CLINICAL STUDY PROTOCOL

[redacted]

An Open-Label Phase 2a Study to Evaluate the Safety and Efficacy of AVB-S6-500 in Patients with IgA Nephropathy

PROTOCOL NUMBER: AVB500-IGA-001

NCT04042623

Sponsor:	Aravive, Inc 3730 Kirby Drive, Ste 1200 Houston, Texas 77098 USA
[redacted]	[redacted]
[redacted]	[redacted]
Current Protocol:	3.0
Version and Date:	08 Oct 2019
Proprietary Notice:	The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Aravive, Inc.
Ethics Statement:	The study will be conducted according to the International Conference on Harmonisation tripartite guideline E6(R2): Good Clinical Practice.

[redacted]

Investigator Protocol Agreement Page

I agree to conduct the study as outlined in the protocol entitled "An Open-Label Phase 2a Study to Evaluate the Safety and Efficacy of AVB-S6-500 in Patients with IgA Nephropathy" in accordance with the guidelines and all applicable government regulations including US Title 21 of the Code of Federal Regulations Part 54, the current requirements of ICH E6(R2) and local regulations. I have read and understand all sections of the protocol, including Section 4, Investigator's Obligations.

Principal Investigator's Name

Principal Investigator's Signature

Date

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PROTOCOL SYNOPSIS

SPONSOR:
Aravive, Inc.

NAME OF FINISHED PRODUCT:
AVB-S6-500

NAME OF ACTIVE INGREDIENT:
AVB-S6-500

STUDY TITLE:
An Open-Label Phase 2a Study to Evaluate the Safety and Efficacy of AVB-S6-500 in Patients with IgA Nephropathy

STUDY NUMBER:
AVB500-IGA-001

PHASE OF DEVELOPMENT:
Phase 2a

PRIMARY OBJECTIVE(S):

- To evaluate the safety and tolerability of AVB-S6-500 in patients with IgAN
- Assess the efficacy of AVB-S6-500 in patients with IgAN at a dose that has the desired pharmacokinetic/pharmacodynamic profile

SECONDARY OBJECTIVE:

- Evaluate and compare changes in pharmacokinetic, pharmacodynamic, anti-drug antibodies and neutralizing antibody responses

STUDY DESIGN:

General:
This is an open-label Phase 2a clinical study designed to evaluate the safety and efficacy of AVB-S6-500 in patients with IgAN. Patients will all receive AVB-S6-500 in an open-label design. Up to approximately 24 patients will be enrolled. Screening must occur within 1 year of diagnostic renal biopsy. [redacted] A follow up visit occurs 2 weeks following the end of treatment (for a total of approximately 99 days study participation) plus up to 28 days of screening time. Patients with IgAN and the following characteristics will be enrolled:

- Persistent proteinuria ≥ 1g/24 hr but no greater than 3 g/24 hr
- On a steady dose of ACE inhibitors (ACEi) or ARB for at least 3 months and throughout screening and who are not expected to have their dose of ACEi or ARB adjusted during the study (patients who are not on ACEi/ARB due to inability to tolerate these therapies are also allowed)
- Patients have not received treatment with systemic immunosuppressive medications (including corticosteroids) within 8 weeks of the first dose of study drug

Safety:

Safety assessment will include evaluation of adverse events (AEs), clinical laboratory results, vital sign measurements, 12-lead ECG measurements, and physical examinations. AEs will be coded using the MedDRA dictionary and concomitant medications using the WHO Drug dictionary.

Efficacy:

Efficacy will be assessed primarily by effect on urine protein excretion (UPE), effect on estimated glomerular filtration rate (eGFR), and effect on urine albumin/creatinine ratio (uACR).

Pharmacokinetics (PK) and Pharmacodynamics (PD):

Blood samples for serum pharmacokinetics (AVB-S6-500) and pharmacodynamics (GAS6) analysis will be collected prior to every dose of AVB-S6-500 (within approximately 45 minutes prior to dosing), on Day 1 at 1 hr (±30 minutes) post-dose, and at EOT.

STUDY POPULATION:

Up to approximately 24 patients will be enrolled in this study.

NUMBER OF SITES:

Patients will be enrolled at approximately 4 sites in the United States and Ukraine

CRITERIA FOR INCLUSION AND EXCLUSION

Inclusion Criteria:

Subjects who meet all listed inclusion criteria may be eligible for enrollment:

1. Male or female age 18 years or older
2. Diagnosis of biopsy-proven IgAN (biopsy to be taken within 1 year of screening)
3. Proteinuria ≥ 1g to 3 g/24 hr as measured at the 24-hr urine collection
4. Estimated Glomerular Filtration Rate (eGFR) has been stable (±15%) for at least 3 months prior to screening and ≥ 45 mL/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
5. Patients who have been on a steady dose of ACE inhibitors or ARB for at least 3 months and throughout screening and who are not expected to have their dose adjusted during the study are allowed on study (patients who are not on ACEi/ARB due to inability to tolerate these therapies are also allowed). Patients may be on other anti-hypertension medications in addition to ACEi or ARB and these medications should be at a stable dose for at least 3 months prior to Screening.)
6. Systolic blood pressure (BP) ≤ 150 mmHg and diastolic BP ≤ 100 mmHg
7. If a sexually-active patient, must agree to use a reliable method of birth control from at least 4 weeks prior to first dose of study drug, during the study and for 1 month following completion of therapy. A reliable method of birth control is defined as one of the following: oral or injectable contraceptives, intrauterine device, contraceptive implants, tubal ligation, hysterectomy, or a double-barrier method (diaphragm with spermicidal foam or jelly, or a condom) or vasectomy

Exclusion Criteria:

Subjects who meet any of the following criteria are not eligible for enrollment:

1. Patients with chronic urinary tract infections (UTIs) (defined as ≥ 2 episodes in a 6-month period or ≥ 4 episodes over 1 year prior to screening) or taking prophylactic antibiotics to prevent recurrent UTIs
2. Treatment with systemic immunosuppressive medications (including corticosteroids) within 8 weeks of the first dose of study drug
3. Rapidly progressing nephropathy defined as falling GFR (≥ 15%) over past 3 months prior to screening
4. Clinical or biological evidence of diabetes mellitus, systemic lupus erythematosus, IgA vasculitis (Henoch-Schonlein purpura), secondary IgAN, or other renal disease
5. Hemoglobin < 9.0 g/dL
6. History of or current clinical evidence of cirrhosis or liver disease, such as serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x upper limit of normal
7. Organ transplant recipient (including bone marrow) or a planned transplant during the study
8. Have a diagnosis of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection, or positive serology at Screening
9. Recent active infection requiring hospitalization or intravenous (i.v.) treatment within 30 days prior to the first dose of study drug
10. Received transfusion, plasmapheresis or plasma exchange, IV immunoglobulin (IVIg) within 90 days prior to screening
11. Malignancy within the past 5 years. (Those with history of malignancy greater than 5 years ago should provide evidence of remission or cure.) Exceptions are squamous cell carcinoma of skin, basal cell carcinoma of skin, and cervical carcinoma in situ which have been excised and are considered cured
12. Females who are nursing, pregnant, or intending to become pregnant during the time of the study, or who have a positive pregnancy test at baseline (if the subject is a female of child-bearing potential). A female is considered to be of child-bearing potential unless she is permanently sterilized or post-menopausal for at least 12 months with no menses and no alternative medical cause
13. Exposure to an investigational drug or device within 90 days or 5 half-lives (whichever is longer) prior to the first dose of study drug
14. Known sensitivity to any of the products to be administered during dosing
15. Subject will not be available for follow-up assessment
16. Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures
17. Prior exposure to AVB-S6-500

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

AVB-S6-500

The investigational product administered to patients in this study is AVB-S6-500 [redacted] Additional dose levels of AVB-S6-500 may be evaluated in this study.

[redacted]

DURATION OF TREATMENT:
Patients will be treated with a dose of AVB-S6-500, [redacted] All patients will undergo an End of Treatment Visit approximately 2 weeks after the last dose and a follow up visit approximately 28 days after their last dose of study drug (± 5 days).

SAFETY ASSESSMENTS:
Safety assessments will include the monitoring of AEs, clinical laboratory evaluations (hematology, and serum chemistry), vital sign measurements (pulse and blood pressure), respiratory rate and body temperature, physical examination findings, 12-lead ECG and anti-drug antibodies (ADA).

STATISTICAL METHODS:
No formal sample size estimate has been made as the study is an exploratory study that has no inferential statistical analysis. However, the number of participating patients in each part of the present study is common in early clinical studies and considered sufficient to evaluate to study objectives.

Safety:

Adverse event data will be summarized by preferred term and primary system organ class.

Efficacy:

This is an exploratory study to understand the impact AVB-S6-500 has on IgAN. The effect of AVB-S6-500 may be analyzed on the following, as well as additional endpoints:

1. Change from baseline (last value in screening) to End of Treatment in 24-hour urine protein excretion (UPE) in g/day.
2. Change from baseline (last value in screening) to End of Treatment in 24-hour urine protein excretion (UPE) in g/day in the subset of patients with baseline high proteinuria (defined as 24-hour UPE ≥ 2 g/day).
3. Proportion of patients with urinary protein equivalent of < 1 g/24 hours at End of Treatment.
4. Proportion of patients who had at least a decrease of 0.5 g/day proteinuria from baseline (last value during screening) to End of Treatment.
5. Change from baseline (last value during screening) to End of Treatment in urine albumin/creatinine ratios (uACRs).
6. Change from baseline (last value during screening) to End of Treatment in estimated glomerular filtration rate (eGFR).

PK/PD:

Individual serum AVB-S6-500 concentrations and noncompartmental analysis (NCA) parameters will be tabulated and descriptive statistics will be presented for both serum concentrations and resulting NCA parameters as appropriate. GAS6 serum levels will be determined as described above and will be combined with AVB-S6-500 exposure data (C_{max}, C_{trough} and AUC) to graphically evaluate possible exposure-response relationships over the dose levels administered.

ADA:

Anti-drug antibody data will be summarized as patients with pre-existing ADA and no increase in titer, pre-existing ADA with increase in titer post dose, and patients with negative ADA at baseline and positive for ADA during treatment.

Exploratory:

Free serum GAS6 levels may also be analyzed in context of any ADA to investigate the potential to develop neutralizing antibodies.

List of Abbreviations and Definition of Terms

Abbreviation	Definition
ACE	Angiotensin-converting enzyme inhibitors
ADA	Anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ARB	Angiotensin-receptor blockers
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AVB	AVB-S6-500
AXL	AXL receptor tyrosine kinase
BLQ	Below the limit of quantitation
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease -Epidemiology collaboration equation
CFR	Code of Federal Regulations
CL/F	apparent oral clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CRA	clinical research associate
CRO	contract research organization
CRF	case report form
DEC	Dose Escalation Committee
DLT	Dose-limiting toxicity
ECG	electrocardiogram
EOT	End of treatment
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
fM	femtomolar
g	Gram
GAS6	Growth arrested specific protein-6 (PD marker)
HIV	human immunodeficiency virus
Hr	Hours
ICF	informed consent form
ICH	International Conference on Harmonisation
IgAN	Immunoglobulin A nephropathy
IEC	independent ethics committee

Abbreviation	Definition
IRB	institutional review board
i.v	Intravenous
kg	Kilogram (s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram (s)
min	Minute (s)
PD	pharmacodynamic
PK	pharmacokinetic
PVG	pharmacovigilance
Q2W	Every two weeks
SAE	serious adverse event
SIR	standard infusion reactions
uACR	urine albumin/creatinine ratio
ULN	upper limit of normal
UPE	Urine protein electrophoresis
UTI	Urinary tract infection
WHO	World Health Organization

1. Introduction

1.1 IgA Nephropathy Overview and Treatment

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide, exhibiting a variable clinical and pathological course, which significantly contributes to the global burden of chronic kidney disease and end-stage renal disease (Penfold 2018). Patients may present at any age, but there is a peak incidence in the second and third decades of life. There is approximately a 2:1 male-to-female predominance in North American and Western European populations, although the sexes are equally affected among populations in East Asia.

IgAN is an autoimmune disease where IgA1 with galactose-deficient O-glycans and anti-glycan autoantibodies form complexes that deposit in the glomerular mesangium. These immune complexes are nephritogenic, contributing directly to glomerular inflammation and mesangial proliferation. In almost all IgAN biopsies, mesangial proliferation and prominent IgA depositions are observed by light microscopy and immunofluorescence microscopy. Approximately 15–20% of patients diagnosed with IgAN will develop end stage renal disease within 10 years, and about 25–30% of patients will develop end stage renal disease by 20 years.

There is no cure for IgA nephropathy and no definite way of knowing what course the disease will take. Treatment with a number of medications can slow the progress of the disease and help manage signs and symptoms such as high blood pressure, protein in the urine (proteinuria), and swelling (edema) in the hands and feet.

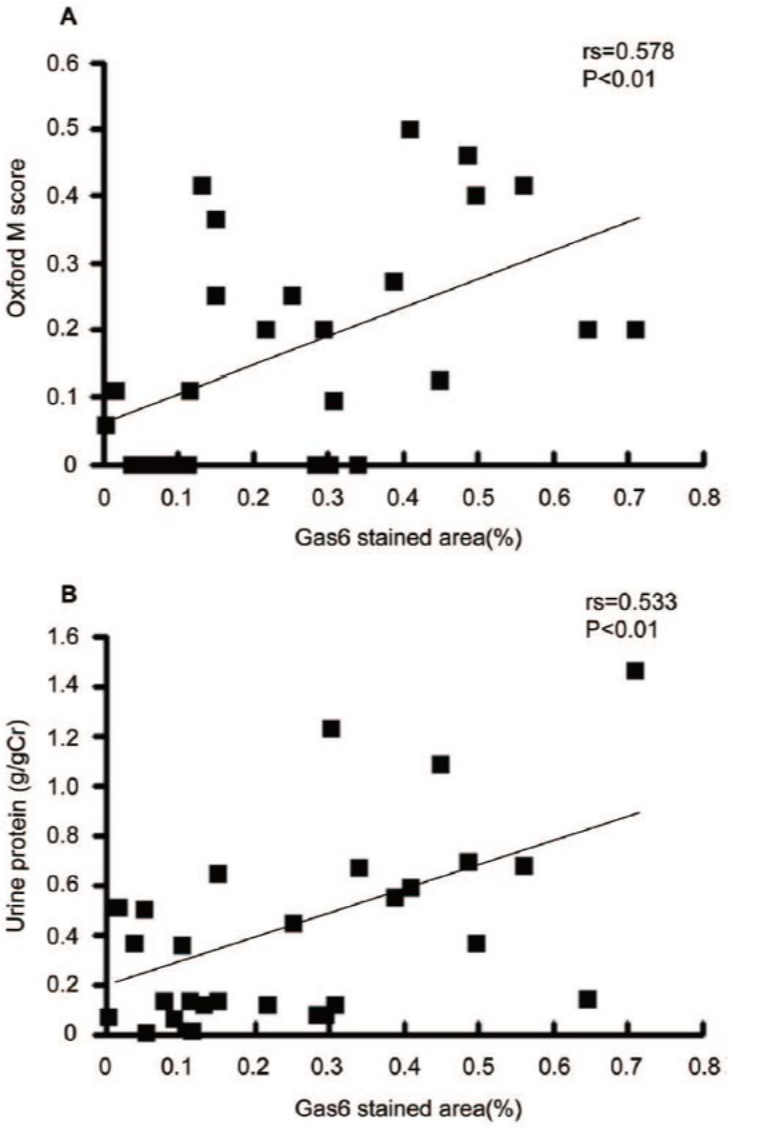
1.2 Study Rationale

1.2.1 The Role of GAS6-AXL Signaling in IgA Nephropathy

Within the kidney, AXL and GAS6 are expressed in vascular smooth muscle cells (VSMCs), glomerular mesangial cells and tubular cells. The basal expression of GAS6/AXL is low in normal kidney. However, its expression can be upregulated in several murine models of chronic kidney disease including: glomerulonephritis induced by Thy1.1 antibody and nephrotoxic nephritis. Patients with chronic kidney disease have elevated plasma GAS6 levels (Lee et al. 2012) and Aravive has found that serum GAS6 levels are significantly increased in IgAN patients compared to age-matched controls (Study PHARM-012).

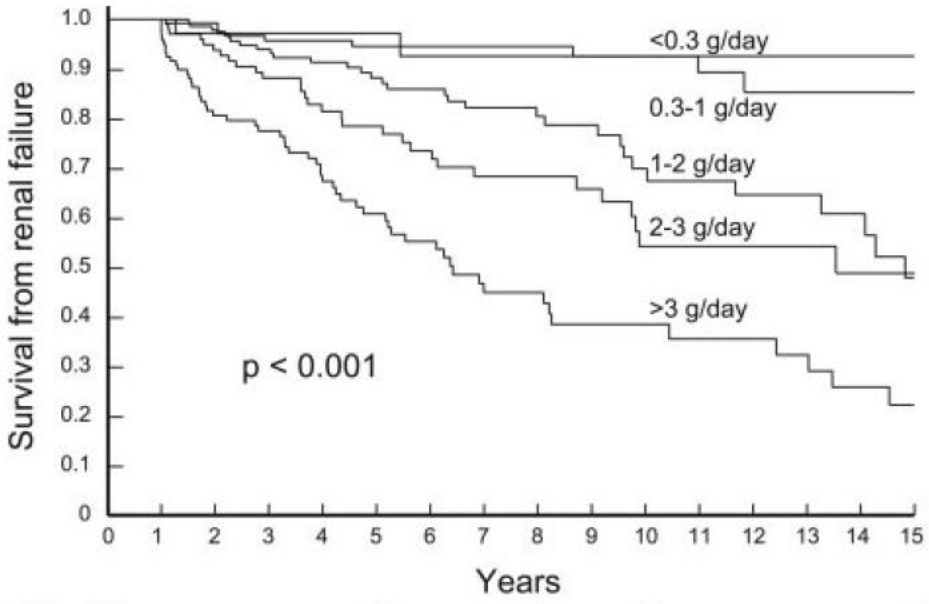
GAS6 is known to play a role in mesangial proliferation (and resulting proteinuria) and fibrosis. Renal biopsies demonstrate evidence of GAS6 pathway activation and the GAS6 expression correlates to severity of the disease (Figure 1-1). Proteinuria is a known predictor of survival from this renal disease (Figure 1-2) and, as such, is a recognized endpoint by FDA for development of therapies to treat IgAN.

Figure 1-1: Correlation of GAS6 Expression with Prognostic Factors



GAS6 stained area in human IgA nephropathy correlated with (A) Oxford mesangial hypercellularity score and (B) urine protein excretion. N = 28. Oxford M score, Oxford mesangial hypercellularity score.
Source: Nagai 2013

Figure 1-2: Effects of Proteinuria on Survival from Renal Failure



<0.3 g/day	37	22	8	1
0.3-1 g/day	134	79	35	11
1-2 g/day	145	79	28	10
2-3 g/day	105	50	18	4
>3 g/day	120	44	13	6

Source: Reich, H. 2007

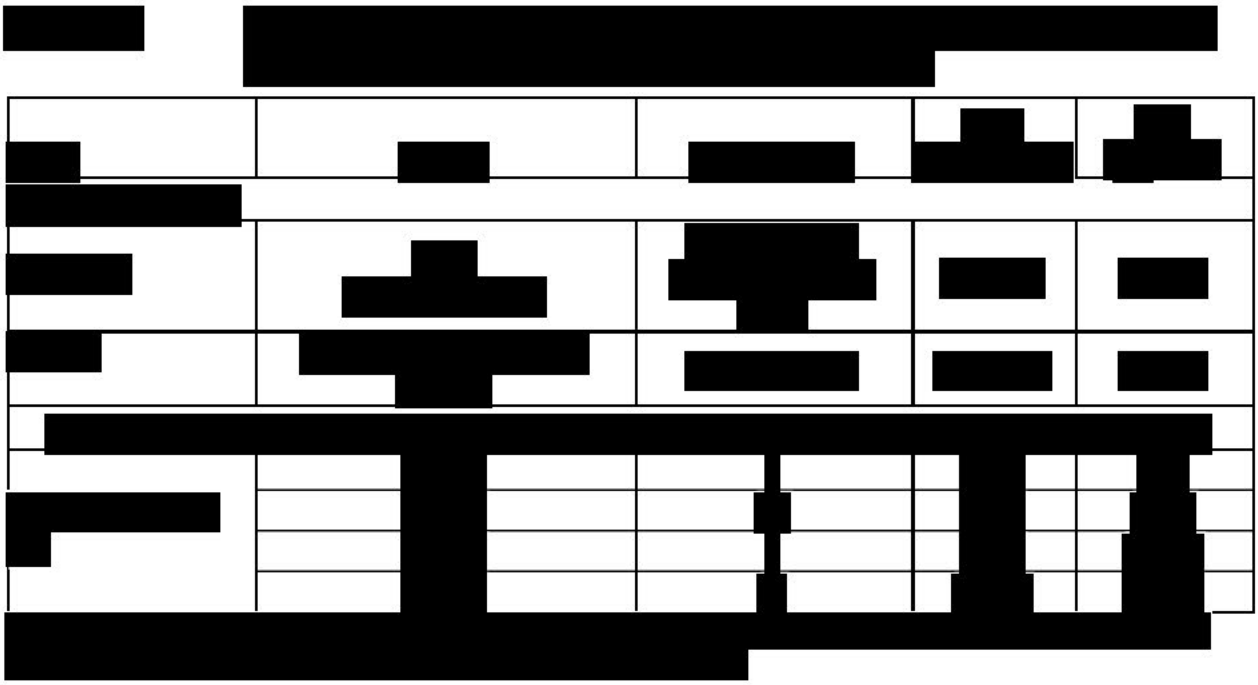
1.2.2 AVB-S6-500 Targets GAS6

[redacted]

However, there are reports of low affinity AXL proteins decreasing kidney disease in animal models that have demonstrated the GAS6/AXL pathway is driving the preclinical disease model (Zhen 2018). Additionally, Yanigata et al reported less mortality and proteinuria in GAS6$^{-/-}$ mice than in wild-type mice following injection of nephrotoxic serum. Glomerular cell proliferation, glomerular sclerosis, crescent formation, and deposition of fibrin/fibrinogen in glomeruli were

also reduced in GAS6$^{-/-}$ mice. Consistent with the hypothesis that GAS6 is important in this process, administration of recombinant wild-type GAS6 to GAS6$^{-/-}$ mice induced massive proteinuria, glomerular cell proliferation, and glomerulosclerosis, comparable to responses seen in wildtype mice. These data suggest that GAS6 induces glomerular cell proliferation in nephrotoxic nephritis and suggest that this factor contributes to glomerular injury and the progression of chronic nephritis (Yanagita et al. 2002). Consistent with the hypothesis that activation of the GAS6/AXL pathway contributes to fibrosis, we found that mice treated with AVB-S6-500 in a pancreatic cancer model demonstrated a dramatic decrease in fibrosis in primary LM-P tumor sections, as assessed by Masson Trichrome staining (Study PP-007).

[redacted]

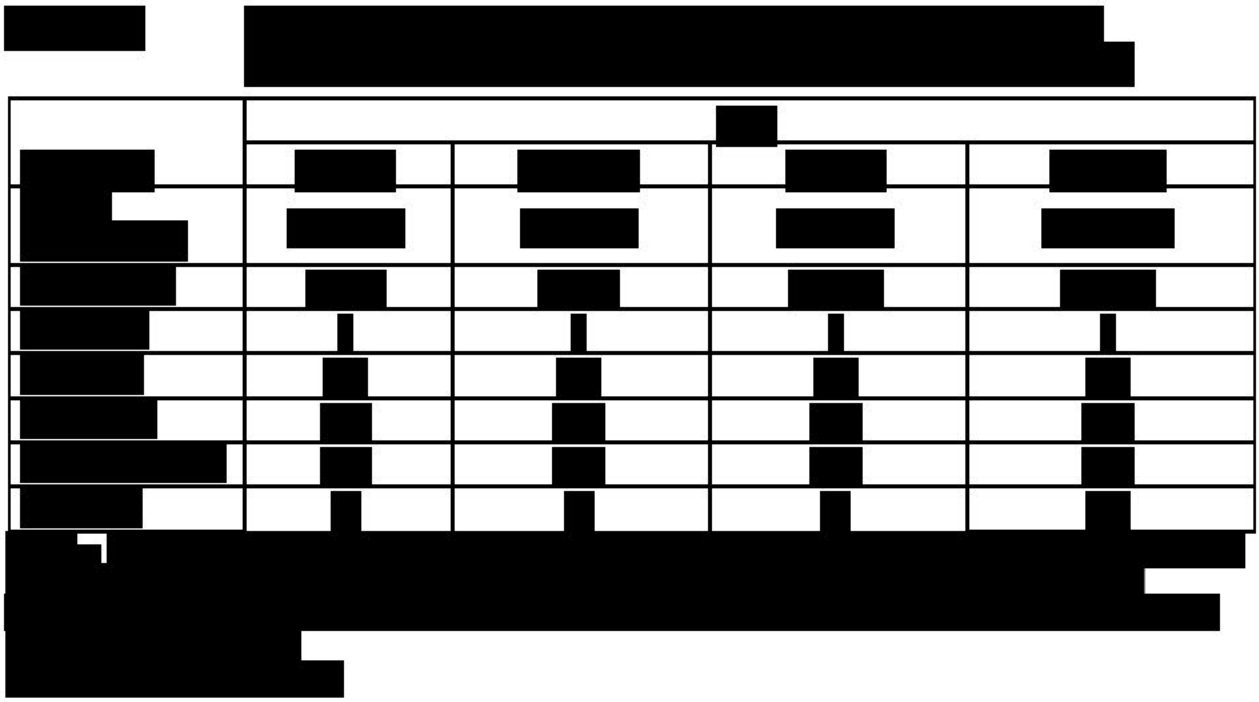


1.2.4 AVB-S6-500 Clinical Data

AVB-S6-500 is currently being tested in clinical oncology studies in the USA. GLP toxicology studies demonstrated a benign safety profile so the initial human study was conducted in healthy volunteers to assess safety, pharmacokinetics and pharmacodynamics (AVB500-HV-001). In summary, all doses tested in the healthy volunteer study (from 1 to 10 mg/kg single doses and 5 mg/kg dose given weekly for 4 weeks) were well-tolerated and suppressed serum GAS6 levels for at least one week. There were no dose-related adverse events (AEs), no serious adverse events (SAEs), and as expected from the GLP toxicology studies, a maximum tolerated dose was not reached. Any AEs based on laboratory values being outside of normal range (which, per protocol, were conservatively deemed as AEs regardless of clinical significance given this was a first in human study) were transient and not dose related.

PK/PD has been very predictable across the nonclinical and clinical studies conducted. PK parameters for single ascending dose cohorts were calculated using noncompartmental analysis (Table 1-2). The pharmacokinetics of AVB-S6-500 displayed characteristics similar to other protein therapeutics such as monoclonal antibodies, displaying generally small volumes of distribution and biphasic elimination. The maximal serum AVB-S6-500 concentration (C_{max}) and area under the concentration versus time curve (AUC) increased with increasing dose. The increase in C_{max} was approximately proportional across this dose range, while the increase in AUC was slightly greater than proportional with dose, suggesting nonlinear elimination kinetics consistent with TMDD.

No anti-drug antibodies were identified in any subjects administered AVB-S6-500 in the AVB500-HV-001 study.



2. Study Objectives

2.1 Primary Objectives

The primary objectives for this study are:

- To evaluate the safety and tolerability of AVB-S6-500 in patients with IgAN
- Assess the efficacy of AVB-S6-500 in patients with IgAN at a dose that has the desired pharmacokinetic/pharmacodynamic profile

2.2 Secondary Objectives

The secondary objectives for the study are:

- Evaluate and compare changes in pharmacokinetic, pharmacodynamic, anti-drug antibodies and neutralizing antibody responses

3. Investigational Plan

3.1 Study Design

This is a Phase 2a clinical study designed to evaluate the safety and efficacy of AVB-S6-500 in patients with IgAN at a dose that has the desired PK/PD profile. Patients will all receive AVB-S6-500 in an open-label design. Up to approximately 24 patients will be enrolled. Screening must occur within 1 year of diagnostic renal biopsy. Patients who have received treatment of systemic immunosuppressive medications (including corticosteroids) within 8 weeks of the first dose of study drug are excluded.

This study consists of a Screening Phase, a Treatment Phase, and a Post-treatment Phase. Patients will receive AVB-S6-500 in the Treatment Phase and will undergo procedures and assessment including regular safety and efficacy evaluations during the entire conduct of the study.

Multiple dosing regimens of AVB-S6-500 may be evaluated in this study. [redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

3.1.2 PK Evaluation of AVB-S6-500 Dosing Regimen

A dosing regimen will be determined to have acceptable PK if all subjects dosed at that Dose Level have trough values at the Day 15 visit of 15,000 ng/mL or greater (a value that is anticipated to have at least 95% target engagement based on PK/PD modeling).

3.2 Selection of Study Population

Up to approximately 24 patients are planned for this study. This sample is not based on a formal statistical power calculation.

Patients will be enrolled at approximately 4 sites in the United States and Ukraine.

3.2.1 Inclusion Criteria

Eligible patients must meet the following inclusion criteria. Unless otherwise specified the criteria below apply to all patients.

1. Male or female age 18 years or older
2. Diagnosis of biopsy-proven IgAN (biopsy to be taken within 1 year of screening)
3. Proteinuria ≥ 1g to 3g/24hr as measured by 24 hr urine collection
4. Estimated Glomerular Filtration Rate (eGFR) has been stable (±15%) for at least 3 months prior to screening and ≥ 45 mL/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
5. Patients who have been on a steady dose of ACE inhibitors or ARB for at least 3 months and throughout screening and who are not expected to have their dose adjusted during the study are allowed on study (patients who are not on ACEi/ARB due to inability to tolerate these therapies are also allowed). Patients may be on other anti-hypertension medications in addition to ACEi or ARB and these medications should be at a stable dose for at least 3 months prior to Screening.)
6. Systolic BP ≤ 150 mmHg and diastolic BP ≤ 100 mmHg
7. If a sexually-active patient, must agree to use a reliable method of birth control from at least 4 weeks prior to first dose of study drug, during the study and for 1 month following completion of therapy. A reliable method of birth control is defined as one of the following: oral or injectable contraceptives, intrauterine device, contraceptive implants, tubal ligation, hysterectomy, or a double-barrier method (diaphragm with spermicidal foam or jelly, or a condom) or vasectomy.

3.2.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. Patients with chronic UTIs (defined as ≥ 2 episodes in a 6-month period or ≥ 4 over 1 year prior to Screening) or taking prophylactic antibiotics to prevent recurrent UTIs
2. Treatment with systemic immunosuppressive medications (including corticosteroids) within 8 weeks of the first dose of the study drug
3. Rapidly progressing nephropathy defined as falling GFR (≥ 15%) over past 3 months prior to screening
4. Clinical or biological evidence of diabetes mellitus, systemic lupus erythematosus, IgA vasculitis (Henoch-Schonlein purpura), secondary IgAN, or other renal disease
5. Have a hemoglobin < 9.0 g/dL
6. History or clinical evidence of cirrhosis or liver disease with serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x upper limit of normal
7. Organ transplant recipient (including bone marrow) or a planned transplant during the study

8. Have a diagnosis of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection, or positive serology at screening
9. Recent active infection requiring hospitalization or i.v. treatment within 30 days prior to the first dose of study drug
10. Received transfusion, plasmapheresis or plasma exchange, IV immunoglobulin (IVIg) within 90 days prior to screening
11. Malignancy within the past 5 years. (Those with history of malignancy greater than 5 years ago should provide evidence of remission or cure.) Exceptions are squamous cell carcinoma of skin, basal cell carcinoma of skin, and cervical carcinoma in situ which have been excised and are considered cured
12. Females who are nursing, pregnant, or intending to become pregnant during the time of the study, or who have a positive pregnancy test at baseline (if the subject is a female of child-bearing potential). A female is considered to be of child-bearing potential unless she is permanently sterilized or post-menopausal for at least 12 months with no menses and no alternative medical cause
13. Exposure to an investigational drug or device within 90 days or 5 half-lives (whichever is longer) prior to the first dose of study drug
14. Known sensitivity to any of the products to be administered during dosing
15. Subject will not be available for follow-up assessment
16. Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures
17. Prior exposure to AVB-S6-500

3.3 Prohibited Medications

There are no prohibited medications beyond those specified in the inclusion/exclusion criteria. AVB-S6-500 is a protein and not expected to have the typical drug interactions involving cytochrome P450s.

3.4 Individual AVB-S6-500 Dose Discontinuation Rule

Patients who experience a definitely, probably, or possibly drug-related SAE or a definitely, probably, or possibly drug-related clinically significant, nonserious AE, which in the opinion of the Investigator warrants discontinuation of participation in the study for that subject's well-being may not be re-dosed with AVB-S6-500. Also, any patient who experiences a DLT should not be re-dosed with AVB-S6-500.

3.5 Withdrawal of Patients from the Study

3.5.1 Reasons for Withdrawal

All patients have the right to withdraw from the study at any time, for any reason, without prejudice. Patients will be discontinued from the study for any of the following reasons:

- Unacceptable toxicity
- Withdrawal of consent for treatment by subject
- The sponsor terminates the study
- The subject is pregnant
- The Investigator decides it is in the subject's best interest to discontinue treatment and/or participation in the study. Reasons may include the following:
    - The subject is not adherent to the protocol
- A medication is begun that may have the ability to alter responses to study drug: Patients who initiate treatment with oral or parenteral corticosteroids, immunosuppressant or whose dose antihypertensive therapy is increased or initiated after screening must be withdrawn from study.

3.5.2 Handling of Withdrawals

If a subject withdraws consent, the investigator should make a reasonable attempt to document the specific reason why consent is being withdrawn in the medical record and eCRF. Any subject who discontinues from the study early, should be encouraged to still participate in the End of Treatment and Follow-Up Visits.

If possible, before the subject withdraws consent or the subject is withdrawn by the investigator, every effort should be made to complete and report the follow-up assessments listed for the End of Treatment and Follow-Up Visits, as thoroughly as possible. The investigator should notify the sponsor of the subject's withdrawal within 48 hours.

If a subject is lost to follow-up and cannot be reached by telephone, a certified letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the investigator.

At any point, the investigator may discontinue the subject's study participation at his/her discretion and ensure the subject receives appropriate medical care if necessary. The investigator may also consult the Medical Monitor.

3.5.3 Replacements

Patients who don't complete all planned doses of AVB-S6-500 and an End of Treatment Visit may be replaced. All subjects will be assigned a unique identifier.

3.6 Early Termination of the Study

The Sponsor reserves the right to terminate the study at any time with appropriate notification. Reasons for terminating the study may include but are not limited to the following:

- Potential health hazard to subjects, as indicated by the incidence or severity of AEs in this or other studies
- Unsatisfactory subject enrollment
- Inaccurate or incomplete data recording

- Administrative reasons

In addition, the regulatory agency or the site's IRB has the authority to stop the study.

3.7 Study Procedures

This study consists of a Screening Phase (Section 3.7.1), a Treatment Phase (Section 3.7.2) including an End of Treatment Visit, and a Post-treatment Phase that includes a Follow-Up Visit (Section 3.7.3). Patients will receive AVB-S6-500 in an open-label design during the Treatment Phase and will undergo procedures and assessments including regular safety and efficacy evaluations during the entire conduct of the study.

The actual sampling times of blood draws for PK/PD/ADA testing will be documented; deviations from the suggested sampling times will not be considered protocol violations.

As with administration of any injectable drug, patients should be monitored for infusion reactions during and for up to an hour after administration of AVB-S6-500. General guidance on management of infusion reactions is provided from UpToDate clinical database (LaCasce 2018):

Intravenous infusion reactions may affect any organ system in the body. The most common signs and symptoms of standard infusion reactions (SIR) to injectable drugs are:

- Fever and/or shaking chills
- Flushing and/or itching
- Alterations in heart rate and blood pressure
- Dyspnea or chest discomfort
- Back or abdominal pain
- Nausea, vomiting, and/or diarrhea
- Various types of skin rashes

Infusion of AVB-S6-500 should be stopped for any patient experiencing an SIR. The patient should be treated symptomatically to resolve the SIR, which could include administration of histamine blockers, corticosteroids, antipyretics, or Demerol (for rigors). Patients should not be re-challenged with AVB-S6-500 if they experience an infusion reaction.

3.7.1 Screening Phase

After providing consent to participate, patients will undergo a screening visit. Screening assessments must occur within 28 days preceding the first dose of study drug for determination of subject's overall eligibility for the study.

A screen failure log will be maintained by the investigator.

Screening assessments will include:

- Demography, including sex, date of birth and race
- Height and weight will be recorded

- Medical history
- Physical examination, excluding rectal and pelvic examinations and breast examinations
- Confirmation of IgAN diagnosis via renal biopsy within 12 months of first dose of study drug
- Vital signs: pulse, blood pressure, respiratory rate, and body temperature
- Complete laboratory evaluation, including hematology and serum chemistry
- Review of inclusion/exclusion criteria
- Serum pregnancy test (for all female patients of childbearing potential)
- 12-lead ECG
- Collection of independent urine sample for albumin/creatinine ratio analysis
- Patient will be provided materials for 24-hour urine collection (protein)
- Prior medications: all medications taken or received within 14 days prior to the first dose of the study drug must be recorded
- Estimated GFR per CKD-EPI formula

The Screening visits will include the assessments shown in the Time and Events Schedule (Table 7-1). Hematology and clinical chemistry samples will be collected and analyzed in local laboratories.

3.7.2 Treatment Phase

3.7.2.1 Treatment Visits

AVB-S6-500 will be administered [redacted] Patients will be treated with a dose of AVB-S6-500 on Day 1 and Q2W thereafter, totaling 6 doses. During the Treatment Phase, subject will undergo procedures and assessments including regular evaluations for safety and efficacy as described in the Time and Events Schedule (Table 7-1). When the 12-lead ECG and blood collection assessments are scheduled for the same time point, the ECG should be taken prior to blood collection. Blood samples for analysis of AVB-S6-500 concentration, GAS6 (the PD marker), and anti-drug antibodies will be collected from patients as outlined in the Time and Events Schedule (Table 7-1). ADA samples will be taken at Day 1 and at the Follow Up visit.

Concomitant medications and AEs will also be collected from the time of first dose of study drug through the end of study participation, as indicated in the Time and Events Schedule (Table 7-1).

3.7.2.2 End of Treatment Visit

At the end of treatment or at early withdrawal from treatment or the study, all patients should complete an End of Treatment (EOT) Visit, as outlined in the Time and Events Schedule (Table 7-1).

The following assessments will be done at the EOT Visit:

- Physical examination, excluding rectal and pelvic examinations and breast examinations
- Pregnancy Test

- 12 -lead ECG
- Vital signs: pulse, blood pressure, respiratory rate, and body temperature
- Collection of blood samples for PK/PD analysis
- Complete laboratory evaluations, including hematology and chemistry
- Collection of blood samples for GFR evaluation
- Collection of independent urine sample for uACR assessment
- Patient will be provided materials for 24-hour urine collection for evaluation of protein, to be completed within the visit window
- Collection of AE/SAE information
- Concomitant medication usage

3.7.3 Post-Treatment Phase

3.7.3.1 Follow-Up

All patients should complete the follow-up visit as outlined in the Time and Events Schedule (Table 7-1).

The following assessments will be done at the Follow-up Visit:

- Physical examination, excluding rectal and pelvic examinations and breast examinations
- Pregnancy Test
- Vital signs: pulse, blood pressure, respiratory rate, and body temperature
- 12 -lead ECG
- Complete laboratory evaluations, including hematology and chemistry
- Concomitant medication usage
- Collection of blood samples for ADA evaluation
- Collection of AE/SAE information

3.7.4 Safety Assessments

Safety evaluations will include the monitoring of AEs, 12-lead ECGs, physical examination findings, vital signs measurements, clinical laboratory assessments, concomitant medications, and pregnancy tests results for females of childbearing potentials.

Adverse events will be followed by the investigator as specified in Section 3.7.4.1.

3.7.4.1 Adverse Events

3.7.4.1.1 Definitions

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study medication or their clinical significance.

Adverse Event: An AE is any untoward medical occurrence in a study patient administered a pharmaceutical product and which does not necessarily have a causal relationship to study

medication. Patients will be instructed to contact the Investigator or Sub-investigator at any time after informed consent if any symptoms develop. Medical events occurring after informed consent but before the first dose of study drug will not be captured in the safety database, however the Investigator will be responsible for ensuring the safety of the subject in these instances. Medical events occurring after informed consent but before the first dose of study drug may either cause the subject to be ineligible for the study based on inclusion/exclusion requirements or will become part of the medical history for those patients who remain eligible to continue in the study. Likewise, any medical condition that is present at the time the patient is screened but does not deteriorate should be captured on the patient's medical history but should not be reported as an AE; however, if it deteriorates at any time during the study after first dose of study drug it should be reported as an AE.

An AE is defined as any event not present before exposure to study medication or any event already present that worsens in either intensity or frequency after exposure to study medication.

Serious Adverse Event (SAE): An SAE is an event that:

Results in death

Is immediately life threatening

Requires inpatient hospitalization for greater than 24 hours or prolongs existing hospitalization

Results in persistent or significant disability and/or incapacity, or

Is a congenital anomaly/birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse events and SAEs must be reported in detail in the appropriate CRF (electronic) page. Adverse events (serious and nonserious) must be followed until the event resolves or is otherwise explained, stabilizes, or the patient is stable or lost to follow-up. Information to be collected is described in Section 3.7.4.1.3. Adverse events and serious adverse events will be captured from the time the patient receives the first dose of study drug through the follow-up visit.

3.7.4.1.2 Eliciting and Documenting Adverse Events

At every study visit starting with Day 1, patients will be asked a standard question to elicit medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over the counter medications).

In addition to patient observations, AEs may be collected from other sources, e.g., laboratory values, physical examination findings, ECG changes, or other documents that are relevant to patient safety and recorded in the AE page of the eCRF.

3.7.4.1.3 Reporting Adverse Events

All AEs reported or observed from the time the patient receives the first dose of study drug through the follow-up visit will be recorded in the AE page of the eCRF. Any adverse medical event that occurs from the time the ICF is signed until the subject receives the first dose of study drug will be recorded in medical history. All AEs will be assigned a severity grade. The description of the AE will include the type of event, onset date, investigator-specified assessment of severity, date of resolution of the event, seriousness, any required treatment or evaluations, and outcome.

3.7.4.1.4 Reporting Serious Adverse Events

Any SAE must be reported to the ProPharma Group Pharmacovigilance (PVG) Department by email or fax within 24 hours of when the study site personnel first learn of the event. The study site personnel must enter the SAE into the eCRF and email or fax the Serious Adverse Event Report Form to ProPharma Group PVG:

All SAEs that occur during the study (regardless of relationship to study drug) must be reported in detail and followed until they resolve, stabilize, or become non-serious.

All SAEs at the investigator's site may be required to be reported to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator, according to local IRB/IEC policy. Medical and scientific judgment should be exercised in deciding whether an AE that does not meet the standard definition of an SAE, but is important from a safety perspective and may jeopardize the subject or require intervention to prevent one of the other outcomes listed in the definition of serious, should be considered as serious.

3.7.4.1.5 Assessment of Severity

The severity or intensity of an AE refers to the extent to which an AE affects the patient's daily activities. The investigator will assess the intensity of the AE and rate the AE as mild, moderate, or severe using the following criteria:

Mild: These events require minimal or no treatment and do not interfere with the patient's daily activities.

Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: These events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

A "severe" AE need not be "serious" in nature and a "serious" AE need not, by definition, be "severe". Changes in the severity of an AE should be documented to allow for an assessment of the duration of the event at each level of intensity to be performed.

3.7.4.1.6 Assessment of Causality of SAEs

Investigator assessment of an SAE's relationship to study drug will be part of the documentation process, as this is necessary to assess whether or not an SAE becomes classified as an expedited IND Safety Report. Thus, all SAEs must have a documented causality assessment; however, the Investigator's assessment of causality is not required for nonserious AEs.

It is the sponsor's responsibility to assess the causality of an SAE and determine whether it meets the criteria for a suspected unexpected serious adverse reaction (SUSAR) requiring regulatory reporting responsibility. For investigator assessment of SAE causality, the relationship or association of the study drug in causing or contributing to the SAE will be characterized using the following classification and criteria:

Definite: SAEs that, after careful medical evaluation, are considered definitely related to the drug treatment, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

Probable: SAEs that, after careful medical evaluation, are considered with a high degree of certainty to be related to the study drug. The following characteristics will apply:

- A reasonable temporal relationship exists between the event and exposure to the study drug, and
- The event is a known reaction to the study drug that can be explained by an alternative cause commonly occurring in the population or individual, or
- The event is not a known reaction to the study drug but cannot be reasonably explained by an alternative cause.

Possible: SAEs that, after careful medical evaluation, do not meet the criteria for a definite or probable relationship to the study drug, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- The event occurs after exposure to the study drug, and
- There is a reasonable temporal relationship to the study drug, but the event is not a known reaction to the study drug and could be explained by a commonly occurring alternative cause, or
- In the absence of a reasonable temporal relationship, the event cannot be explained by an alternative cause.

Unlikely: SAEs that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to the study drug and for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from study drug dosing, or
- The event may have been produced by environmental factors, and
- There is no apparent pattern of response to the study drug.

Not related: SAEs in this category will have either of the following characteristics:

- The event occurs before exposure to the study drug, or
- The event does not have a reasonable temporal relationship to study drug and can be explained by a commonly occurring alternative cause.

Events classified as definite, probably, or possible will be considered related to drug for reporting purposes.

3.7.4.2 Electrocardiograms

For all patients enrolled in the study, a standard 12-lead ECG will be conducted with the patient in a supine position at times indicated in the Time and Events Schedule. The investigator or designee will be responsible for reviewing the ECG for any abnormalities and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. Additional assessments can be done at any time if clinically indicated or as per investigator discretion.

3.7.4.3 Physical Examinations

A complete physical examination of all body systems (excluding rectal and pelvic examinations and breast examinations) will be performed at Screening visit, at the End-of-Treatment (or Early Withdrawal), and Follow-Up visit. A brief physical exam (symptom directed) will be performed at Days 1, 15, 29, 43, 57, and 71. Additional assessments can be done at any time if clinically indicated or as per investigator discretion.

3.7.4.4 Vital Signs Measurements

Vital sign measurements include temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure and will be collected at times indicated in the Time and Events Schedule. When scheduled to occur at the same time point as the collection of clinical laboratory blood samples, vital sign measurements should be obtained before blood sample collection if possible. For vital sign measurements, patients may be either in a semi-recumbent or seated position and measurements will be collected after a 5-minute rest period. Additional assessments can be done at any time if clinically indicated or as per investigator discretion.

3.7.4.5 Laboratory Analyses

Clinical laboratory tests will be performed by local laboratories. Blood samples for hematology and chemistry will be prepared using standard procedures. All patients will have samples of

blood (approximately 16 mL for safety labs and 6 mL for PK/PD/ADA analysis) and urine collected at times shown in the Time and Events Schedule.

The blood samples collected for clinical laboratory assessments per schedule will be used for the following tests:

Hematology: hemoglobin, hematocrit, platelet count, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential

Serum chemistry: albumin, alkaline phosphatase, ALT, amylase, AST, blood urea nitrogen (or urea), calcium (albumin corrected), chloride, creatinine, glucose (Screening only), lactate dehydrogenase, lipase, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, thyroid stimulating hormone (Screening only), and uric acid

Serology: human immunodeficiency virus (HIV), hepatitis B, hepatitis C

Additional assessments can be done at any time if clinically indicated or as per investigator discretion.

Urine for albumin/creatinine ratio: At least 40 mL urine should be collected from the patient

24-hour urine collections will be obtained at times shown in the Time and Events Schedule. A 24-hour urine collection is done by collecting urine in a special container over a full 24-hour period. The container must be labelled and kept refrigerated until the urine is returned to the clinic. Urine must be returned to the clinic within the next 24 hours following completion of collection.

In addition, female patients of childbearing potential will have a serum pregnancy test at screening and urine pregnancy test (or a serum pregnancy test if preferred at the discretion of the investigator or if required by local regulations) will be performed at other time points.

3.7.4.6 Anti-drug Antibodies (ADA) Assessment

Each subject will have blood samples (6 mL) collected at the Day 1 prior to dosing and at the Follow-Up visit for analysis of the presence of ADA.

3.7.4.7 Pregnancy

Any pregnancy that occurs after the first dose of the study drug or within 30 days of the last dose of the study drug must be reported using a Pregnancy Notification Form. To ensure subject safety, each pregnancy must be reported to PVG as soon as possible after learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child and reported on the Pregnancy Outcome Form. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any subject who becomes pregnant will be discontinued from the study.

Any SAE occurring in association with a pregnancy, which is brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study drug, must be promptly reported to the ProPharma Group PVG. The pregnancy should be reported immediately, using a Pregnancy Notification Form, to ProPharma Group PVG.

[redacted]

If the subject agrees to have her primary care physician informed, the investigator should notify the subject's primary care physician that she was participating in a clinical study at the time that she became pregnant, and the investigator should provide the details of the treatment that the subject received.

All pregnancies will be followed until final outcome using the Pregnancy Outcome Form and indicating that it is a follow-up report. The outcome, including any premature termination, must be reported to ProPharma PVG.

3.7.5 Pharmacokinetic Assessments

The following PK parameters will be assessed for AVB-S6-500 using noncompartmental methods, if estimable:

Parameter	Description
AUC_{0-24}	Area under the AVB-S6-500 concentration-time curve from the time of dosing (0 hour) to 24 hours following dose administration
AUC_{0-t}	Area under the AVB-S6-500 concentration-time curve from the time of dosing (0 hour) to the time of the last quantifiable concentration following dose administration
$AUC_{0-\infty}$	Area under the AVB-S6-500 concentration-time curve from the time of dosing (0 hour), extrapolated to infinity
$AUC_{\%extrap}$	Percentage of AUC0-∞ estimated by extrapolation from the time of last measurable plasma concentration to infinity
C_{max}	Maximum observed AVB-S6-500 concentration from the time of dosing (0 hour) to the time of the last quantifiable AVB-S6-500 concentration following dose administration
C_{trough}	Minimum observed AVB-S6-500 concentration from the time of dosing (0 hour) to the time of the last quantifiable AVB-S6-500 concentration following dose administration prior to the start of the next infusion
T_{max}	Time of maximum observed AVB-S6-500 concentration (post-dose)
$t_{1/2}$	Apparent terminal phase half-life
CL	Total body clearance
V_z	Volume of distribution based on the terminal phase

3.7.5.1 Collection, Handling, and Shipment of Pharmacokinetic, Pharmacodynamic, and Anti-drug Antibody Samples

Blood samples (serum) for analysis of AVB-S6-500 concentration, GAS6 (comprising the PD marker) levels, and ADA will be collected from patients at the following time points relative to dosing:

Table 3-2: Blood Sample Collection for Pharmacokinetic, Pharmacodynamic, and/or ADA Analyses

Visit Day	Sampling Times
1	Within 45 minutes before dosing (predose), and post-dose time at 1hr ± 30 min
15	Within 45 minutes before dosing (predose)
29	Within 45 minutes before dosing (predose)
43	Within 45 minutes before dosing (predose)
57	Within 45 minutes before dosing (predose)
71	Within 45 minutes before dosing (predose)
85	EOT Visit
99	FU Visit

*Blood collection outside of these suggested time points will not be considered a protocol deviation or violation.

In addition to the time points indicated in the Schedule of Events (Table 7-1), ADA may be analyzed at any time point from samples collected and designated for PK or PD analyses if needed at the discretion of the Sponsor.

For PK and PD analyses, blood samples (6 mL) will be collected into serum separator tubes and processed as described in the laboratory manual. Samples for anti-drug antibody analysis can be prepared from the same sample collected for PK/PD on Day 1.

Serum samples for the PK assessment of AVB-S6-500 and pharmacodynamic assessment of GAS6 levels will be sent to EPL Archives, LLC:

One set of primary serum samples from each subject will be shipped. The remaining duplicate samples will be stored at the clinical site as a backup only upon confirmed receipt of the primary

samples. After the receipt of the serum samples for PK/PD analyses, the backup serum samples will be shipped.

All frozen primary samples for ADA analysis (collected prior to dosing on Day 1 and at Follow-Up) should be shipped via overnight courier to EPL. Backup samples are to be stored at the clinical site and sipped upon confirmed receipt of primary samples. Frozen ADA samples should be shipped to the following address:

[redacted]

3.8 Treatments

3.8.1 Method of Assigning Patients to Treatment Groups

This is an open-label study. No randomization will be performed.

The dose of study drug will be dispensed, administered, and recorded by study clinic personnel, and any deviations from the dosing schedule will be entered the subject's eCRF.

3.8.2 Treatments Administered

AVB-S6-500 will be administered [redacted]

All treatments will be administered in the clinic by clinic staff.

3.8.3 Identity of Investigational Product

The investigational product will be provided in vials containing 10 mL of AVB-S6-500 (concentration 20 mg/mL). The pharmacist or a properly trained designee will prepare the study drug for intravenous administration. AVB-S6-500 vials are to be stored at 2–8 °C until time of use.

The investigational product administered to patients in this study will be AVB-S6-500. AVB-S6-500 solution for infusion will be packaged and labeled according to current Good Manufacturing Practices and supplied to the clinical site in 20 mL-vials containing 10 mL in each vial with the composition described in Table 3-3 as a sterile solution and is intended to be diluted prior to infusion.

[redacted]

The sponsor will provide to study sites adequate supplies of AVB-S6-500.

3.8.4 Management of Clinical Supplies

3.8.4.1 Study Drug Packaging and Labeling

AVB-S6-500 will be packaged and labeled for administration to individual study patients according to current site practices and applicable local regulations.

3.8.4.2 Test Article Accountability

The investigator will maintain accurate records of receipt of AVB-S6-500, including dates of receipt. In addition, accurate records will be kept regarding when and how much AVB-S6-500 is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all AVB-S6-500 will be reconciled.

3.8.5 Blinding

This is an open-label study; the investigational product will not be blinded or masked. All patients enrolled will receive AVB-S6-500.

3.8.6 Prior and Concomitant Therapy

All medications taken within 14 days prior to the first dose of study drug will be recorded as prior medications.

All medications taken after the first dose of study drug and through the end-of-study visit will be recorded as concomitant therapy. Any changes in concomitant medications will also be recorded in the subject's eCRF.

3.8.6.1 Medications Prohibited/Restricted in Combination with AVB-S6-500

AVB-S6-500 is a biologic Fc-fusion protein and thus degraded to the component amino acids. Therefore, there are no known or anticipated drug-drug interactions with any other medications.

3.8.7 Sample Size Calculations

Up to approximately 24 patients will be enrolled in this study. No formal sample size estimate made as the study is an exploratory study that has no inferential statistical analysis. However, the

number of participating patients in each part of the present study is common in early clinical studies and considered sufficient to evaluate to study objectives.

3.8.8 Analysis Sets

The following analysis sets will be used in the statistical analyses:

Pharmacokinetic (PK) Analysis Set: The PK analysis set will be defined as all enrolled patients who received 1 dose of AVB-S6-500 and have sufficient PK samples to allow accurate calculation of PK parameters.

Safety Analysis Set: The safety analysis set will be defined as all patients enrolled who received at least one dose of study drug.

Efficacy Analysis: All patients who received at least four doses of study drug and have one post-baseline urine will be included. [redacted]

3.9 Statistical Analysis

3.9.1 Exploratory Efficacy Analyses

This is an exploratory study to understand the impact AVB-S6-500 has on IgAN. The effect of AVB-S6-500 may be analyzed on the following, as well as additional endpoints:

1. Change from baseline (last value in screening) to End of Treatment in 24-hour urine protein excretion (UPE) in g/day.
2. Change from baseline (last value in screening) to End of Treatment in 24-hour urine protein excretion (UPE) in g/day in the subset of patients with baseline high proteinuria (defined as 24-hour UPE $\geq$ 2 g/day).
3. Proportion of patients with urinary protein equivalent of $<$ 1 g/24 hours at End of Treatment.
4. Proportion of patients who had at least a decrease of 0.5 g/day proteinuria from baseline (last value during screening) to End of Treatment.
5. Change from baseline (last value during screening) to end of treatment in albumin/creatinine ratios (uACRs). Additionally, change from baseline to each month of treatment (i.e. Days 29 and 57)
6. Change from baseline (last value during screening) in estimated glomerular filtration rate (eGFR). Additionally, change from baseline to each month of treatment (i.e. Days 29 and 57)

3.9.2 Pharmacokinetic Analyses

PK parameters will be calculated using a validated version of Phoenix™ WinNonlin® 7.0 or later. Summary tables and/or figures will be generated using a validated version of Phoenix™ WinNonlin® 7.0 or later. Tables, listings, and figures will be generated using R v3.3.3 (or higher).

PK parameters for AVB-S6-500 will be calculated from concentration profiles calculated relative to the end of AVB-S6-500 IV infusion. The actual PK sampling time will be used in all calculations. The actual dose administered, and the actual infusion duration time will be used to calculate the PK parameters. No negative actual times will be included in the calculation of PK parameters. Blood samples for AVB-S6-500 measurements that were taken prior to the start of infusion of the study medication will be assigned to time 0 hours for the calculation of PK parameters. C_{max} and C_{min} values from subsequent doses will also be tabulated and reported. Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK parameters. If actual sampling times are not available, nominal times may be used.

Concentration values of AVB-S6-500 that are reported as BLQ will be set to zero for PK and statistical analyses. There will be no substitutions made to accommodate missing data points.

Visual inspection of AVB-S6-500 concentration-time profiles will be performed to determine dataset integrity. Patients with observations that are deviating from the mean by ±3 standard deviations (SD) and, thus, are different from 99.73% of the rest of the observations for the same treatment group, will be reviewed for inclusion/exclusion from the descriptive statistics. If deemed necessary, a sensitivity analysis will be performed (i.e., outputs will be generated with and without deviating profiles).

Patients with incomplete dosing information (e.g., missing dosing record) will be reviewed for inclusion/exclusion into the PK analysis set to determine the disposition of these patients. Nominally, patients who received a dose of AVB-S6-500 with no major protocol deviations and with sufficient AVB-S6-500 sample data to assess PK parameters for each individual concentration-time profile of AVB-S6-500 will be included in the analysis.

3.9.3 Pharmacodynamic and Anti-drug Antibody Analyses

ADA data will be summarized as patients with pre-existing ADA (based on baseline value) and no increase in titer, pre-existing ADA with increase in titer post dose, negative ADA at baseline and no ADA during treatment, and patients with negative ADA at baseline and positive for ADA during treatment. The circulating concentration of free serum GAS6 will be analyzed and described in tabular and graphical formats. Analysis of the serum free GAS6 concentrations in the context of ADA may be included to assist with identification of any neutralizing antibody activity.

3.9.4 Safety Analyses

All safety endpoints will be summarized by treatment group using the safety analysis set. Descriptive statistics will be tabulated for both categorical (number of patients, %) and continuous (number of patients, mean, standard deviation, minimum, median, and maximum) safety variables including, but not limited to AEs, clinical laboratory parameters, ECGs, vital sign measurements, and concomitant medications.

3.9.4.1 Adverse Events

Adverse events will be coded using the most updated version of MedDRA. Data will be summarized using the preferred term and primary system organ class. The coded events will be summarized in subsets of all AEs. All nonserious AEs will be summarized by severity for each treatment group. Patients who have discontinued due to an AE or who experienced an SAE will be tabulated by treatment group.

Serious AEs and treatment-related SAEs will be summarized and listed.

3.10 Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of a qualified investigator and appropriate study center, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of blood and plasma samples.

The eCRFs will be provided to the clinical contact and the CRA will review them with site personnel. The investigator, or designee, will enter study data required by the protocol into an electronic data eCRF system. The clinical research associates will visit each study site, at a frequency documented in the monitoring plan, to review eCRF for completeness and accuracy. Any discrepancies found between source documents and completed CRF (electronic) will be entered as a discrepancy in the EDC system by the clinical research associate. Appropriate study site personnel should then address those discrepancies in the EDC system. Uniform procedures for CRF (electronic) correction (queries) will be discussed during the study site initiation visits, and will be documented in the study operations manual.

4. Investigator's Obligations

The following administrative items are meant to guide the Investigator (Principal Investigator or Subinvestigator) in the conduct of the study but may be subject to change based on industry and government standard operating procedures (SOPs), working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

4.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be deidentified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the Sponsor, its designee, or the local regulatory authorities, or ethics committees.

The Principal Investigator or Subinvestigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

4.2 Institutional Review

Federal regulations and the International Conference on Harmonisation (ICH) guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent form, advertisements to be used for the recruitment of study patients and any other written information regarding this study to be provided to the patient must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the study site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title and/or protocol number, and the date approval and/or favorable opinion was granted.

The Principal Investigator or Subinvestigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Principal Investigator or Subinvestigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

4.3 Subject Consent

A written informed consent shall be obtained from each patient before the patient enters the study or before any unusual or nonroutine procedure that involves risk to the patient is performed. An ICF will be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor and/or its designee, if appropriate before IRB/IEC submission. Once reviewed, the consent will be submitted by the Investigator to the IRB/IEC for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all active participating patients should sign the revised form, if applicable, especially if the rights, well-being, and the safety of the patient are impacted by the revision.

Before enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the Investigator or designee is assured that the patient understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the informed consent form.

The Investigator or designee shall retain the signed original ICFs and provide a copy of the signed original to the subject.

4.4 Study Reporting Requirements

By participating in this study, the Principal Investigator or Subinvestigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the Principal Investigator or Subinvestigator agrees to submit annual reports to his/her IRB/IEC as appropriate.

4.5 Financial Disclosure and Obligations

Principal Investigators or Subinvestigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 Code of Federal Regulations (CFR) 54. In addition, the Investigator (Principal Investigator or any Subinvestigators) must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor CRO is financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor CRO is financially responsible for further treatment of the patient's disease.

4.6 Investigator Documentation

Before beginning the study, the Principal Investigator will be asked to comply with ICH E6(R2) 8.2 and 21 CFR (Parts 50, 54, 56, and 312) by providing essential documents, including but not limited to the following:

- An original signed Investigator Protocol Agreement Page of the protocol.
- An IRB/IEC approved informed consent, samples of site advertisements for recruitment for this study (if applicable), and any other written information regarding this study that is to be provided to the patient.
- IRB/IEC approval.
- Form Food and Drug Administration (FDA) 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curriculum vitae for the Principal Investigator and each Subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. They will be signed and dated by the Principal Investigators and Subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the

Investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

4.7 Study Conduct

The Principal Investigator agrees that the study will be conducted according to the principles of the ICH E6(R2). The Principal Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

4.8 Data Collection

4.8.1 Case Report Forms Completion

Case report forms are provided for each subject in electronic format.

Electronic data capture (EDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an eCRF. The electronic file will be considered the CRF. Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the patients' source documentation. All data relating to the study must be recorded in the eCRF approved by the sponsor. Designated site personnel must complete eCRFs as soon as possible after a subject visit but preferably within approximately 48 hours of completing the subject's visits, and the forms should be available for review at the next scheduled monitoring visit.

The investigator is responsible for approval of the entered/corrected data.

All eCRF entries, corrections, and alterations must be made by authorized study site personnel. If necessary, queries will be generated in the EDC tool. An authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

1. Site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool),
2. The clinical research associate (CRA) can generate a query (field data collection form) for resolution by the investigational staff, or
3. The clinical data manager can generate a query for resolution by the investigational staff

4.9 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with the ICH E6(R2) guidelines and applicable government regulations.

4.10 Reporting Adverse Events

By participating in this study, the Principal Investigator or Subinvestigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol (Section 3.7.4.1.4). In addition, the Principal Investigator or Subinvestigator agrees to submit annual reports to his/her IRB/IEC as appropriate.

4.11 Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform his/her institution of study completion; the Investigator/institution should provide the IRB/IEC with a summary of the study's outcome.

4.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study medication. These documents should be retained for a longer period, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Principal Investigator or Subinvestigator/institution as to when these documents no longer need to be retained.

4.13 Publications

After completion of the study, study data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

5. Study Management

5.1 Monitoring

5.1.1 Monitoring of the Study

The clinical research associate (CRA), as a representative of the sponsor will visit the Principal Investigator or Subinvestigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Principal Investigator or Subinvestigator and study site personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and current standard operating procedures.

5.1.2 Inspection of Records

Principal Investigators or Subinvestigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Principal Investigator or Subinvestigator agrees to allow the sponsor, representatives of the sponsor, the FDA, or other regulatory agency access to all study records.

The Principal Investigator or Subinvestigator should promptly notify the sponsor and CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

5.2 Management of Protocol Amendments and Deviations

5.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the Principal Investigator's or Subinvestigator's IRB/IEC for approval before patients are enrolled into an amended protocol.

5.2.2 Protocol Violations and Deviations

The Principal Investigator or Subinvestigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Principal Investigator or Subinvestigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the IRB/IEC and agreed to by the Principal Investigator or Subinvestigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the patient, when the patient or Principal Investigator or Subinvestigator has failed to adhere to significant protocol requirements (e.g. inclusion/exclusion criteria) and the patient was enrolled without prior sponsor approval, or when there is nonadherence to FDA regulations and/or ICH E6(R2) guidelines.

Protocol violations and deviations will be documented by the clinical research associate throughout the course of monitoring visits. Investigators should notify their IRB/IEC of all protocol violations and deviations in a timely manner.

5.3 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study report is prepared and provided to the regulatory agencies as required by the applicable regulatory requirements. The sponsor will also ensure that the clinical study report in marketing applications meet the standards of the harmonised tripartite guideline E3: Structure and Content of Clinical Study Reports.

6. References

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7. Appendices

7.1 Appendix 1: Time and Events Schedule

Table 7-1: Time and Events Schedule

	Screening Phase	Treatment Phase							Post-treatment Phase
Activity/Assessment	Screening[1] Day -28 to -1	Day 1	Day 15[2] (±2 days)	Day 29 (±2 days)	Day 43 (±2 days)	Day 57 (±2 days)	Day 71 (±2 days)	EOT Day 85 (±2 days)	Follow-up Visit[14] Day 99 (±5 days)
Informed Consent[3]	X								
Inclusion/Exclusion Criteria	X								
Height, weight	X								
Medical History	X								
Demographics	X								
Prior Meds[4]	X	X							
Physical Exam[5]	X	X	X	X	X	X	X	X	X
Pregnancy Test[6]	X	X						X	X
ECG[7]	X	X						X	X
Vital Signs[8]	X	X	X	X	X	X	X	X	X
Enrollment[9]	X								
PK/PD Samples[10]		X	X	X	X	X	X	X	
Anti-AVB antibody Samples		X							X
Blood collection for clinical labs[11]	X	X	X	X	X	X	X	X	X
Estimate GFR[12]	X			X		X		X	
Urine sample collection for uACR	X			X		X		X	
24-hour urine collection	X							X	
Adverse Events		X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X

	Screening Phase	Treatment Phase							Post-treatment Phase
Activity/Assessment	Screening[1] Day -28 to -1	Day 1	Day 15[2] (±2 days)	Day 29 (±2 days)	Day 43 (±2 days)	Day 57 (±2 days)	Day 71 (±2 days)	EOT Day 85 (±2 days)	Follow-up Visit[14] Day 99 (±5 days)
AVB-S6-500 Dosing[13]		X	X	X	X	X	X		

[1] Screening: Must occur within 28 days of first dose of study drug

[2] Any patients enrolled at DL-1: Assessments shown at this visit should be performed for D9 and D22 visits during each month of treatment.

[3] Informed Consent: Written informed consent should be obtained prior to the performance of any study procedure

[4] Prior Meds: All medications taken within 14 days of the first dose of study drug should be recorded.

[5] Physical Exam: A complete physical examination of all body systems (excluding rectal and pelvic examinations and breast examinations) will be performed at Screening visit, at the End-of-Treatment (or Early Withdrawal) and Follow-Up visits. A brief physical exam (symptom directed) will be performed at Days 1, 15, 29, 43, 57, and 71. Height and weight will be recorded at the Screening visit only. Additional assessments can be done at any time if clinically indicated or as per investigator discretion. Perform prior to dosing on days where assessment occurs and study drug is administered.

[6] Pregnancy test: A serum pregnancy test is required at screening. Urine pregnancy test (unless a serum pregnancy test is preferred at the discretion of the investigator or if required by local regulations) will be performed at other time points.

[7] ECG: Obtain a 12-lead ECG at baseline (Screening) and at 2 hours post completion of AVB-S6-500 infusion on Day 1. ECG will also be obtained on Day 85 (EOT) and at the Follow-up Visit.

[8] Vital signs: pulse, blood pressure, respiratory rate, and body temperature. Collect vital signs pre-dose (within 2 hours prior to infusion). When scheduled to occur at the same time point as the collection of blood samples, vital sign measurements should be obtained before blood sample collection if possible. Subjects may be either in a semi-recumbent or seated position and measurements will be collected after a 5-minute rest period.

[9] Enrollment: Enroll patient after successful completion of all screening requirements by entering baseline data into the electronic case report form (eCRF) anytime during the Screening or prior to dosing on Day 1.

[10] PK/PD Samples: Serum samples will be taken predose (within 45 min before dosing) before each AVB-S6-500 dose and on Day 1 at 1 hour after dosing. A blood sample will also be collected on Day 85 (EOT). It is important that all serum samples collected for this analysis are taken from the arm that is not used for administration of AVB-S6-500.

[11] Clinical labs: Blood samples will be collected at screening and prior to each dosing (within approximately 2 hours before dosing), at EOT and at the Follow-up Visit.

[12] eGFR: Estimate GFR using the CKD-EPI formula.

[13] [redacted]

[14] Follow-up Visit: To be scheduled approximately 4 weeks after the last dose of study drug