Summary of Amended Protocol Changes

A Randomized, Double-blind, Placebo-Controlled, Dose Escalation Study to Assess Safety, Efficacy and Pharmacokinetics of GMA301 in Subjects with Pulmonary Arterial Hypertension

Protocol Version 3.0 Status: Final
Original Protocol Date: 14 August 2019
Protocol Date: 17 March 2020

Study Drug: GMA301 Injection

Sponsor Reference Number: GETA_MAD_01
Covance Study Number: 000000180905

Sponsor:
Gmax Biopharm LLC.
Room 302, Building No. 2, 288 Qiuyi Road
Binjiang District, Hangzhou, 310052, China

Sponsor Signatory:
Shuqian JING

Principal Investigators:
Raymond L. Benza M.D

Zhicheng JING M.D

The primary changes in this amendment, along with the rationale for the changes as appropriate, are:

1. To update the English protocol based on Chinese protocol version 4.0 (dated 25Feb2020).
    - To update the version of Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) calculator to be used in the study
    - To clarify exclusion criteria regarding echocardiogram
    - To clarify drug concentration will be determined in serum
    - To clarify the dose delivery method should be IV injection
2. To clarify that pregnancy test will be done in females of reproductive potential.
3. To specify Baseline REVEAL score should be collected at randomization.

Minor changes:

1. The synopsis was updated according to the changes in the protocol body, as applicable.
2. The amendment/version number and date were updated throughout the protocol.
3. Typographical errors and formatting errors were corrected, as necessary.
4. Abbreviations were added and/or removed, as appropriate.

A detailed summary of changes is presented below:

Section 2.2.2

Previously read:

- Pharmacokinetics
    - Area under the plasma concentration- time curve from time zero to the last measurable concentration (AUC_{0-t})
    - Area under the plasma concentration- time curve over a dosing interval (AUC_{0-tau})
    - Observed maximum serum concentration (C_{max})
    - Time to maximum Area under the serum concentration-time curve from time zero to infinity (AUC_{0-inf})
    - serum concentration (T_{max})
    - Terminal elimination half-life ($t_{1/2}$)
    - Volume of distribution
    - Trough concentration
    - Clearance
    - Accumulation ratio

Now reads:

- Pharmacokinetics
  - Area under the serum concentration- time curve from time zero to the last measurable concentration (AUC_{0-t})
  - Area under the serum concentration- time curve over a dosing interval (AUC_{0-tau})
  - Observed maximum serum concentration (C_{max})
  - Area under the serum concentration-time curve from time zero to infinity (AUC_{0-inf})
  - Time to maximum serum concentration (T_{max})
  - Terminal elimination half-life ($t_{1/2}$)
  - Volume of distribution
  - Trough concentration
  - Clearance
  - Accumulation ratio

Section 3.1

Previously read:

Subjects will be sequentially recruited into 3 ascending dose treatment cohorts with GMA301-assigned subjects receiving either 300, 600 or 1000 mg injections of the study drug depending on their assigned cohort. Each cohort will contain 12 subjects, 9 of whom will be administered active GMA301 and 3 of whom will be administrated placebo. All subjects will undergo IV infusion at baseline, Week 4, and Week 8.

Now reads:

Subjects will be sequentially recruited into 3 ascending dose treatment cohorts with GMA301-assigned subjects receiving either 300, 600 or 1000 mg injections of the study drug depending on their assigned cohort. Each cohort will contain 12 subjects, 9 of whom will be administered active GMA301 and 3 of whom will be administrated placebo. All subjects will undergo IV injection at baseline, Week 4, and Week 8.

Section 3.3

Previously read:

The selection of the GMA301 dosing frequency of Q4W via IV infusion at baseline and then at 4 and 6 weeks was based on the available clinical safety, tolerability and PK data obtained from healthy human subjects.[18]

Now reads:

The selection of the GMA301 dosing frequency of Q4W via IV injection at baseline and then at Week 4 and Week 8 was based on the available clinical safety, tolerability and PK data obtained from healthy human subjects.[18]

Section 4.1

Previously read:

5. Right heart catheterization (RHC) result meets below criteria when screening.
    a. Mean pulmonary arterial pressure (PAP) ≥25 mmHg
    b. Pulmonary vascular resistance (PVR) >3 Woods units
    c. PA wedge pressure (PAWP) ≤15 mmHg

if subject has undergone RHC within 3 months before screening, the waveform results will serve as baseline data if they meet entry criteria and the baseline RHC will not be repeated.

6. Has been taking at least one oral PAH targeted drug that has been approved by local guidelines for at least 3 months before screening with a stable dosage and associated PAH symptoms in this period.

Now reads:

5. Has been taking at least one oral PAH targeted drug that has been approved by local guidelines for at least 3 months before screening with a stable dosage and the disease did not worsen during this period.
6. Right heart catheterization (RHC) result meets below criteria when screening.
    d. Mean pulmonary arterial pressure (PAP) ≥25 mmHg
    e. Pulmonary vascular resistance (PVR) >3 Woods units
    f. PA wedge pressure (PAWP) ≤15 mmHg

if subject has undergone RHC within 3 months before screening, the waveform results will serve as baseline data if they meet entry criteria and the RHC at Screening will not be repeated.

Section 4.2

Previously read:

5. Pulmonary function test: FEV1<60%, TLC<60%, DLCO<60%;
   […]
10. Echocardiogram (ECHO) demonstrating at least 1 of the following:

a. LVEF ≤50%
b. Mean end-diastolic left ventricular septal and posterior wall thickness of >12 mm and one of the following:
   i. Left atrial (LA) area on apical 4 chamber view >20 cm^2
   ii. LA volume by biplane modified Simpsons or area-length methods >55 mL
   iii. LA volume index >29 mL/m^2
c. Significant valvular heart disease including moderate or severe mitral or aortic stenosis with an aortic valve area <1.0 cm^2 or mitral valve area <1.5 cm^2), greater than moderate aortic or mitral regurgitation, greater than moderate tricuspid or pulmonic stenosis

Now reads:

5. Pulmonary function test: FEV1<60% of predicted, TLC<60% of predicted, DLCO<60% of predicted;
   […]
10. Echocardiogram (ECHO) demonstrating at least 1 of the following:
    a. LVEF ≤50%
    b. Mean end-diastolic left ventricular septal and posterior wall thickness of >12 mm
    c. Left atrial (LA) area on apical 4 chamber view >20 cm^2
    d. LA volume by biplane modified Simpsons or area-length methods >55 mL
    e. LA volume index >29 mL/m^2
    f. Significant valvular heart disease including moderate or severe mitral or aortic stenosis with an aortic valve area <1.0 cm^2 or mitral valve area <1.5 cm^2), greater than moderate aortic or mitral regurgitation, greater than moderate tricuspid or pulmonic stenosis

Section 5.2

Previously read:

The 300 (5 mg/kg), 600 (10 mg/kg), and 1000 mg (16.6 mg/kg) doses of GMA301 and matching placebo will be administered Q4W via IV injection by slow push for 12 weeks.

Now reads:

The 300, 600, and 1000 mg doses of GMA301 and matching placebo will be administered Q4W via IV injection by slow push for 12 weeks.

Section 7.1.2

Previously read:

Plasma concentrations of GMA301 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

Now reads:

Serum concentrations of GMA301 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

Section 7.2.2

Previously read:

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

Now reads:

For females of reproductive potential, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

Section 7.3.3

Previously read:

The 6MWT will be collected at the times indicated in the Schedule of Assessments in Appendix 6. The operation details of 6MWT is described in the Site Operation Menu.

Now reads:

The 6MWT will be collected at the times indicated in the Schedule of Assessments in Appendix 6. The operation details of 6MWT is described in the Site Operation Menu. Borg index score will be collected immediately after 6MWTs.

Section 8.5

Previously read:

Non-compartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of GMA301 and PK parameters will be listed and summarized using descriptive statistics. Individual and mean GMA301 concentration-time profiles will also be presented graphically.

Now reads:

Non-compartmental PK analysis will be performed on individual serum concentration data, using commercial software such as Phoenix® WinNonlin®. Serum concentrations of GMA301 and PK parameters will be listed and summarized using descriptive statistics. Individual and mean GMA301 concentration-time profiles will also be presented graphically.

Section 8.6

Previously read:

AEs will be coded by System Organ Class and Preferred Term using the current version of the MedDRA dictionary. Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Safety data will be summarized by dose group. Incidences of TEAEs (those events that started after exposure to study drug or worsened in severity after dosing) will be presented by dose group as well. Incidences of TEAEs will be presented by maximum severity and relationship to study medication. AEs will be classified according to whether they are covered by the Standardized MedDRA Query of Pulmonary Hypertension, and incidences will be presented by maximum severity.

Now reads:

AEs will be coded by System Organ Class and Preferred Term using the current version of the MedDRA dictionary. Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Safety data will be summarized by dose group. Incidences of TEAEs (those events that started after exposure to study drug or worsened in severity after dosing) will be presented by dose group as well. Incidences of TEAEs will be presented by maximum severity and relationship to study medication.

Appendix 6: Schedule of Assessments

Changes to the Schedule of Assessments:

- Footnote d was added to clarify that Week 12 tests can also be done on the last day of Week 11. If a subject discontinues the visit in advance, it would be better to ask the subject to complete the Week 12 examinations.
- Baseline REVEAL risk score will be collected at randomization.

Appendix 6: Pharmacokinetics sampling

Previously read:

Pharmacokinetics sampling:

Pharmacokinetics plasma samples will be obtained for PK assessments at the following timepoints (±Time window):

Now reads:

Pharmacokinetics sampling:

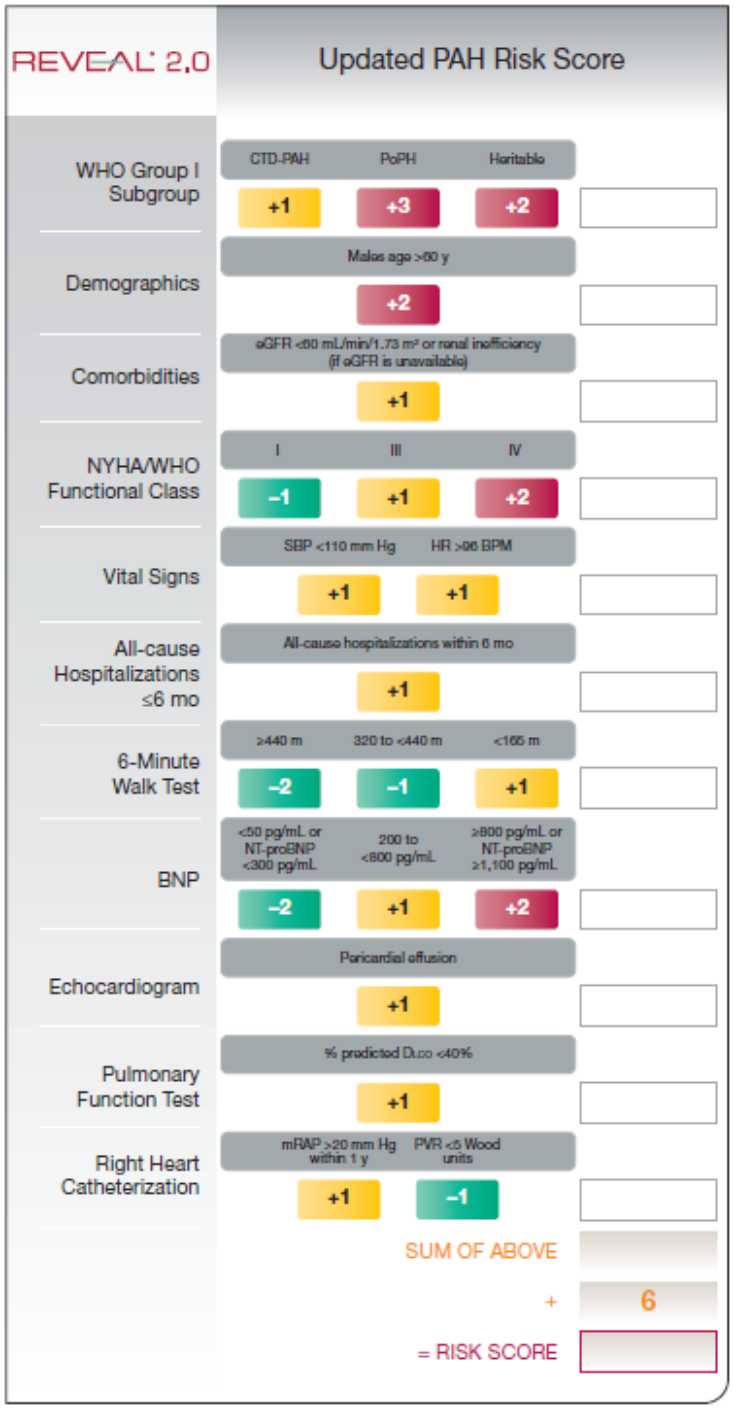
Pharmacokinetics serum samples will be obtained for PK assessments at the following timepoints (±Time window):

Appendix 7

Previously read:

Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk). If N-terminal proBNP is available and BNP is not, listed cut points are replaced with, 300 pg/mL and 1500 pg/mL. APAH 5 associated pulmonary arterial hypertension; BNP 5 brain natriuretic peptide; BPM 5 beats per minute; CTD 5 connective tissue disease; DLco 5 diffusing capacity of lung for carbon monoxide; FPAH 5 familial pulmonary arterial hypertension; HR 5 heart rate; mRAP 5 mean right atrial pressure; NYHA 5 New York Heart Association; PAH 5 pulmonary arterial hypertension; PoPH 5 porto pulmonary hypertension; PVR 5 pulmonary vascular resistance; REVEAL Registry 5 Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SBP 5 systolic BP; WHO 5 World Health Organization.

Now reads:



Calculated risk scores can range from 0 (lowest risk) to 23 (highest risk). BNP = brain natriuretic peptide; BPM = beats per minute; CTD-PAH = PAH associated with connective tissue disease; DLco = diffusing capacity of the lungs for carbon monoxide; eGFR = estimated glomerular filtration rate; FC = functional category; HR = heart rate; mRAP = mean right atrial pressure; NT-proBNP = N-terminal fragment of pro-brain natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PoPH = pulmonary hypertension associated with portopulmonary hypertension; PVR = pulmonary vascular resistance; REVEAL Registry = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SBP = systolic BP; WHO = World Health Organization.

Protocol

A Randomized, Double-blind, Placebo-Controlled, Dose Escalation Study to Assess Safety, Efficacy and Pharmacokinetics of GMA301 in Subjects with Pulmonary Arterial Hypertension

Protocol Status: Final
Protocol Date: 17 Mar 2020
Protocol Version: 3.0

Investigational Product: GMA301 Injection

Protocol Reference Number: GETA_MAD_01

Sponsor:
Gmax Biopharm LLC.
Room 302, Building No. 2, 288 Qiuyi Road
Binjiang District, Hangzhou, 310052, China

Sponsor Signatory:
Shuqian JING

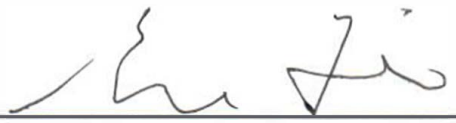
Principal Investigators:

Raymond L. Benza M.D

Zhicheng JING M.D

SPONSOR APPROVAL SIGNATURE

I have read the protocol and approve it to be conducted in compliance with the International Council for Harmonisation guidelines for Good Clinical Practice and applicable regulatory requirements.



04/17/2020

Shuqian JING
Chief Executive Officer, Gmax Biopharm LLC.

Date

INVESTIGATOR APPROVAL SIGNATURE

This study will be conducted in compliance with the clinical study protocol (and amendments), the International Council for Harmonisation guidelines for current Good Clinical Practice and applicable regulatory requirements.

Zhi-Cheng J.

Zhicheng JING M.D.

2020-4-1

Date

INVESTIGATOR APPROVAL SIGNATURE

This study will be conducted in compliance with the clinical study protocol (and amendments), the International Council for Harmonisation guidelines for current Good Clinical Practice and applicable regulatory requirements.

May 22, 2020

Raymond L. Benza M.D. | Date

STUDY PERSONNEL

Sponsor	Gmax Biopharm LLC. Room 302, Building No. 2, 288 Qiuyi Road Binjiang District, Hangzhou, 310052, China
Sponsor Contact (Project)	Quanyu SU, Project Director Gmax Biopharm LLC. Room 308, Building No.1, 288 Qiuyi Road Binjiang District, Hangzhou, 310052, China
Sponsor Contact (Medical)	Chuan YOU. Medical Director Gmax Biopharm LLC. Room 308, Building No. 1, 288 Qiuyi Road Binjiang District, Hangzhou, 310052, China
Principal Investigators	Zhicheng JING M.D. Peking Union Medical College Hospital No.1 Shuaifuyuan Wangfujing Dongcheng District, Beijing, China 100730 Tel: (0086) 10-69156114 Dr. Raymond L. Benza M.D. Allegheny General Hospital 20 East North Avenue 16th Floor – South Tower Pittsburgh, Pennsylvania, 15212, US Tel: (001) 412-359-3584
Clinical Laboratory	Covance Pharmaceutical Research and Development (Shanghai) Co., Ltd
Bioanalytical Laboratory	Covance Pharmaceutical Research and Development (Shanghai) Co., Ltd
Statistical Analysis	Covance Pharmaceutical Research and Development (Beijing) Co., Ltd Shanghai Branch

SYNOPSIS

Title of Study: A Randomized, Placebo-Controlled, Double-blind, Dose Escalation Study to Assess Safety, Efficacy and Pharmacokinetics of GMA301 Injection in Subjects with Pulmonary Arterial Hypertension

Objectives:

The primary objective is:

- To assess the safety and tolerability of GMA301 following repeated intravenous (IV) doses in subjects with World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH)

The secondary objectives are:

- To determine the pharmacokinetics (PK) and dose/exposure-response relationships of GMA301
- To evaluate the effects of GMA301 on hemodynamics
- To evaluate the effects of GMA301 on exercise tolerance
- To evaluate the effects of GMA301 on relevant PAH biomarkers

The exploratory objectives are:

- To evaluate the effects of GMA301 on REVEAL 2.0 risk score

Study Design:

This is a randomized, placebo-controlled, double-blind, dose escalation study to assess the safety, efficacy and PK of GMA301 in PAH subjects with WHO functional class II to III who are taking approved targeted therapy other than endothelin receptor antagonists (ERAs). Treatment will include 3 sequential dose-ascending cohorts, each with 9 subjects receiving GMA301 injection and 3 subjects receiving GMA301 matching placebo injection (total of 36 subjects; in the ratio of 3:1). Patients in the ascending dose cohorts who are assigned to active GMA301 will be administered 300, 600, or 1000 mg of GMA301 based on their assigned cohort as described above.

Subjects will undergo a Screening Period of up to 4 weeks and those proceeding to randomization will receive GMA301 or placebo at baseline, Week 4 and Week 8 visits. Subjects will be evaluated for safety, efficacy and pharmacokinetics at Weeks 4, 8, and 12 visits.

Dose escalation criteria for each cohort will be assessed by a Safety Review Committee (SRC) prior to escalating to the next higher dose cohort. The initial SRC meeting will review safety data from the initial 8 subjects in Cohort 1 who have completed 3 doses of the study drug and have been followed for 28 days following the third dose. If no safety issues are identified, Cohort 2 will be opened for recruitment once the residual 4 subjects have been randomized in Cohort 1. The second meeting of the SRC will review safety data from the initial 8 subjects in Cohort 2 **and the 4 residual subjects from Cohort 1 who were not yet reviewed.** If no safety issues are identified, once the residual 4 subjects in Cohort 2 are randomized, there will be notification to sites that Cohort 3 can be initiated for recruitment. If fewer than 8 subjects (including 8) in a cohort, with some drop-outs, have

completed administration and follow-up regimen, their safety data will be reviewed by SRC aiming to determine whether the next cohort with a higher dose can be started.

Number of Subjects:
A total of 36 subjects will be recruited from approximately 7 PAH sites in China and 3 in the United States (US).

Subject Eligibility:
The subject eligibility will be determined by the following inclusion and exclusion criteria:

Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male or female, aged 18 to 75 years inclusive
2. WHO Group 1 PAH related to one of the following conditions:
    a. Idiopathic
    b. Heritable
    c. Drugs or toxins-induced
    d. Associated with connective tissue disease
    e. Associated with congenital heart disease if subjects underwent surgical correction more than 12 months before Screening
3. Symptoms due to PAH are consistent with WHO functional class II- III;
4. Have not taken endothelin receptor antagonists (ERAs) within 3 months before randomization.
5. Has been taking at least one oral PAH targeted drug that has been approved by local guidelines for at least 3 months before screening with stable dosage and the disease did not worsen during this period.
6. Right heart catheterization (RHC) result meets below criteria when screening.
    a. Mean pulmonary arterial pressure (PAP) ≥25 mmHg
    b. Pulmonary vascular resistance (PVR) >3 Woods units
    c. PA wedge pressure (PAWP) ≤15 mmHg

* if a subject has undergone RHC within 3 months before screening, the waveform results will serve as baseline data if they meet entry criteria; and the RHC at Screening will not be repeated.

7. Has a six-minute walk test (6MWT) with distance between 150 to 450 meters at Screening.
8. The dosage of digitalis drugs or L-arginine supplementation must be stable for at least 1 month before Screening, if applicable.
9. No new use of an IV diuretic, cardiotonic or vasoactive drug within 30 days before screening.
10. Both male and female subjects agree to use a medically acceptable method of contraception throughout the entire study period from informed consent signing to 90 days after last dose, if the possibility of conception exists. Medically acceptable methods of contraception include oral, implantable, or injectable contraceptives (starting 2 months before dosing); diaphragm with vaginal spermicide; intrauterine device; condom and partner using vaginal spermicide; and surgical sterilization (6 months after surgery). Women who are surgically sterile or those who are postmenopausal for at least 2 years are not considered to be of childbearing potential. Eligible male and female subjects must agree not to participate in a

conception process (i.e. active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization) during the study and for 90 days after the last dose of study drug.

11. Body weight no less than 40 kg at Screening.
12. Able to understand and willing to sign the Informed Consent Form (ICF) and comply with the study procedures.

Exclusion Criteria

Subjects who meet any of the following criteria will not be allowed to participate in this study:

1. Diagnosed with WHO Group II, III, IV, V of PH;
2. Using calcium channel blockers when Screening;
3. BP>160/100mmHg at Screening;
4. Systolic BP <90 mmHg at Screening;
5. Pulmonary function test: FEV1<60% of predicted, TLC<60% of predicted, DLCO<60% of predicted;
6. One of the following tests with confirmed pulmonary embolism and/or chronic thrombo-embolic pulmonary hypertension (CTEPH) following initial diagnosis of PAH:
    a. Pulmonary ventilation/perfusion scan
    b. CT pulmonary angiogram
    c. Contrast dye pulmonary angiogram
7. History of sleep apnea.
8. Limited full participation in the 6MWT due to arthritic, neuromuscular, vascular or other diseases unrelated to PAH.
9. History of acute cardiovascular and/or cerebrovascular events within 6 months before screening.
10. Echocardiogram (ECHO) demonstrating at least one of the following:
    a. LVEF $\underline{\leq 50}$%
    b. Mean end-diastolic left ventricular septal and posterior wall thickness of >12 mm
    c. Left atrial (LA) area on apical 4 chamber view >20 cm^2
    d. LA volume by biplane modified Simpsons or area-length methods >55 mL
    e. LA volume index >29 mL/m^2
    f. Significant valvular heart disease including moderate or severe mitral or aortic stenosis with an aortic valve area <1.0 cm^2 or mitral valve area <1.5 cm^2), greater than moderate aortic or mitral regurgitation, greater than moderate tricuspid or pulmonic stenosis
11. Restrictive, dilated or hypertrophic cardiomyopathy or constrictive pericarditis
12. Using non-oral prostacyclin when screening;
13. Laboratory parameters during screening:
    a. Baseline aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2 times the upper limit of normal (ULN) or total bilirubin ≥1.5 times ULN
    b. Estimated glomerular filtration rate (eGFR) <60 mL/min by Cockcroft-Gault formula
    c. Hemoglobin concentration ≤100 g/L at screening
14. QTc interval by Fridericia's criteria (QTcF) ⩾500 msec at screening

15. Malignancy within 5 years before screening visit (with the exception of localized non-metastatic basal cell carcinoma of the skin, non-metastatic carcinoma of the prostate or in-situ carcinoma of the cervix excised with curative results)
16. Alcohol or drug abuse within 1 year before screening
17. A psychiatric, addictive or other disorder that compromises the ability to give informed consent for participating in this study
18. History of organ transplantation
19. Pregnant or nursing females
20. History of HIV
21. Positive hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV-Ab), or HIV antibody (HIV-ab).
22. Enrolled in another interventional study within 30 days before screening.
23. Any condition that, in the opinion of the investigator, prevents a potential subject from safely participating in the study.

Investigational products, dose, and mode of administration:
Test products: GMA301
Proposed dose levels: 300, 600, and 1000 mg every 4 weeks (Q4W) for 12 weeks
Administration route: IV

Duration of subject participation in the study:
Planned Screening duration: up to 4 weeks.
Planned study duration (Screening to Follow-up): approximately 22 weeks.

Endpoints:

Primary Endpoints

The incidence of Treatment Emergent Adverse Events (TEAE) after the start of GMA301 dosing compared with placebo.

Secondary Endpoints

- Pharmacokinetics
    - Area under the serum concentration- time curve from time zero to the last measurable concentration (AUC_{0-t})
    - Area under the serum concentration- time curve over a dosing interval (AUC_{0-tau})
    - Observed maximum serum concentration (C_{max})
    - Area under the serum concentration-time curve from time zero to infinity (AUC_{0-inf})
    - Time to maximum serum concentration (T_{max})
    - Terminal elimination half-life ($t_{1/2}$)
    - Volume of distribution
    - Trough concentration
    - Clearance
    - Accumulation ratio

- Comparison of GMA301 treatment effect at Week 12 versus baseline regarding the hemodynamic parameters based on RHC. Parameters include:
    - Pulmonary vascular resistance (PVR)
    - Mean PAP
    - Cardiac index

- Comparing the following treatment effect metrics:
    - 6MWT distance (Week 12 versus screening)
    - NT-pro BNP level (Weeks 4, 8, and 12 versus baseline)
    - WHO functional class (Weeks 8 and 12 versus baseline)

Exploratory Endpoints

- Changes in REVEAL 2.0 risk score at Week 12 compared with baseline

Statistical methods:

Safety:
Adverse events (AEs) will be coded by System Organ Class and Preferred Term using the current version of the MedDRA dictionary. Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Safety data will be summarized by dose group. Incidences of TEAEs (those events that started after exposure to study drug or worsened in severity after dosing) will be presented by dose group as well. Incidences of TEAEs will be presented by maximum severity and relationship to study medication.

Laboratory test results, ECG results, vital sign results and their changes from baseline will be summarized using descriptive statistics. Shift tables comparing baseline results to the worst post baseline results will be presented for laboratory results and ECG overall interpretation. Other safety measurements like physical examinations will be presented in listings.

Pharmacokinetics:
Individual serum concentrations of GMA301 will be listed and summarized using descriptive statistics. Individual and mean GMA301 concentration-time profiles will be presented graphically.

Where data are available, GMA301 dose proportionality will be examined across the dose level. The PK parameters will be analyzed for dose proportionality using a power model approach or analysis of variance (ANOVA) model as appropriate.

Efficacy:

Efficacy endpoints include hemodynamic parameters, 6-minute walk distance, NT-pro BNP levels, WHO functional class, and their change from baseline will be listed and summarized by treatment group using descriptive statistics as appropriate at each collection timepoint.

Exploratory Analyses:
REVEAL 2.0 risk score and their change from baseline will be listed and summarized descriptively by treatment group at each collection timepoint.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	6-Minute Walk Test
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
$AUC_{0\text{-}Inf}$	Area Under the Serum Concentration-Time Curve from Time Zero to Infinity
$AUC_{0\text{-}T}$	Area Under the Serum Concentration-Time Curve from Time Zero to the Last Measurable Concentration T Time
$AUC_{0\text{-}Tau}$	Area Under the Serum Concentration- Time Curve Over a Dosing Interval
BP	Blood Pressure
CFR	Code of Federal Regulations
cGMP	Cyclic Guanosine Monophosphate
CHO	Chinese Hamster Ovary
C_{max}	Observed Maximum Serum Concentration
CRO	Contract Research Organization
CSA	Clinical Study Agreement
SRC	Safety Review Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
ERA	Endothelin Receptor Antagonist
ET	Endothelin
ET_A	Endothelin Receptor Type A
ET_B	Endothelin Receptor Type B
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
Gmax	Gmax Biopharm Australia Pty Ltd
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product

INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
LA	Left Atrial
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No Observed Adverse Effect Level
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Artery Pressure
PH	Pulmonary Hypertension
PI	Primary Investigator
PK	Pharmacokinetic
PVR	Pulmonary Vascular Resistance
Q4W	Every Four Weeks
QTc	QT Interval Corrected for Heart Rate
QTcF	QT Interval Corrected for Heart Rate Using Fridericia's Method
REMS	Risk Evaluation Mediation Strategy
RHC	Right Heart Catheterization
RVSP	Right Ventricular Systolic Pressure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
$t_{1/2}$	Terminal Elimination Half-Life
T_{max}	Time to aximum serum concentration
TMF	Trial Master File
ULN	Upper Limit of Normal
WHO	World Health Organization

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive, life-threatening disease caused by obliteration of the small, peripheral pulmonary arteries by endothelial and smooth muscle cell proliferation and in-situ thrombosis. Progressive obstruction of the distal arteries leads to increasing pulmonary vascular resistance (PVR), pulmonary artery pressure, right heart failure, severe debilitation and, eventually death.[1] Of the 5 categories of pulmonary hypertension described at the 5th World Symposium on Pulmonary Hypertension held in Nice, France, in 2013, PAH is classified as Group 1 indicating that it is a primary vascular disease and not caused by post-capillary pressure backup from left heart disease, parenchymal lung disease or pre-capillary chronic thromboembolic disease. PAH most commonly has no clear cause or association (idiopathic) but can be genetically based, drug or toxin-induced or associated with collagen vascular disease, congenital heart disease, human immunodeficiency virus (HIV), portal hypertension or schistosomiasis.[2] While an imbalance of vasoconstrictive and vasorelaxant factors is felt to be an underlying cause of progressive disease in all forms of PAH, the end results in all cases include pulmonary arteriolar constriction, in-situ thrombosis and pulmonary vascular remodeling.[3]

An array of pharmacotherapeutic approaches for PAH have been developed over the past two decades and provide dramatic improvement in PAH-associated symptoms and quality of life. [4] Most of these molecules have been approved based on short-term (12 to 24 week) studies demonstrating improvement in exercise tolerance primarily demonstrated by increasing distance on the 6MWT. More recently, reduction of disease progression with the mixed endothelin receptor antagonist macitentan and the selective prostacyclin receptor agonist selexipag has been reported. [5,6]

Based on data obtained over three decades ago by the US National Institutes of Health, patients with untreated PAH have a median survival of 2.8 years. To date, no single therapy, with the possible exception of intravenous epoprostenol,[7] has been clearly associated with increased survival. This may be due to the small sample sizes and limited follow-up of individual studies. Indeed, there are clear trends in improved survival. Meta-analysis combining studies averaging 14.8 weeks of follow-up suggest that current treatment modalities may have had a substantial impact on survival though this has yet to be clearly documented in a long-term outcome study. [8]

Current pharmacologic treatment of PAH leverages imbalances in vasoconstrictive/ vasodilatory pathways including the endothelin, nitric oxide and prostacyclin systems. Based on some studies showing improvement in clinical outcomes, there is an increasing use of initial combined therapy.[9] The actual sequencing of treatment additions is not entirely clear though prostanoids are not usually prescribed as initial therapy.[9] Treatment options currently include prostanoids, synthetic analogues of prostacyclin, and the prostacyclin receptor agonist, selexipag, which have vasodilatory as well as antiproliferative effects. Vasodilator drugs work by increasing cyclic guanosine monophosphate (cGMP) downstream and include the phosphodiesterase-5 inhibitors (e.g. sildenafil and tadalafil), which reduce cGMP degradation and the soluble guanylate cyclase agonists (e.g. riociguat) which both stimulate soluble guanylyl cyclase production and sensitize cGMP to nitric oxide.

Endothelin-1 (ET-1) is a 21 amino acid endothelial cell-derived polypeptide and one of the most potent vasoconstrictors known. Stimulation of the endothelin type A and B

g-protein-coupled receptors (ET_A and ET_B) causes vascular smooth muscle contraction and stimulates smooth muscle proliferation. Thus, blockade of ET-1 may have both vasodilatory and antiproliferative effects which could blunt or even reverse pulmonary vascular remodeling. While principally found in endothelial cells, a range of other cells types have also been shown to express endothelin including cardiac myocytes, lung epithelium, glomerular kidney cells, mesangial cell, leukocytes, and macrophages.

ET_A receptors, found largely in smooth muscle cells, play an important vasoconstrictive role in PAH. In contrast, the ET_B receptors which are found mostly in smooth muscle, primarily promote vasodilation by mediating ET-1 clearance as well as endothelial production of nitric oxide and prostacyclin.[10,11,12] Current endothelin receptor antagonists (ERAs) employed in PAH are designed to selectively block the ET_A receptor but are incompletely selective. Bosentan, the first of the ERAs approved for clinical use, is relatively non-selective and has an affinity for the ET-A receptor which is 20 times that of the ET-B receptor. In contrast, ambrisentan has over 4000-fold higher the affinity for the ET_A receptor.[13,14] Macitentan is a modification of bosentan designed to reduce side effects. While generally considered a dual ERA, it actually has greater selectivity for the ET_A receptor. Also, macitentan is more tissue specific. [15]

Despite having a strong therapeutic track record since bosentan first became clinically available in 2002, the ERAs have some safety concerns. Anemia, headache and nasal congestion are common in all of the ERAs. Bosentan has the risk for hepatotoxicity and the Food and Drug Administration (FDA) requires monthly monitoring of liver function tests in patients taking this drug. While ambrisentan and macitentan have not shown strong evidence of hepatotoxicity in clinical trials the FDA still considers this a possible class effect and requires baseline liver function testing and warning to patient about possible hepatotoxicity symptoms.

Due to concerns about fetal toxicity in all ERAs, the FDA has mandated risk evaluation mediation strategy (REMS) programs which require female patients of child-bearing potential to undergo a formal education in the ERA risks.

Gmax Biopharm LLC. has invented GMA301 as a potential new drug for the treatment of PAH.

1.1. Overview

GMA301 is an anti-endothelin receptor type A humanized monoclonal antibody. The molecular weight is around 148kDa.

1.2. Summary of Nonclinical Pharmacology

The completed nonclinical studies of GMA301 include in vitro potency testing, in vivo efficacy study in cynomolgus monkeys, single and repeat doses pharmacokinetics (PK) and toxicity studies also in cynomolgus monkeys.

An in vitro study of the biological activity of GMA301 was conducted in Chinese hamster ovary (CHO) cells with rats, monkey and human ET_A expressed. Ambrisentan was used as a positive control. Results showed that GMA301 has a similar IC50 value on monkey and human ET_A (67.55 and 57.50 nM) but does not bind to rat ET_A, which proved that GMA301 has a species specificity in ET_A binding. The positive control,

ambrisentan, showed similar inhibitory potency in 3 cell lines with IC50 of 1.61, 2.84, and 8.07 nM on rat, monkey, and human ET_A. [18]

In an efficacy study of GMA301 administered intravenously twice per week for 6 weeks in a monocrotaline-induced PAH model in cynomolgus monkeys, right ventricular systolic pressure (RVSP) of GMA301 decreased by 13.6%, 45.7%, and 54.0% in 1.5, 5, and 15 mg/kg dose groups ($p<0.01$ in 5 and 15 mg/kg groups compared to the model group) and Fulton's index (weight of right ventricular/(weight of left ventricular plus weight of interventricular septum)*100%) decreased by 31% in the 5 mg/kg group. [18]

The results indicated that the efficacy of 5 mg/kg GMA301 was similar to ambrisentan. The dose of ambrisentan used in this study is 1 mg/kg, which is administrated once a day for 6 weeks by oral gavage.

1.3. Summary of Safety Pharmacology

Although mice are not relevant species to GMA301, a single dose toxicity study was still conducted. Both GMA301 injection and placebo result in some death after IV injection at a very high dosage (equal to 6.9-gram GMA301injected in a 60 kg human). The cause of death may need further study, however, according to International Council for Harmonisation (ICH) S6, "Toxicity studies in non-relevant species may be misleading and are discouraged". Therefore, the results of acute toxicity study in mice may not be relevant for the preclinical safety evaluation of GMA301.

The preclinical toxicity studies included single and repeat doses of GMA301 were conducted in cynomolgus monkeys.

In single dose toxicity study, cynomolgus monkeys were administrated at 75, 250, and 750 mg/kg, No GMA301-related changes were noted in clinical observations, body weight, hematology and clinical chemistry tests. The no observed adverse effect level (NOAEL) was 750 mg/kg.

In a multiple dose toxicity study in cynomolgus monkeys, GMA301 was administrated at 25, 75, and 250 mg/kg twice weekly for 4 weeks and 25, 75, and 250 mg/kg once weekly for 13 weeks followed by a six-week recovery period. No changes were noted in clinical observations, body weight, body temperature, hematology and clinical chemistry. No GMA301-related histopathology abnormality was found. [18]

1.4. Summary of Nonclinical Pharmacokinetics

A total of 24 naive cynomolgus monkeys (3 males and 3 females in each group) were used in a single and repeat dose PK study. In the single dose study, GMA301 was injected at 5, 15, 50 mg/kg and in the multiple dose study, injected at 15 mg/kg once weekly for 4 consecutive weeks. Blood was collected at different timepoints and PK parameters were calculated. GMA301 showed a long half-life of approximately 244.74, 173.15, and 173.41 hours in 5, 15, and 50 mg/kg group after single dose injection. After a total of 4 injections, the AUC of the last dose of 15 mg/kg was 1.96 times higher than that of the first dose, at 47.96 and 24.50 h·mg/mL, respectively. [18]

Table 1: Pharmacokinetics Parameters of GMA301 in monkeys

Group	Dose (mg/kg)	$t_{1/2}$ (h)	C_{max} (μg/mL)	AUC_{inf} (h·mg/mL)	
Single dose	5	244.74±30.29	98.22±16.81	16.10±2.31	
	15	173.15±63.14	317.57±38.19	40.26±15.21	
	50	173.41±24.65	1014.96±73.63	137.50±23.34	
Group	**Dose**	**$t_{1/2}$ (h)**	**C_{max} (μg/mL)**	**$AUC_{(0\text{-}168\ h)}$ (h·mg/mL)**	**F**
Repeat dose*	15mg/kg-first dose	182.81±46.82	326.27±41.49	24.50±2.75	
	15mg/kg-last dose	263.54±38.67	481.76±59.05	47.96±3.59	1.96

*: 15 mg/kg once per week for 4 weeks. $F=AUC_{last}/AUC_{first;}$ $t_{1/2}$=Terminal Elimination Half Life; C_{max}=Maximum Observed Serum Concentration

1.5. Summary of Clinical Experience

1.5.1. Safety

A single-center, double-blind, placebo-controlled, dose escalation study to assess the safety, tolerability, and PK of GMA301 in healthy subjects was performed in Australia. Four sequential dosing cohorts, each with 6 subjects receiving GMA301 and 2 subjects receiving placebo (total of 32 subjects), were given increasing single doses of GMA301. The administered doses were 75, 200, 500, and 1000 mg, or matching placebo. The most frequent Treatment Emergent Adverse Events (TEAEs) across the 4 groups were headache (39.4%), nausea (12.1%) and pharyngitis (12.1%). All of these TEAEs were well tolerated without further medical intervention needed.

1.5.2. Pharmacokinetics

Pharmacokinetic results were obtained from the same study that was performed in Australia. All individuals in the study exhibited quantifiable plasma GMA301 concentrations at the first timepoint of 4 hours. Most individuals appeared to exhibit mono-exponential pharmacokinetics, with a slow decline in plasma concentrations after attainment of Maximum Observed Serum Concentration (C_{max}). Terminal half-life was long with average values ranging from 503.75 hours to 565.63 hours.

Other pharmacokinetic values of GMA301 refer to clinical study report of GMA301 Australia study. [19]

1.6. Study Rationale

The selection of GMA301 doses and dosing frequency was based on the available clinical safety, tolerability and PK data obtained from healthy human subjects[19]. The dose level of 1000 mg GMA301 observed in the previous Phase Ia study has been proven safe for human subjects. Based on that, we believe that GMA301 dosed at 300, 600, and 1000 mg every 4 weeks (Q4W) should be safe for human subjects.

The principal aim of this study is to obtain safety and tolerability data when GMA301 is administered as multiple doses in subjects with PAH. This information, together with the PK data, will help establish the doses and dosing regimen for future studies. The efficacy parameters of GMA301 will also be investigated.

1.7. Benefit-risk Assessment

Subjects enrolled in this study will receive no known benefit from the study drug. Subjects will undergo additional testing (e.g. right heart catheterization [RHC], echocardiography, 6MWT and biomarkers) that may help their practitioner better characterize their disease. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP). In addition, there may also be some discomfort or morbidity from the RHC and collection of blood samples and other study procedures.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) associated with GMA301 may be found in the Investigator's Brochure [18].

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To assess the safety and tolerability of GMA301 following repeated intravenous (IV) dosing in subjects with World Health Organization (WHO) Group-1 PAH

2.1.2. Secondary Objectives

- To determine the PK and dose/exposure-response relationships of GMA301
- To evaluate the effects of GMA301 on hemodynamics
- To evaluate the effects of GMA301 on exercise tolerance
- To evaluate the effects of GMA301 on relevant PAH biomarkers

2.1.3. Exploratory Objectives

- To evaluate the effects of GMA301 on REVEAL 2.0 risk score (See Appendix 7)

2.2. Endpoints

2.2.1. Primary Endpoints

The incidence of TEAEs in subjects assigned to GMA301 compared with those assigned to placebo

2.2.2. Secondary Endpoints

- Pharmacokinetics
  - Area under the serum concentration- time curve from time zero to the last measurable concentration (AUC_{0-t})
  - Area under the serum concentration- time curve over a dosing interval (AUC_{0-tau})
  - Observed maximum serum concentration (C_{max})
  - Area under the serum concentration-time curve from time zero to infinity (AUC_{0-inf})
  - Time to maximum serum concentration (T_{max})
  - Terminal elimination half-life ($t_{1/2}$)
  - Volume of distribution
  - Trough concentration
  - Clearance
  - Accumulation ratio

- Comparison of GMA301 treatment effect at Week 12 versus baseline regarding the hemodynamic parameters based on RHC. Parameters include but are not limited to:
  - Pulmonary vascular resistance (PVR)
  - Mean pulmonary arterial pressure (mPAP)
  - Cardiac index

- Comparing the following treatment effect metrics:
  - 6MWT distance (Week 12 versus Screening)
  - NT-pro BNP level (Weeks 4, 8, and 12 versus baseline)
  - WHO functional class (Weeks 8 and 12 versus baseline)

2.2.3. Exploratory Endpoints

- Changes in REVEAL 2.0 risk score at Week 12 compared with baseline

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 1b randomized, double-blind, placebo-controlled, on top of background therapy, dose escalation study to assess safety, efficacy and PK of GMA301 in subjects with PAH. The study will be carried out at sites in China and the US.

After signing informed consent, subjects will participate in a Screening Phase. The subjects' medical history will be obtained through interview and a chart review before the subject undergoes a physical examination.

Subjects will be selected and enrolled from the PAH population who are taking local-approved, non-ERA agents, including but not limited to calcium channel blockers, phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators, non-intravenous prostacyclin receptor agonists and prostacyclin analogues.

The dosage of PAH medication must be stable for 3 months before Screening.

Subjects who underwent RHC within the 3 months prior to Screening will not be required to repeat another RHC if the investigators accept the quality of the saved waveforms and pressure measurements and these meet study entry criteria.

Subjects meeting screening criteria for baseline metrics will then be randomized by Interactive Web Response System (IWRS). Each treatment cohort will be randomized at a 3:1 ratio of active treatment to placebo in each cohort. Subjects will be randomized to receive either:

- Q4W GMA301 IV injections

  or

- Q4W placebo IV injections (indistinguishable from GMA301).

Subjects will be sequentially recruited into 3 ascending dose treatment cohorts with GMA301-assigned subjects receiving either 300, 600 or 1000 mg injections of the study drug depending on their assigned cohort. Each cohort will contain 12 subjects, 9 of whom will be administered active GMA301 and 3 of whom will be administrated placebo. All subjects will undergo IV injection at baseline, Week 4, and Week 8.

Dosing will proceed in a cohort-based dose escalation sequence from 300 mg GMA301 in the initial cohort. Pre-specified criteria for dose escalation based on subjects' safety will be assessed by a Safety Review Committee (SRC) before progressing to the next higher dose level as described below. The efficacy parameters will include disease-relevant hemodynamic parameters derived from RHC, REVEAL 2.0 risk score, WHO functional class, ECG, 6MWT, biomarkers and echocardiography measures of right ventricular function.

All key efficacy parameters will be assessed at 4, 8, and 12 weeks following baseline evaluation and an ECG will be performed as scheduled. The protocol will include a

6-week follow-up (from Week 12 to Week 18) at which time subjects will be assessed to identify any AEs and conducting the PK assessment.

Routine clinical and laboratory parameters including antigenicity and AE reporting will be examined.

Overall, 36 subjects, with 3 cohorts each composed of 12 subjects, will participate in a multiple-dose, sequential-group fashion. An overview of the study design is shown in Figure 1 and the planned dose levels in Figure 2.

The total duration of the study for an individual subject will be approximately 22 weeks including up to 4 weeks of screening, 12 weeks of double-blind treatment period, and 6 weeks of follow-up. During the double-blind treatment period (12 weeks), the subjects will receive the IV injections at Week 0 (baseline), Week 4, and Week 8, respectively.

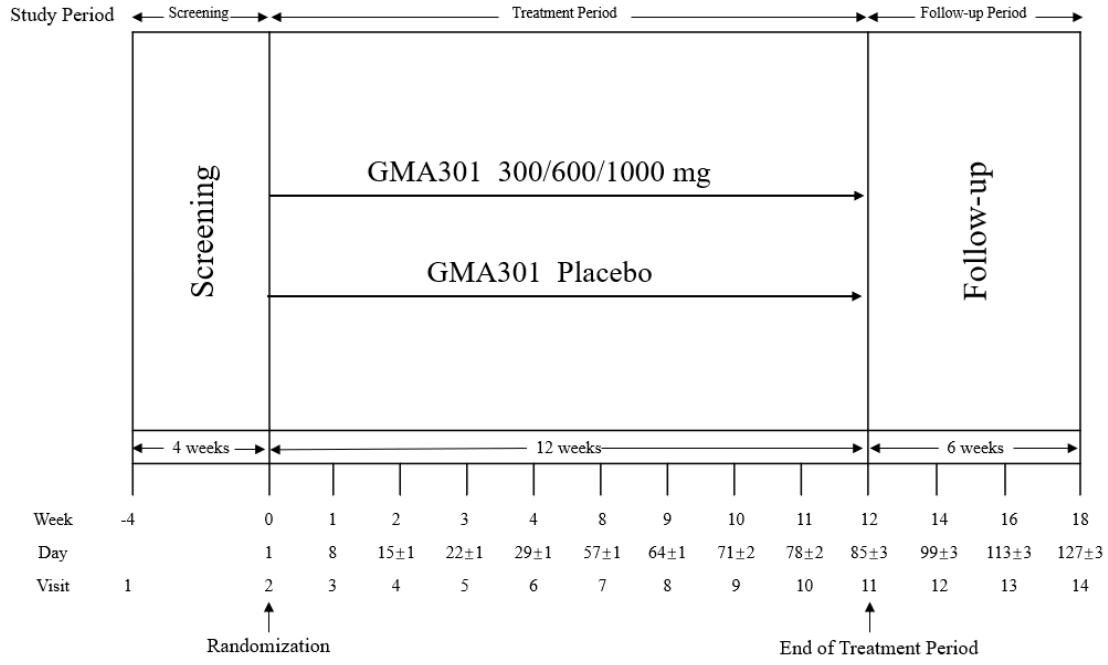

Figure 1: Study Schematic

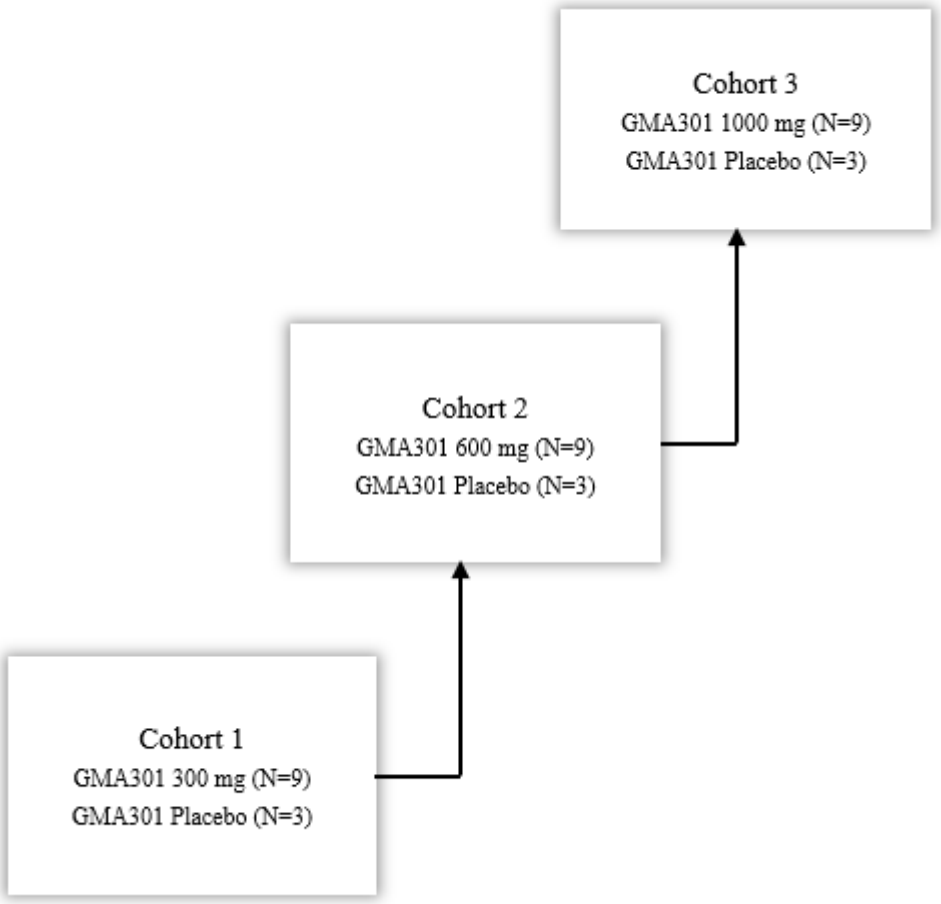

Figure 2: Planned Dose Levels

A Schedule of Assessments is presented in Appendix 6.

3.2. Study Start and End of Study Definitions

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of the subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Discussion of Study Design, Including the Choice of Control Groups

A sequential-group, ascending-dose design has been chosen for safety reasons as GMA301 is in the early stage of clinical development. Intravenous doses have been chosen for the study, as this is the intended clinical route of administration.

Based upon the nonclinical data, the duration of each treatment period is considered adequate to achieve the study objectives. Details of the dosing regimen and duration used for the study will be documented in the trial master file (TMF).

The selection of the GMA301 dosing frequency of Q4W via IV injection at baseline and then at Week 4 and Week 8 was based on the available clinical safety, tolerability and PK data obtained from healthy human subjects.[18]

To estimate and determine the levels and frequency of GMA301 dosing for the upcoming Phase Ib study, a simulation of GMA301 for a Q4W repeated dosing in human subjects has been established based on all previous observations in cynomolgus monkeys and healthy human volunteers. The simulation indicated that a steady state could be achieved after the 3rd dose, and the Q4W dose interval has been deemed safe for human subjects.

3.4. Dose selection in the Study

GMA301 300, 600 and 1000 mg IV injection Q4W for 3 months was based on the available clinical safety, tolerability and PK data obtained from healthy human subjects.

The proposed GMA301 dose levels are shown in Table 2.

Table 2: Proposed Investigational Medicinal Product Dose Levels

Cohort	Intervention	Treatment
1	300 mg GMA301 (N=9)	**Drug:** GMA301, 300 mg IV Q4W at Week 0 (baseline), Weeks 4 and 8
	Placebo (N=3)	**Drug:** Placebo, IV, Q4W at Week 0 (baseline), Weeks 4 and 8
2	600 mg GMA301 (N=9)	**Drug:** GMA301 600 mg IV, Q4W at Week 0 (baseline), Weeks 4 and 8
	Placebo (N=3)	**Drug:** Placebo IV, Q4W at Week 0 (baseline), Weeks 4 and 8
3	1000 mg GMA301 (N=9)	**Drug:** GMA301 1000 mg IV, at Week 0 (baseline), Weeks 4 and 8
	Placebo(N=3)	**Drug:** Placebo IV, Q4W at Week 0 (baseline), Weeks 4 and 8

Details of all doses administered in the study will be documented in the TMF.

3.5. Safety Review Committee (SRC)

A SRC will be established to assess safety profile for each cohort to determine dose escalation. The SRC will be composed of 3 investigators, the Covance Lead Project Physician, the Gmax Lead Project Physician, and another unblinded physician who is not involved in this study.

SRC Operation. The SRC will meet after 8 of 12 subjects have received 3 doses of the study drug with a 28-day follow-up and the entire cohort of 12 subjects has been randomized.

The initial SRC meeting will review safety data from the initial 8 subjects in Cohort 1 who have completed 3 doses of the study drug and have been followed for 28 days following the third dose. Upon SRC's approval, Cohort 2 will be opened for recruitment once the residual 4 subjects have been randomized in Cohort 1. The second meeting of the SRC will review safety data from the initial 8 subjects in Cohort 2 **and the 4 residual subjects from Cohort 1 who were not yet reviewed.** Upon SRC's approval, once the residual 4 subjects in Cohort 2 are randomized, Cohort 3 can be initiated for recruitment. If fewer than 8 subjects (including 8) in a cohort have completed administration and follow-up regimen, with some drop-outs, their safety data will be reviewed by SRC aiming to determine whether the next cohort with a higher dose can be started. Additionally, ad hoc meetings will be organized in case of any SAE or adverse event with maximum severity that could be drug-related.

SRC reviews will include, but not limited to, clinical findings, vital signs, hematology and biochemistry results, ECG, AEs, and SAEs. The composition, operation, and management of the SRC will be described in detail in the SRC charter.

3.6. Stopping and Subjects withdraw Criteria

The following criteria will result in immediate discontinuation of the subject dosing:

- An SAE that is related to GMA301;
- QTcF >500 msec or extension 60 msec against baseline.
- Liver function test abnormalities for severe liver injury (based upon US FDA "Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation", July 2009):
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)>3x upper limits of normal (ULN) with total bilirubin > 2X ULN (Hy's Law)
  - ALT or AST >3x ULN with international normalized ratio (INR)>1.5
  - ALT or AST >8X ULN
  - ALT or AST >5X ULN persisting for more than 2 weeks
  - ALT or AST >3x ULN or 3 times baseline value with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

Close follow-up of subjects must be organized in any of the above cases including:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases
- Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin)
- Obtaining gastroenterology or hepatology consultations

If a treatment-related SAE is suspected by investigators, immediate discontinuation of study drug must occur and medical care must be applied and the case immediately reported to the SRC. An ad hoc SRC meeting will be organized to make decisions for the study accordingly.

A subject is free to withdraw from the study at any time. A subject is requested to withdraw by the investigators if any of the following criteria are met:

- Subjects' non-compliance with the study procedure that might affect subject safety or study assessments/objectives, by the investigators
- Any clinically relevant sign or symptom (eg, Class IV heart failure) that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

Subject who didn't get IMP treatment within protocol defined timeline with any reason can get back to the IMP treatment with investigator or SRC's evaluation and agreement.

All the discontinuation must be documented accordingly. If a subject is withdrawn, the Sponsor will be notified in 24 hours and the date and reason(s) for the withdrawal will be documented in electronic Case Report Form (eCRF). In this case, efforts in any ways must be made to complete the follow up assessments. (Appendix 6). Other medical procedures may be performed at the Investigator's discretion. The Investigator may also request subjects to return for additional Follow-up visits. All AEs will be followed until recovery or stabilization.

Cohort discontinuation and study termination

The SRC will discontinue or stop the cohort or even the study in case of **:**

- Two cases discontinuations in a cohort due to events related to the study drug under the diagnosis of the investigators;
- Single case with severe allergic event related to study drug;
- Known and expected AEs are with increased frequency, severity and or long lasting.

The sponsor can terminate the study with notification to the investigators.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male or female, aged 18 to 75 years inclusive
2. WHO Group 1 PAH related to one of the following conditions:
    a. Idiopathic
    b. Heritable
    c. Drugs or toxins-induced
    d. Associated with connective tissue disease
    e. Associated with congenital heart disease if subjects underwent surgical correction more than 12 months before Screening
3. Symptoms due to PAH are consistent with WHO functional class II- III
4. Have not taken endothelin receptor antagonists (ERAs) within 3 months before randomization.
5. Has been taking at least one oral PAH targeted drug that has been approved by local guidelines for at least 3 months before screening with a stable dosage and the disease did not worsen during this period.

6. Right heart catheterization (RHC) result meets below criteria when screening.
    a. Mean pulmonary arterial pressure (PAP) ≥25 mmHg
    b. Pulmonary vascular resistance (PVR) >3 Woods units
    c. PA wedge pressure (PAWP) ≤15 mmHg

if subject has undergone RHC within 3 months before screening, the waveform results will serve as baseline data if they meet entry criteria and the RHC at Screening will not be repeated.

7. Has a six-minute walk test (6MWT) with distance between 150 to 450 meters at Screening.
8. The dosage of digitalis drugs or L-arginine supplementation, if applicable, must be stable for at least 1 month before Screening.
9. No new use of an IV diuretic, cardiotonic, or vasoactive drug within 30 days before screening.
10. Both male and female subjects agree to use a medically acceptable method of contraception throughout the entire study period from informed consent signing to 90 days after last dose, if the possibility of conception exists. Medically acceptable methods of contraception include oral, implantable, or injectable contraceptives (starting 2 months before dosing); diaphragm with vaginal spermicide; intrauterine device; condom and partner using vaginal spermicide; and surgical sterilization (6 months after surgery). Women who are surgically sterile or those who are postmenopausal for at least 2 years are not considered to be of childbearing potential. Eligible male and female subjects must agree not to participate in a conception process (i.e. active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization) during the study and for 90 days after the last dose of study drug.
11. Body weight no less than 40 kg at Screening.
12. Able to understand and willing to sign the Informed Consent Form (ICF) and comply with the study procedures.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will not be allowed to participate in this study:

1. Diagnosed with WHO Group II, III, IV, V of PH.
2. Using calcium channel blockers when screening.
3. BP >160/100 mmHg at Screening
4. Systolic BP <90 mmHg at Screening
5. Pulmonary function test: FEV1<60% of predicted, TLC<60% of predicted, DLCO<60% of predicted
6. One of the following tests with confirmed pulmonary emboli and chronic thromboembolic pulmonary hypertension (CTEPH) following initial diagnosis of PAH:
    a. Pulmonary ventilation/perfusion scan
    b. CT pulmonary angiogram
    c. Contrast dye pulmonary angiogram
7. History of sleep apnea
8. Limited full participation in the 6MWT due to arthritic, neuromuscular,

vascular or other diseases unrelated to PAH

9. History of acute cardiovascular and cerebrovascular events within 6 months before screening.
10. Echocardiogram (ECHO) demonstrating at least 1 of the following:
    a. LVEF ≤50%
    b. Mean end-diastolic left ventricular septal and posterior wall thickness of >12 mm
    c. Left atrial (LA) area on apical 4 chamber view >20 cm^2
    d. LA volume by biplane modified Simpsons or area-length methods >55 mL
    e. LA volume index >29 mL/m^2
    f. Significant valvular heart disease including moderate or severe mitral or aortic stenosis with an aortic valve area <1.0 cm^2 or mitral valve area <1.5 cm^2), greater than moderate aortic or mitral regurgitation, greater than moderate tricuspid or pulmonic stenosis
11. Restrictive, dilated or hypertrophic cardiomyopathy or constrictive pericarditis
12. Using non-oral prostacyclin when screening;
13. Laboratory parameters during screening:
    a. Baseline aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2 times the upper limit of normal (ULN) or total bilirubin ≥1.5 times ULN.
    b. Estimated glomerular filtration rate (eGFR) <60 mL/min by Cockcroft-Gault formula
    c. Hemoglobin concentration ≤100 g/L at screening
14. QTc interval by Fridericia's criteria (QTcF) ≥500 msec at screening
15. Malignancy within 5 years before screening visit (with the exception of localized non-metastatic basal cell carcinoma of the skin, non-metastatic carcinoma of the prostate or in-situ carcinoma of the cervix excised with curative results)
16. Alcohol or drug abuse within 1year before screening
17. A psychiatric, addictive or other disorder that compromises the ability to give informed consent for participating in this study
18. History of organ transplantation
19. Pregnant or nursing females
20. History of HIV
21. Positive hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV-Ab), or HIV antibody (HIV-ab).
22. Enrolled in another interventional study within 30 days before screening.
23. Any condition that, in the opinion of the investigator, prevents a potential subject from safely participating in the study

4.3. Subject Number and Identification

Subjects will have unique identification numbers used at Screening and randomization. Assignment of subject numbers will be in ascending order and no numbers will be omitted.

All study documentation will be identified by Screening number only. A list identifying the subjects by subject number will be kept in the Site Master File.

5. STUDY DRUGS

5.1. Description, Storage, Packaging, and Labeling

The IMPs (300, 600, and 1000 mg GMA301 Injection) and their matching placebos will be supplied by the Sponsor, along with the batch/lot numbers and Certificate of Analysis. The IMP will be provided in glass vial and stored according to the instructions on the label.

The placebo treatment will be composed of the same ingredients as the GMA301. The appearance of the placebos should be identical to either GMA301, to ensure the study is blinded.

All IMPs will be stored at the study site in a location that is locked with restricted access.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The IMPs will be transferred from bulk supplies into the subject's dose container by qualified clinical staff.

GMA301 and placebo injections should be stored at 2～8°C and protected from direct sunlight. Protection from light is not required during preparation and injection.

5.2. Study drug Administration

The 300, 600, and 1000 mg doses of GMA301 and matching placebo will be administered Q4W via IV injection by slow push for 12 weeks.

The study drug will be injected at an approximate rate of no more than 4 mL/min. The syringes should be connected to the previously inserted cannula for administration.

5.3. Randomization

An IWRS will be used to randomly assign subjects to treatments. Nine subjects per cohort will be randomly assigned to active GMA301 and three subjects per cohort will be randomly assigned to receive placebo.

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

The placebo will be identical in appearance to the GMA301.

The Investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

All doses will be administered by suitably qualified study site staff.

At each dosing occasion, a pre-dose and post-dose inventory of IMP will be performed.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug dispensation record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

The administration of any concomitant medications during the study is prohibited without prior approval of the investigator. Any medication taken by a subject during the study and the reason for its use will be documented in the source data.

6.2. Diet

Subjects will be fasted at least 8 hours and cannot drink water for 2 hours before any blood sample collections for safety examination purpose.

Consumption of alcohol will not be permitted from 48 hours prior to Screening to the last follow-up visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Screening until the last follow-up visit.

6.4. Exercise

Subjects are required to refrain from intensifying strenuous exercise from 7 days before screening until the Follow-up visit, but will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

7. STUDY ASSESSMENTS AND PROCEDURES

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, and blood drawings.

7.1. Pharmacokinetic Assessments

7.1.1. Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6.

Up to 3 additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF.

7.1.2. Analytical Methodology

Serum concentrations of GMA301 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Safety and Tolerability Assessments

7.2.1. Adverse Events

AE definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All non-serious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of study drug until study completion. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

AEs recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator’s (or designee’s) discretion.

The Adverse Event(s) related to RHC is listed in the separated document.

7.2.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6.

Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

For females of reproductive potential, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.2.3. Vital Signs

Seated blood pressure, seated pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 pre-dose blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges. Body temperature will be measured singly.

Subjects must be seated or lie for at least 5 minutes before blood pressure and pulse rate measurements.

7.2.4. Electrocardiogram

7.2.4.1. 12-Lead Electrocardiogram

A resting 12-lead ECG will be recorded after the subject has been supine and be seated or lie for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6.

ECGs will be recorded at screening, Week 4, Week 8, and Week 12.

The 12-lead ECGs will be repeated 3 times, and an average taken of the 3 readings. The QTcF will be averaged and any subject meeting the following criteria will have study medication held and will be followed up:

- QTcF value >500 msec
- QTcF change from the baseline (predose) >60 msec.
- Second- or third-degree heart block or bundle branch block

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 pre-dose 12-lead ECGs will serve as the baseline assessment. The mean values of PR, QRS, and QTcF will be entered into the eCRF. Averaged values for subsequent ECG intervals should also be entered into the eCRF.

7.2.5. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6. Full physical examination will usually only be performed at Screening or Day-1.

7.2.6. Body Weight

Body weight will be recorded at the timepoints indicated in the Schedule of Assessments in Appendix 6.

7.2.7. Immunogenicity (ADA)

Blood samples for immunogenicity (anti-drug antibodies [ADA]) will be collected at the times indicated in the Schedule of Assessments in Appendix 6.

Neutralization activity will be evaluated if ADA is positive.

7.2.8. Pregnancy test

Females of reproductive potential will be tested at the times indicated in the Schedule of Assessments in Appendix 6.

7.3. Efficacy Assessments:

7.3.1. Right heart catheterization (RHC)

The data will be collected at the times indicated in the Schedule of Assessments in Appendix 6.

7.3.2. Echocardiogram (ECHO)

Echocardiogram will be recorded at the times indicated in the Schedule of Assessments in Appendix 6.

7.3.3. Six-minute walk test (6MWT)

The 6MWT will be collected at the times indicated in the Schedule of Assessments in Appendix 6. The operation details of 6MWT is described in the Site Operation Menu. Borg index score will be collected immediately after 6MWTs.

7.3.4. NT-pro-BNP

The data will be collected at the times indicated in the Schedule of Assessments in Appendix 6.

7.3.5. WHO functional class

The data will be collected at the times indicated in the Schedule of Assessments in Appendix 6.

7.3.6. The REVEAL risk score

The data will be collected at the times indicated in the Schedule of Assessments in Appendix 6.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. General Analysis

Statistical analyses will be descriptive only, with no hypothesis testing. Analyses will be performed in SAS®. Summary tables will present results for each of the three GMA301 doses. Descriptive statistics including the number (n), the arithmetic mean (Mean), standard deviation (SD), median, the minimum value (Min), and the maximum value (Max) will be presented for continuous variables, and the number of subjects (n) and the percentage (%) will be presented for categorical and ordinal variables. All study data will also be presented in by subject data listings. The details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

8.2. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted. Approximately 36 subjects will be randomized into 3 treatment cohorts with GMA301-assigned subjects receiving either 300, 600, or 1000 mg injections of the study drug depending on their assigned cohort. Each cohort will include 12 subjects, 9 of whom will be administered active GMA301 and 3 of whom will receive placebo.

The number of subjects in each cohort of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

8.3. Analysis Populations

8.3.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of study drug (GMA301) and have at least 1 evaluable PK data.

8.3.2. Safety Population

The safety population will include all subjects who received at least 1 dose of study drug. The safety population will be analyzed according to treatment actually received.

Any subject who did not receive the treatment randomly assigned will be listed, but will be included in all analyses according to the treatment actually received.

8.4. Demographics and Other Baseline Characteristics

8.4.1. Baseline demographics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for the Safety Population. Characteristics will include but not limited to age, weight, height, body mass index, sex, and race. No formal statistical comparisons will be made between treatment groups.

8.4.2. Medical History

Medical History will be coded according to the current version of MedDRA. The Medical Histories will be listed and numbers and percentages of any medical history will be summarized for the safety population by system organ class and preferred term for each treatment group, and overall.

8.5. Pharmacokinetic Analyses

Non-compartmental PK analysis will be performed on individual serum concentration data, using commercial software such as Phoenix® WinNonlin®. Serum concentrations of GMA301 and PK parameters will be listed and summarized using descriptive statistics. Individual and mean GMA301 concentration-time profiles will also be presented graphically.

In the study, where data are available, GMA301 dose proportionality will be examined across dose groups. The PK parameters will be analyzed for dose proportionality using a power model approach or analysis of variance (ANOVA) model as appropriate.

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the SAP.

8.6. Safety Analysis

All safety analyses will be performed on the Safety Population. No formal statistical analysis of safety data is planned.

AEs will be coded by System Organ Class and Preferred Term using the current version of the MedDRA dictionary. Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Safety data will be summarized by dose group. Incidences of TEAEs (those events that started after exposure to study drug or worsened in severity after dosing) will be presented by dose group as well. Incidences of TEAEs will be presented by maximum severity and relationship to study medication.

Laboratory test results, ECG results, vital sign results and their changes from Baseline will be summarized by dose group using descriptive statistics. Shift tables (low, normal, high) comparing baseline results to the worst post baseline results will be presented by parameters and dose group for laboratory results. Shift tables (normal, abnormal not clinically significant, abnormal clinically significant) comparing baseline results to the worst post baseline results will be presented by parameters and dose group for ECG results. Other safety measurements like physical examinations will be presented in listings.

Prior and Concomitant Medications will be classified according to the WHO Drug Dictionary. All usage will be listed. The current version of the WHO Drug Dictionary will be used. The frequency of usage of each medication class will be summarized using the WHO Drug hierarchy. The percentage of subjects in each dose using each class of medication after baseline will be presented.

The number and percentage of positive ADA and the positive neutralizing antibody at each timepoint will be summarized descriptively.

8.7. Efficacy Analyses

The Safety Population will be used for efficacy analyses.

Efficacy endpoints including hemodynamic parameters, 6-minute walk distance, NT-proBNP levels, WHO functional class, and their change from baseline will be listed and summarized by treatment group using descriptive statistics as appropriate at each collection timepoint.

8.8. Exploratory Analyses

REVEAL 2.0 risk score and their change from baseline will be listed and summarized descriptively by treatment group at each collection timepoint.

8.9. Interim Analysis

Not applicable.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

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

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: event is medically significant but produces no disruption to daily activity;
- **Moderate**: event is medically significant and reduces or affects normal daily activity;
- **Severe**: event is medically significant and results in inability to work or perform normal daily activity.

Relationship to Study drug

The Investigator will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the IMP or study procedures at the Follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any

subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

A SAE is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires in subject hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study drug and considered by the Investigator to be possibly related to the study drug, will be reported to the Sponsor.

Definition of Life-threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

AEs requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the Clinical Research Unit. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

FDA-reportable SAEs are AEs that are associated with the use of the drug and are serious and unexpected. Food and Drug Administration-reportable AEs will be reported by the study site to the Sponsor, and the responsible Institutional Review Board (IRB).

The Sponsor and Medical Monitor will be notified in writing (eg, facsimile) within 24 hours when a SAE that is FDA-reportable is firstly recognized or reported.

Subsequently, a written confirmation or summary of the AE (using FDA Form 3500A or equivalent) will be sent to the Sponsor within 3 working days of the original notification.

The IRB will be notified of any FDA-reportable AEs within the timeframe required by the IRB. The IRB Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

The responsibility for reporting SAEs will be transferred to the Sponsor 30 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

All the female subjects of child-bearing potential will be educated formally before they sign the ICF in order to be compliance with FDA's requirements.

Appendix 2: Clinical Laboratory and other Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Gamma-glutamyl transferase Glucose Potassium Sodium Total bilirubin[a] Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils **Coagulation profile:** Activated partial thromboplastin time International normalized ratio Prothrombin time	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen
Serology[b]:	**Drug screen**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency - antibodies	Not applicable	Follicle-stimulating hormone[b] (postmenopausal females only) Serum or Urine pregnancy test [c]

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated
[b] Only analyzed at Screening.
[c] All females will perform pregnancy test in serum at Screening and in urine at all other times.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Hematology, clinical chemistry, and coagulation	10	5	50
Serology	5	1	5
GMA301 pharmacokinetics	2	21	42
ADA	6	6	36
NT-proBNP	2.5	4	10
FSH and pregnancy test	5	1	5

Blood volumes for clinical chemistry, hematology, coagulation, serology test, FSH, and pregnancy test will meet local laboratory requirement. The volumes in above table are only for reference.

Appendix 4: Contraception Guidance

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use an acceptable method of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Acceptable methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
  - bilateral tubal ligation
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant

- hormonal or non-hormonal intrauterine device
- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject.

Female subjects of childbearing potential should refrain from donation of ova from Check-in (Day -1) until 90 days after the Follow-up visit.

Male Subjects

Male subjects will be surgically sterile for at least 90 days, with documented azoospermia, or when sexually active with female partners of childbearing potential will be required to use a male condom with spermicide (even if participant has a history of vasectomy) from Check-in until 90 days after the Follow-up visit. Sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

Consensus ethical principles derived from international guidelines including the declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.

Applicable ICH Good Clinical Practice (GCP) Guidelines.

Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents must be submitted to an IRB/Ethics Committee (EC) by the Investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.

Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary, and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject’s records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or CRO auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or Covance electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.

A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) (US site) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Sponsor or Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6: Schedule of Assessments

	Screening [a]	Randomization [b]	Treatment period									Follow-up			
Week	**-4**	**Day -1**	**0** [c]	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**11**	**12**[d]	**14**	**16**	**18**
Day (range)		**-1**	**1**	**8**	**15±1**	**22±1**	**29±1**	**57±1**	**64±1**	**71±2**	**78±2**	**85±3**	**99±3**	**113±3**	**127±3**
Visit	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Informed consent	×														
Inclusion/exclusion criteria	×														
Demographic data	×	×													
Medical history	×	×													
Concomitant medication	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Vital signs	×	×					×	×				×			
Height	×														
Body weight	×	×					×	×				×			
Physical examination	×	×					×	×				×			
Serology tests [e]	×														
Hematology, clinical chemistry, and coagulation	×	×					×	×				×			
Urinalysis	×	×					×	×				×			

	Screening [a]	**Randomization** [b]	**Treatment period**									**Follow-up**			
Week	**-4**	**Day -1**	**0** [c]	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**11**	**12**[d]	**14**	**16**	**18**
Day (range)		**-1**	**1**	**8**	**15±1**	**22±1**	**29±1**	**57±1**	**64±1**	**71±2**	**78±2**	**85±3**	**99±3**	**113±3**	**127±3**
Visit	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Pregnancy test [f]	×	×					×	×				×			
FSH [g]	×														
Pulmonary function	×											×			
Injection of GMA301 or placebo			×				×	×							
Pharmacokinetics sampling			×	×	×	×	×	×	×	×	×	×	×	×	×
Immunogenicity (ADA) [h]			×		×		×	×				×			×
NT-proBNP		×					×	×				×			
AE recording	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
12-lead ECG	×	×					×	×				×			
RHC	×											×			
Echocardiogram	×							×				×			
6MWT (Borg dyspnea scale)	×											×			
WHO function classification	×	×						×				×			

	Screening [a]	Randomization [b]	Treatment period									Follow-up			
Week	**-4**	**Day -1**	**0** [c]	**1**	**2**	**3**	**4**	**8**	**9**	**10**	**11**	**12**[d]	**14**	**16**	**18**
Day (range)		**-1**	**1**	**8**	**15±1**	**22±1**	**29±1**	**57±1**	**64±1**	**71±2**	**78±2**	**85±3**	**99±3**	**113±3**	**127±3**
Visit	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
REVEAL risk score		×										×			

Abbreviations: 6MWT = six-minute walk test; ADA = Anti-drug antibodies; ECG = electrocardiogram; FSH= follicle stimulating hormone; RHC = right heart catheterization.

a. Screening period will be up to 4 weeks. If a Screening test was performed within 3 days prior to Week 0, the results can be used as baseline (Week 0) results. No need to repeat the test at Week 0.
b. Day -1 the randomization day can also be the first day of Week 0, ie, the baseline blood sampling and information collection can be conducted just before the first dosing.
c. The samples at Week 0 will be collected on Day 1 of Week 0 before the first dosing.
d. Tests can also be done on the last day of Week 11. If a subject discontinues the visit in advance, it would be better to ask the subject to complete the Week 12 examinations.
e. Serology tests refer to Hepatitis B surface antigen, Hepatitis C antibody, and Human Immunodeficiency Virus antibodies (Appendix 2).
f. Women of childbearing potential will perform pregnancy test in serum at Screening and in urine at randomization and Weeks 4, 8, and 12.
g. FSH test will be performed at the same time with serum pregnancy test at Screening.
h. ADA will be collected at: Week 0 (pre-dose of the 1st dose), Week 2, Week 4 (prior to 2nd dose), Week 8 (prior to 3rd dose), Week 12 and Week 18 (end of follow-up).

Pharmacokinetics sampling:

Pharmacokinetics serum samples will be obtained for PK assessments at the following timepoints (±Time window):

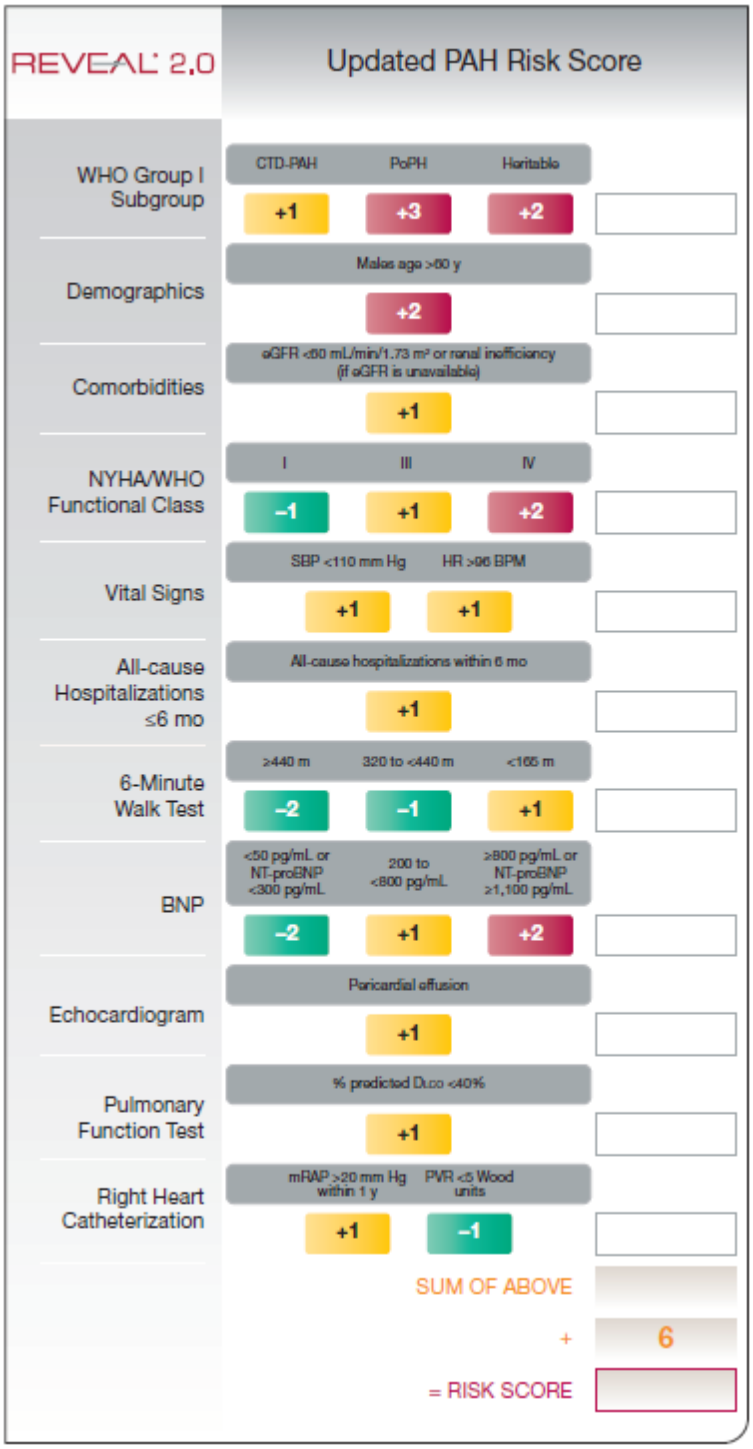
Dose 1st: predose, 4 (±15 min), 8 (±30 min), 24 (±120 min), 72 (±240 min), 168 (Day 8; ±480 min), 336 (Day 15; ±1 day), 504 (Day 22; ±1 day), and 672 (Day 29; ±1 day) hours post dose.

Dose 3rd: predose, 4 (±15 min), 8 (±30 min), 24 (±120 min), 72 (±240 min), 168 (Day 8; ±480 min), 336 (Day 15; ±1 Day), 504 (Day 22; ±1 day), 672 (Day 29; ±1 day), 1008 (Day 43; ±2 day), 1344 (Day 57; ±3 day), 1680 (Day 71; ±3 day) hours postdose.

The samples of the 672h post 1st dose will be collected before the 2nd dose.

Appendix 7: The REVEAL Risk Score

The REVEAL risk score can be implemented to identify predictors of short- and long-term survival in the context of current treatment and clinical variables. The calculator is as follows.



Calculated risk scores can range from 0 (lowest risk) to 23 (highest risk). BNP = brain natriuretic peptide; BPM = beats per minute; CTD-PAH = PAH associated with connective tissue disease; DLco = diffusing capacity of the lungs for carbon monoxide; eGFR = estimated glomerular filtration rate; FC = functional category; HR = heart rate; mRAP = mean right atrial pressure; NT-proBNP = N-terminal fragment of pro-brain natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PoPH = pulmonary hypertension associated with portopulmonary hypertension; PVR = pulmonary vascular resistance; REVEAL = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SBP = systolic BP; WHO

= World Health Organization.