CLINICAL STUDY PROTOCOL

Study Title: An Open-Label, Single-Arm, Historically Controlled, Prospective, Multicenter Phase III Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Immune Globulin Intravenous (Human) GC5107 in Subjects with Primary Humoral Immunodeficiency

SPONSOR: Green Cross Corporation
107 (Mogam Building), Ihyeon-ro
30beon-gil, Giheung-gu, Yongin-si,
Gyeonggi-do, Korea

PROTOCOL NUMBER: GC5107B_P3

VERSION 1.0: JANUARY 19, 2016
Date of Amendment 1 February 19, 2016
Date of Amendment 2 March 11, 2016
Date of Amendment 3 March 24, 2016

VERSION 2.0: JUNE 29, 2016
Date of Amendment 1: March 16, 2017
Date of Amendment 2: September 29, 2017
Date of Amendment 3: January 04, 2019

Confidentiality Statement:

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SYNOPSIS

STUDY TITLE	An Open-Label, Single-Arm, Historically Controlled, Prospective, Multicenter Phase III Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Immune Globulin Intravenous (Human) GC5107 in Subjects with Primary Humoral Immunodeficiency
SPONSOR	Green Cross Corporation 107 (Mogam BLDG), Ihyeon-ro 30beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do, Korea
INVESTIGATIONAL PRODUCT	Immune globulin intravenous (human) solution, 10% liquid, GC5107
CLINICAL TRIAL DESIGN	Phase III, open label, single-arm, historically controlled prospective, multicenter study
INDICATION AND CLINICAL USE	Treatment of subjects with primary humoral immunodeficiency (PHID)
OBJECTIVES	To assess the safety, efficacy, and pharmacokinetics (PK) of GC5107 in subjects with PHID
INFUSION RATE	<u>First infusion</u>: Initial rate: 1.0 mg/kg/min (0.01 mL/kg/min) for 30 minutes Incremental rate: • 2.0 mg/kg/min (0.02 mL/kg/min) at 30 minutes • 4.0 mg/kg/min (0.04 mL/kg/min) at 60 minutes • 8.0 mg/kg/min (0.08 mL/kg/min) at 90 minutes <u>If the first infusion is well tolerated, infusions 2-13(17)</u>: Initial rate: 2.0 mg/kg/min (0.02 mL/kg/min) for 15 minutes Incremental rate: • 4.0 mg/kg/min (0.04 mL/kg/min) at 15 minutes • 8.0 mg/kg/min (0.08 mL/kg/min) at 30 minutes Maximum rate: 8.0 mg/kg/min (0.08 mL/kg/min)

STUDY POPULATION	• Male or female aged 2 to 70 years with PHID requiring immune globulin intravenous (IGIV) treatment • Total Number of Subjects: Up to 50 subjects will be enrolled to obtain at least 42 subjects to be included into the study: o Adults: at least 26 subjects o Adolescents: at least 8 subjects aged ≥ 12 to < 17 years o Children: at least 8 subjects aged ≥ 2 to < 12 years • PK population: at least 20 adult and adolescent subjects • Subjects already stabilized (trough level of 500 mg/dL) on regular IGIV treatment
DOSAGE REGIMEN	• All subjects will receive intravenous infusions of the investigational product at the same dose and interval as used for their previous IGIV maintenance therapy • Dose of 300 – 900 mg/kg (of body weight) every 21 or 28 days (± 4 days) for 12 months
TARGET TROUGH LEVEL	≥ 500 mg/dL (5 g/L)
STUDY PERIOD	Approximately 14 months / each subject: • Screening: up to 28 days • Treatment (investigational product infusions) period: 12 months • Follow-up period: 3 or 4 weeks
INCLUSION CRITERIA	1. Subject has a confirmed clinical diagnosis of a PHID disease as defined by International Union of Immunological Societies (IUIS) and requires treatment with IGIV, and has documented agammaglobulinemia or hypogammaglobulinemia. 2. Male or female, aged 2 to 70 years. 3. The subject has received 300-900 mg/kg of IGIV therapy at 21(±4 days) or 28(±4 days)day intervals for at least 3 infusion prior to this study. 4. At least 2 documented IgG trough levels of ≥ 500 mg/dL are obtained at two infusion cycles

	(21(±4 days) or 28(±4 days) days) within 12 months prior to study treatment. 5. Subject is willing to comply with all requirements of the protocol. 6. Females of child-bearing potential with a negative pregnancy test at screening and females who agree to employ adequate birth control measures during the study. 7. Males who agree to practice adequate birth control measures during the study. 8. Subject, parent or guardian has signed the informed consent form and an assent form for children (≥ 2 to < 12 years of age at study entry) and adolescents (≥ 12 to < 17 years of age at study entry) as appropriate per study documentation and regulations of the local jurisdiction. 9. Authorization to access personal health information. 10. Subject currently participating in a clinical trial with another experimental IGIV may be enrolled if he/she has received stable IGIV therapy for at least 3 infusion cycles prior to receiving GC5107 and all inclusion and exclusion criteria are satisfied. • Other IGIVs will be prohibited for an infusion cycle (21(±4 days) or 28(±4 days) days) prior to the first infusion of GC5107 until the completion of Follow-up visit. 11. Subject currently participating in a trial of subcutaneous immunoglobulin (SCIG) can be enrolled if he/she is switched to IGIV for three infusion cycles (21(±4 days) or 28(±4 days) days) prior to enrollment in this study.
EXCLUSION CRITERIA	1. Subject has secondary immunodeficiency. 2. Subject was newly diagnosed with PHID and has not yet been treated with immunoglobulin. 3. Subject has been diagnosed with dysgammaglobulinemia or isolated IgG subclass deficiency or isolated IgA deficiency with known anti-IgA antibodies.

	4. History of severe reaction or hypersensitivity to IGIV or other injectable forms of IgG. 5. Subject has a lifetime history of at least one thrombotic event including deep vein thrombosis, cerebrovascular accident, pulmonary embolism, transient ischemic attacks, or myocardial infarction. 6. Subject has received blood products other than human albumin or human immunoglobulin within 12 months prior to enrollment. 7. Subject has protein losing enteropathy, nephrotic syndrome or lymphangiectasia. 8. Subject has had clinical signs or symptoms of an acute infection within 7 days prior to screening. 9. Subject has a known history or is positive at enrollment for HIV type 1/2 by nucleic acid testing (NAT), hepatitis B virus (HBsAg and NAT), hepatitis C virus (by NAT), or hepatitis A virus (by NAT). 10. Subject has levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times of the upper limit of normal for the laboratory designated for the study. 11. Subject has profound anemia (hemoglobin [Hgb] ≤ 8 g/dL) or persistent severe neutropenia (≤ 1000 neutrophils per mm^3). 12. Subject has a severe chronic condition such as renal failure (creatinine concentration > 2.0 times the upper limit of normal), congestive heart failure (New York Heart Association III/IV), cardiomyopathy, cardiac arrhythmia associated with thromboembolic events (e.g., atrial fibrillation), unstable or advanced ischemic heart disease, hyperviscosity, or any other condition that the investigator believes is likely to interfere with evaluation of the investigational product or with satisfactory conduct of the trial. 13. Subject has a history of a malignant disease, other than properly treated carcinoma in situ of the cervix or basal cell or squamous cell carcinoma of the skin within 24 months prior to enrollment. 14. Subject has history of epilepsy or migraines not completely controlled by medication.

	15. Subject is receiving the following medication: • Corticosteroids (oral or parenteral daily dose of ≥ 0.15 mg/kg/day of prednisone or equivalent). • Other immunosuppressive drugs or chemotherapy. 16. Females who are pregnant, breast feeding or planning a pregnancy during the study. Women who become pregnant during the study will be withdrawn from the study. Males who do not agree to use contraception will not qualify to be enrolled in the study. Males are not allowed to donate sperm during the study. 17. Subject has participated in another clinical study within 3 weeks prior to study enrollment.
EFFICACY ENDPOINT	**1) Primary Efficacy Endpoint:** The incidence of acute serious bacterial infections meeting Food and Drug Administration (FDA) guidance criteria (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis). **2) Secondary Efficacy Endpoints** • The incidence of infections other than acute serious bacterial infections meeting FDA guidance criteria. • The number of days missed from work/school/kindergarten/daycare, or days unable to perform normal daily activities due to infections. • The number of days that the care provider of the pediatric subject had to miss work in order to care for the child due to infections. • The number days of unscheduled physician visits due to infections. • The number of days of hospitalizations due to infections. • The number of days of intravenous (IV) therapeutic antibiotics. • The number of days of oral therapeutic antibiotics. • Time to resolution of infections. • The incidence of infections other than serious bacterial infections by trough IgG levels.
SAFETY ENDPOINTS	**1) Primary Safety Endpoint:** The proportion of infusions with temporally associated adverse events

	(AEs) that occur during or within 1 hour, 24 hours, and 72 hours following an infusion of investigational product (including AEs that were determined to be unrelated to the product). **2) Secondary Safety Endpoints** • The overall incidence of all AEs that occur during or within 1 hour, 24 hours ,and 72 hours following an infusion of investigational product. • The frequency of all AEs that occur during the study regardless of the investigator's assessment of their relationship to investigational product. • The frequency of suspected adverse reactions as defined by all AEs either classified by investigator or sponsor as at least possibly related to GC5107. • Changes in vital signs, physical examinations, and laboratory test results. • The number and proportion of GC5107 infusions for which the infusion rate was decreased due to AEs. • The proportion of AEs considered by the investigator to be investigational product related. • Viral safety (freedom from transmission of blood-borne viral diseases): the human immunodeficiency virus (HIV) 1&2, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and parvovirus B19.
PHARMACOKINETIC ENDPOINTS	**1) Primary PK Endpoints** • PK parameters of total IgG (assessed in PK population). • Trough serum total IgG levels before each infusion of GC5107 in all subjects and the interval between infusions will be recorded. **2) Secondary PK Endpoints** • PK parameters of IgG subclasses (assessed in PK population) • Trough serum level of IgG subclasses and specific IgG antibodies before Infusion 1, 5, 9, 13 (for 28-day infusion subject) or Infusion 1, 5, 11, 17 (for 21-day infusion subject) o anti-*Hemophilus influenza* type b

	○ anti-*Streptococcus pneumonia* serotypes ○ anti-Tetanus toxoid ○ anti-Cytomegalovirus (CMV) • Number and proportion of subjects who failed to meet the target IgG trough level (500 mg/dL) at any time point equal to or subsequent to 5th infusion (estimated 5 half-lives).
ANALYTICAL PLAN / STATISTICAL METHOD	Efficacy data will be evaluated by comparing the number of acute serious bacterial infections per subject per year according to the FDA guideline of an upper one-sided 99% confidence limit < 1.0 per subject per year. The primary safety endpoint will be analyzed with the objective of demonstrating that the percentage of infusions with one or more infusion-related AE is less than 40%. Pharmacokinetic parameters (clearance, mean residence time, volume of distribution, and terminal half-life) will be estimated by fitting noncompartmental analysis individually to the data for each subject in the PK population, except for the AUC which will be determined using a (log-) trapezoidal rule as the area above the previous trough level. Pharmacokinetic parameters will be derived from serum IgG levels and presented descriptively. Trough levels of IgG subclasses will be summarized relative to dosing interval. All other data will be reported descriptively.

Authorization Page

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Protocol Number	**GC5107B_P3**
Version	**V 2.0 Amendment 3**
Sponsor	[redacted]

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List of Abbreviations

AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
AMS	Aseptic Meningitis Syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BP	Blood pressure
BUN	Blood urea nitrogen
bw	Body weight
°C	Degrees Celsius
CK	Creatine kinase
CL	Total body clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CMV	Cytomegalovirus
CPMP	Committee for Proprietary Medicinal Products
CR	Clinical Research
CRF	Case report form
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CT	Computed tomography
CVID	Common variable immunodeficiency
D5W	Dextrose 5 % in water
DAT	Direct Antiglobulin (Coombs) test
DSMB	Drug Safety Monitoring Board
EU	European Union
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
h	Hour
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IDF	Immune Deficiency Foundation

IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGIV	Immunoglobulin intravenous
IgM	Immunoglobulin M
IP	Investigational product
IRB	Institutional Review Board
ITP	Immune Thrombocytopenic Purpura
ITT	Intention-to-treat
IV	Intravenous
Kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
min	Minute
mL	Milliliter
MRI	Magnetic resonance imaging
No.	Number
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PCR	Polymerase chain reaction
PHID	Primary humoral immunodeficiency
PI	Principal investigator
PK	Pharmacokinetic
PO	Oral
PP	Per protocol
PPS	Per protocol data set
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cells
SAE	Serious adverse event
SCIG	Subcutaneous immunoglobulin
$t_{1/2}$	Elimination half-life
t_{max}	Time point of maximum concentration (C_{max})
TRALI	Transfusion related acute lung injury
USA	United States of America
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization