inc. or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the IRB or Independent Ethics Committee (IEC) of all SAEs/AESIs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs/AESIs.

14. STATISTICS

14.1. General Considerations for Data Analysis

For continuous data, number of observations, the mean, standard deviation, median, minimum and maximum will be reported. For categorical data, percent and frequency will be reported. Details of the statistical analysis will be specified in a separate Statistical Analysis Plan (SAP).

14.1.1. Analysis Set

14.1.1.1. Safety analysis set

Safety analysis set includes all subjects who received any dose of IP. The safety, pharmacodynamics, and anti-drug antibody analyses will be based on the safety analysis set.

14.1.1.2. Efficacy evaluable set

Efficacy evaluable set includes all subjects who received the revised regimen of Thymoglobulin and steroids, and any dose of IP. The efficacy analysis will be based on the efficacy evaluable set.

14.1.1.3. Pharmacokinetic analysis set

Pharmacokinetic (PK) analysis set includes all subjects who received IP and have at least one quantifiable plasma PK observation post-first dose. The PK analysis will be based on the PK analysis set.

14.1.2. Procedure for Accounting for Missing Data

All analyses will be based on actual observed data. Missing values will not be imputed.

14.2. Statistical Methods

14.2.1. Efficacy

14.2.1.1. Primary Efficacy Endpoint

The primary efficacy variable is the incidence of efficacy failure, defined as treated biopsy-proven acute rejection (tBPAR) of grade 1A or higher, graft loss or death, at Week 24 post-transplantation. For the primary analysis the acute rejection rating will be based on the consensus of the pathologists at the initial two participating sites.

14.2.1.2. Primary Efficacy Analysis

The primary efficacy endpoint will be analyzed descriptively. The incidence of efficacy failure, defined as tBPAR of grade 1A or higher, graft loss or death, at Week 24 post-transplantation will be calculated, and the corresponding 80% 2-sided exact confidence interval will be calculated.

14.2.1.3. Secondary Efficacy Endpoints

In addition to Week 24, the incidence of efficacy failure as defined in Section 14.2.1.2 will be analyzed at Week 12 and Week 48.

The following secondary efficacy variables will be analyzed at Weeks 12, 24 and 48:

- Incidence of tBPAR, graft loss, death or loss to follow-up (LTFU)
- Incidence of antibody-mediated rejection
- Incidence of tBPAR
- Incidence of BPAR
- Incidence of treated acute rejections
- Proportion of subjects with dnDSA

14.2.1.4. Secondary Efficacy Analyses

The secondary efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint, at Weeks 12, 24 and 48.

14.2.2. Safety

14.2.2.1. Safety Endpoints

Safety endpoints will include:

- TEAEs and SAEs
- TEAE of special interest
  - Thrombotic and embolic events
  - Hepatic function abnormality (meeting the definition of Hy's Law)
  - Anaphylaxis and clinically significant (CTCAE grade 3 or higher) hypersensitivity reactions
  - Immune complex disease
  - Severe infusion-related reactions (CTCAE Grade 3 or higher)
  - Malignant neoplasm
  - Infections:
    - Clinically significant (CTCAE Grade 3 or higher) infections
    - Opportunistic infections (including but not limited to reactivation of latent viral infection [varicella zoster virus (VZV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), JC virus (JCV), cytomegalovirus (CMV), and BK polyoma virus], fungal infections and tuberculosis
- Laboratory data (laboratory variables by visit, change from baseline of laboratory variables by visit)
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and body weight) by visit
- ECG by visit

14.2.2.2. Safety Analysis

AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). All TEAEs will be summarized overall and by MedDRA System Organ Class and Preferred Term, by severity and by relationship to investigational product. Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. In addition, SAEs and AEs of special interest (AESIs) will be summarized. Other safety parameters, including laboratory assessments, vital signs, and ECG, will be summarized by absolute value at each visit, together with the corresponding changes from baseline, and shift from baseline if applicable.

14.2.2.3. Immunogenicity

The number and percentage of subjects who develop detectable ADA will be summarized. The impact of ADA on PK and the association with AEs and SAEs will be assessed if data allow.

14.2.3. Analysis of Pharmacokinetics

Descriptive statistics of the VIB4920 plasma concentration will be summarized over visits. Individual and mean plasma concentration-time profiles of VIB4920 will be generated. Non-compartmental analysis will be performed.

When possible, the following PK parameters will be accessed for VIB4920 concentration: maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), systemic clearance (CL), and terminal elimination half-life ($t_{½}$). Additional PK parameters may be determined and reported as appropriate. Descriptive statistics for PK parameters will be provided.

The potential PK exposure-response relationship for efficacy and safety outcomes with VIB4920 when combined with belatacept will be evaluated in an exploratory manner.

14.2.4. Exploratory endpoints:

- Proportion of subjects with eGFR ≥ 60 mL/min at 12, 24 and 48 weeks
- Changes in CCI [redacted] between Week 4 and Week 24; Week 4 and Weeks 48; Week 24 and Week 48
- Changes over time in CCI [redacted] to VIB4920 pharmacology or disease activity
- Changes over time in the CCI [redacted].

14.2.5. Interim Analysis

No interim analysis is planned for the study.

14.2.6. Sample Size and Power Considerations

Belatacept added to standard induction therapy (basiliximab, MMF, corticosteroids) resulted in efficacy failure in 21.7% of recipients of living- and standard criteria deceased-donor kidneys by 1 year (Nulojix® USPI). With 20 subjects, if we observe 3 or fewer subjects with efficacy failure (i.e., response rate ≥ 85%) at week 24, we have > 89% confidence that the response rate is at least 70%.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Viela Bio, Inc. or of the CRO will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Viela Bio, Inc. or its representatives. This will be documented in a Clinical Study Agreement between Viela Bio, Inc. and the investigator.

During the study, a monitor from Viela Bio, Inc. or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm compliance with the principles of GCP and regulatory requirements.
- Review of written informed consent forms for subjects screened/enrolled
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study for accuracy and completeness. This will require direct access to all original medical and other trial related records for each subject (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Viela Bio, Inc.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Viela Bio, Inc. or representative and those SAEs that met criteria for reporting have been forwarded to the IRB.

During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the study, make necessary corrections to CRF entries, respond to data clarification requests and respond to any other study-related inquiries of the monitor.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of Viela Bio, Inc., a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Viela Bio, Inc. audit or inspection is to systematically and independently examine all study-

related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council for Harmonization (ICH), and any applicable regulatory requirements.

Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

In addition to the above, representatives of Viela Bio, Inc.'s auditing staff or government inspectors may review the conduct/results of the study at the investigational site.

The investigator should contact Viela Bio, Inc. immediately if contacted by a regulatory agency about an inspection. The Investigator cooperates with the auditor(s), makes available to the auditor all requested documentation, and ensures that issues detected during the course of these audits are satisfactorily resolved. The Investigator supplies Viela Bio, Inc. with copies of all documentation and correspondence related to regulatory agency audits as outlined in the Clinical Trial Agreement. If the results of the audit result in a Form FDA-483 (or similar document from another regulatory agency), the Investigator promptly provides a copy to a Viela Bio, Inc. representative and a draft response to Viela Bio, Inc. prior to submission to the regulatory agency.

16. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Viela Bio, Inc. may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to Viela Bio, Inc. or representative before he or she can enroll any patient into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible to adhere to requirements stipulated by the respective IRB/IEC and for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Viela Bio, Inc. will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

Copies of all correspondence between the Investigator and the IRB/IEC is provided to Viela Bio, Inc.'s representative.

17.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the Viela Bio, Inc.'s policy on Bioethics.

17.3. Written Informed Consent

The PI(s) and other members of the study site's treating team will ensure that the patient or legally authorized representative is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients or legally authorized representative must also be notified that they are free to discontinue from the study at any time. Patients or legally authorized representative will be informed that their study record and medical records/documents that pertain directly to the study will be reviewed and possibly copied by Viela Bio, Inc. or its designee, or a governmental agency (such as the FDA), and that every effort will be made to maintain patient confidentiality. The patient or legally authorized representative should be given the opportunity to ask questions and allowed time to consider the information provided.

The Informed Consent must be witnessed and dated by the Investigator or his/her designee, and the original retained by the Investigator/Study Site as part of the patient's study record.

The patient's or legally authorized representative's signed and dated informed consent must be obtained before conducting any study procedures.

The PI(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient or legally authorized representative.

Subjects may be re-screened within 30 days under the current and signed ICF.

The informed consent document must be fully approved by an institutional review board (IRB) or an independent ethics committee (IEC) prior to its use with study participants.

18. DATA HANDLING AND RECORD KEEPING

18.1. Inspection of Records

Viela Bio, Inc. will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

18.2. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Viela Bio, Inc. or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

19. PUBLICATION POLICY

Publication of study data is addressed in the Clinical Trial Agreement between Viela Bio, Inc. and Investigator(s) and/or Institution(s).

20. LIST OF REFERENCES

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APPENDICES

APPENDIX 1. INVESTIGATOR'S AGREEMENT

I have received and read the latest version of the Investigator's Brochure for VIB4920 (formerly MEDI4920). I have read the protocol VIB4920.P2.S1 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Site Number

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

APPENDIX 2. NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE (NIAID) AND FOOD AND ALLERGY ANAPHYLAXIS NETWORK (FAAN) GUIDANCE FOR ANAPHYLAXIS DIAGNOSIS

NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (Sampson, Munoz-Furlong et al. 2006). They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to >95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

APPENDIX 3. AN APPROACH TO MANAGEMENT OF ANAPHYLACTIC AND HYPERSENSITIVITY REACTIONS

Severity of Symptoms	Treatment
Mild Mild reactions such as headache, nausea, nonpruritic rash, or mild hypersensitivity reactions including localized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mmHg change in systolic BP from pre-infusion measurement	Evaluate subject, including close monitoring of vital signs. At the discretion of the investigator, treat subject, for example, with: • Normal saline (~500-1000 mL/hour IV) and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500-650 mg or equivalent dose of paracetamol and/or • Topical antihistamines and/or low-potency topical corticosteroid preparations and/or • Anti-nausea medication, as needed
Moderate Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mmHg change in systolic BP from pre-infusion measurement	Evaluate subject, including close monitoring of vital signs. Treat subject, for example, with: • Normal saline (~500-1000 mL/hour IV) and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500-650 mg or equivalent dose of paracetamol and/or • IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20-40 mg
Severe Above plus fever with rigors, hypo- or hypertension with ≥ 40 mmHg change in systolic BP from pre-infusion measurement, signs of end organ dysfunction (e.g., symptomatic hypotension such as pre-syncope, syncope, seizure), or wheezing, angioedema, or stridor	Evaluate subject, including close monitoring of vital signs. Treat subject, for example, with: • Normal saline (~500-1000 mL/hour IV) and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500-650 mg or equivalent dose of paracetamol and/or • IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20-40 mg Call emergency medical transport for transport to emergency hospital based on judgment of the investigator
Life threatening Defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion	Evaluate subject, including close monitoring of vital signs. Maintain airway, oxygen if available. Treat subject immediately, for example with: • Normal saline (~500-1000 mL/hour IV) • Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local standard of care, example, epinephrine 1:1000, 0.5-1.0 mL administered SC for mild cases and intramuscular for more severe cases • IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20-40 mg • Diphenhydramine 50 mg IV or equivalent • Acetaminophen 500-650 mg or equivalent dose of paracetamol Call emergency medical transport for transport to emergency hospital based on judgment of the investigator
BP = blood pressure; IV = intravenous; SC = subcutaneous	

APPENDIX 4. ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

Introduction

This Appendix describes the process to be followed to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The investigator participates, together with Viela Bio clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AE) and serious adverse events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) together with total bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of investigational product irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

To identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor study representative
- Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law Criteria Are Not Met

If the subject does not meet PHL criteria the investigator will:

- Inform the sponsor representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria Are Met

If the subject does meet PHL criteria the investigator will notify the sponsor study representative who will then inform the central study team. The medical monitor contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. After this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the investigational product. The medical monitor and safety physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow the sponsor standard processes

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Report an SAE (report term 'Hy's Law') according to sponsor standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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