1. Title page

Clinical trial protocol

Clinical trial protocol number:	E6011-ET2
Clinical trial name:	Early phase 2 clinical trial of E6011 in patients with active Crohn's disease
Sponsor:	EA Pharma Co., Ltd. 2-1-1 Irifune, Chuo-ku, Tokyo 104-0042
Sponsor and Coordinating Investigator's contact information:	See Attachment 2
IMP name:	E6011
Target disease:	Crohn's disease
Clinical trial phase:	Phase 2
Created on:	Version 11.0 18 April 2022
EudraCT Number:	2018-002109-70
GCP compliance:	This clinical trial is to be carried out in strict compliance with the ICH GCP and GCP of participating countries, as well as other regulations. All documents and materials related to the clinical trial are to be stored in accordance with the regulations of regulatory bodies.
Confidentiality:	The protocol of this clinical trial contains confidential information of the Sponsor. The information contained in the protocol must not be read or disclosed without obtaining prior written permission of the Sponsor. The information contained in the protocol may only be used for the purposes of reviewing or carrying out this clinical trial.

Clinical Trial Protocol Approval

E6011-ET2
Early phase 2 clinical trial of E6011 in patients with active Crohn's disease

PPD
Clinical Trial Administrative Division Director
EA PHARMA Co., Ltd.

_____ DATE

_____ SIGNATURE

PPD
Clinical Trial Team Lead
EA PHARMA Co., Ltd.

_____ DATE

_____ SIGNATURE

PPD
BIOSTATISTICIAN
EA PHARMA Co., Ltd.

_____ DATE

_____ SIGNATURE

Coordinating Investigator agreement

Signature of Coordinating Investigator Date

PPD

Investigator agreement

I confirm that I have read and that I understand this protocol entitled “E6011-ET2. Early phase 2 clinical trial of E6011 in patients with active Crohn’s disease”, the investigator brochure, and other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice E6.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

Signature of Investigator Date

Investigator Name (print or type)

Investigator’s Title

Name of Facility

Location of Facility (City)

2. Clinical trial protocol outline

Name of Sponsor EA Pharma Co., Ltd. 2-1-1 Irifune, Chuo-ku, Tokyo 104-0042	**Compound** E6011 (First-in-class humanised anti-fractalkine antibody)
Title of Protocol Early phase 2 clinical trial of E6011 in patients with active Crohn's disease	
Study Number E6011-ET2	**Phase** 2
EudraCT Number 2018-002109-70	
Centers The study will be conducted in anticipated 18 sites in Japan, Czech Republic, Hungary, Poland and Russian Federation.	
Institutional Review Boards / Independent Ethics Committees The study will be evaluated by the Institutional Review Boards / Independent Ethics Committees of all the participant centers.	
Study Monitoring Linical Co. Ltd. 10th floor, Shin-Osaka Brick Building, 6-1 Miyahara 1-chome, Yodogawa-ku, Osaka 532-0003, Japan https://www.linical.co.jp/en/	
Study design Multinational, multicentre, randomised, double-blind, placebo-controlled, parallel-group, early phase 2 clinical trial to be performed in Japan and Europe (Czech Republic, Hungary, Poland, Russian Federation). Upon having carried out the screening test within 42 days prior to the start of the IMP administration after obtaining consent, this clinical trial will have a double blind period of 12 weeks to assess remission-induction, including an open-label rescue period of another 12 weeks (for non-responders to Remission-induction), followed by an open-label extension period of additional 40 weeks. All patients will have a post-observation period (28 days and 70 days after the last IMP administration) and a 2 years follow-up (after the last IMP administration).	
Disease or disorder under study Patients with active Crohn's disease	
Objectives To perform the following evaluation after administering E6011 to patients with moderate to severe active Crohn's disease. Primary objective · To examine the efficacy and safety of E6011 at 12 weeks after administration by means of double-blind placebo-controlled trial.	

Secondary objective

· To examine the efficacy and safety of a long-term administration of E6011.

· To evaluate the pharmacokinetics and immunogenicity of E6011.

Exploratory objective

[redacted]

Anticipated Number of Subjects	**Anticipated number of sites**
40 completed patients (20 patients in the E6011 groups and 20 patients in the placebo group) • 22 Japanese patients : 18 non-Japanese patients • 8 biologic-naïve patients	18 (Japan, Czech Republic, Hungary, Poland, Russian Federation)
Dose levels 10 mg/kg E6011 dosing solution (approximately 100 mL) and matching placebo	**Route of Administration** Intravenous infusion pump
Duration of Treatment Maximum 64 weeks per subject (52 weeks for responders to the remission-induction)	**Period of Evaluation** Screening of 6 weeks Remission-induction of 12 weeks Rescue of 12 weeks Extension of 40 weeks Post-observation of 70 days Follow-up of 2 years

Main Criteria for Inclusion

Subjects who meet all of the following criteria are eligible to participate in this clinical trial.

(1) Crohn's disease patients aged 18 or over and under 65 on the date of consent.

(2) Patients diagnosed on basis of clinical findings, endoscopic findings, etc. with small intestine-type, small and large intestine-type, or large intestine-type Crohn's disease at least 12 weeks before giving consent.

(3) Patients with a baseline (at Week 0 before the start of IMP administration) disease severity ranging from moderate to severe. CDAI score between 220 and 450, and a PRO2 score between 14 and 34.

(4) Patients with a Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥ 7(or for patients with isolated ileal disease, ≥4 in ileum segment) in the screening period, with one or more ulcers (in SES-CD score, ulcer presence subscore ≥ 1 in any segment) assessed by colonoscopy and confirmed by a centralised review.

(5) Patients who received adrenocorticosteroids or immunomodulators in the past, but showed no therapeutic response (insufficient response) or the drugs were not tolerated (intolerance). Alternatively, patients who cannot taper adrenocorticosteroids (dependence). Alternatively, patients who showed no therapeutic response after administering biologic(s) (primary nonresponse), patients who initially showed therapeutic response but it lessened or disappeared afterwards (secondary nonresponse), or patients who did not tolerate the drug (intolerance). (Detailed criteria are described in Attachment 7 and Attachment 8).

(6) If the patients are taking 1,200 kcal/day or less enteral nutrition, the dosage and administration have not changed for at least 4 weeks prior to the start of the IMP administration.
(7) If the patients are taking aminosalicylic acid (5-ASA), salazosulfapyridine, or antibiotics for the treatment of Crohn's disease (metronidazole, ciprofloxacin, etc.), the dosage and administration have not changed for at least 4 weeks prior to the start of the IMP administration.
(8) If the patients are taking under 30 mg/day of oral prednisolone (or equivalent adrenocorticosteroid) or 9 mg/day or less of oral budesonide, the dosage and administration have not changed for at least 4 weeks prior to the start of the IMP administration.
(9) If the patients are taking azathioprine (AZP), 6-mercaptopurine (6-MP) or methotrexate (MTX), the dosage and administration have not changed for at least 8 weeks prior to the start of the IMP administration.
(10) Patients who have received a sufficient explanation about the compliance rules of this clinical trial, who are willing to comply with them, and who are able to do so.
(11) Patients who voluntarily gave a written consent to participate in this clinical trial.

Main Criteria for Exclusion:

Patients who meet any of the following criteria shall be excluded from this clinical trial.

(1) Patients diagnosed with ulcerative colitis or indeterminate colitis (refers to cases in which there is a difficulty distinguishing between Crohn’s disease and ulcerative colitis, intermediate colitis).
(2) Patients diagnosed with gastrointestinal epithelial dysplasia.
(3) Patients who have an abscess or are suspected to have one (however, patients with anal abscess whose symptoms are stable with treatment, such as drug treatment or drainage, are not excluded).
(4) Patients with an artificial anus, ileo-anal pouch or fistula (however, patients with fistula-in-ano whose symptoms are stable with treatment, such as drug treatment or drainage, are not excluded).
(5) Patients with symptomatic or high-grade gastrointestinal stenosis (patients who require expansion by endoscopy or who have SES-CD score stenosis sub-score of 3, etc.).
(6) Patients who, after undergoing small bowel resection, have been diagnosed with a short bowel syndrome, which makes maintaining caloric intake difficult.
(7) Patients who have newly started seton drainage treatment within 12 weeks prior to the start of the IMP administration.
(8) Patients who have undergone bowel resection or a gastrointestinal surgery within 24 weeks prior to the start of the IMP administration.
(9) Patients who tested positive for *C. difficile* toxin test in the screening period.
(10) Patients who tested positive for HIV, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis B virus DNA (HBV-DNA), hepatitis C virus antibody (anti-HCV), or human T cell leukemia virus type 1 antibody (anti-HTLV-1) in the screening period (however, this excludes patients who tested positive only for anti-HBs, clearly shown to be due to hepatitis B vaccination). Patients who tested negative for HBsAg and quantitative HBV-DNA and positive for anti-HBc antibody and/or anti-HBs antibody may participate in the clinical trial as long as the Principal Investigator or Sub-investigator takes proper measures such as

monitoring HBV-DNA based on (not restricted to the following)

- For Japan: Guidelines for measures against hepatitis B arising due to immunosuppression or chemotherapy
- For Poland: Recommendations for the treatment of chronic viral hepatitis B in 2018 by Polish Group of Experts for HBV
- For Hungary: Diagnosis and treatment of chronic hepatitis B and D. Hungarian national consensus guideline
- For Czech Republic: EASL (European Association for the Study of the Liver) 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection
- For Russian Federation: Order of Ministry of Health of Russian Federation #786н “On approval of the standard of specialized medical care for chronic viral hepatitis B" dd. 09.11.2012

In addition, patients who tested positive for HCV antibody and who were at least 24 weeks post-treatment may participate in the clinital trial as long as negative HCV-RNA is confirmed during the screening period.

(11) Patients with positive or repeated indeterminate (inconclusive) results on the TB test (QuantiFERON® -TB Gold test or T-SPOT® TB test). However, patients with indeterminate (inconclusive) results on repeated tests may be included in this clinical trial if they are started on prophylactic isoniazid least 21 days prior to the start of IMP administration. (The dose is generally 300 mg/day. If the patient has a low body weight, the dose is to be 5 mg/kg a day. The drug is administered for approximately 9 months.) Prophylactic treatment should be given in accordance with the local guidelines.

(12) Patients with findings showing a history of tuberculosis on a chest X-ray test in the screening period.

(13) Patients with findings of neurological symptoms such as motor impairment, cognitive disorder, language disorder or dysphagia in the evaluations during the screening period.

(14) Patients with a WBC count of less than 3,000/μL or blood $CD4^+$ cell count under 200/μL in the screening period tests.

(15) Patients with a medical history of clinically significant vasculitis.

(16) Acute myocardial infarction, unstable angina pectoris, cerebral infarction, and symptomatic cerebral haemorrhage patients.

(17) Patients whose AST or ALT was more than three times the upper normal limit in the screening period tests or patients whose serum creatinine level was more than 1.5 times the upper normal limit in the screening period tests.

(18) Patients with a QTcF exceeding 450 ms repeatedly in standard 12-lead ECG tests in the screening period tests.

(19) Patients who have undergone cytoapheresis (granulocytapheresis; GCAP) within 2 weeks prior to the start of the IMP administration.

(20) Patients who required any one of the following treatments of infection; "hospitalization within 4 weeks prior to the start of IMP administration", "intravenous treatment of antibiotics (including antiviral drugs) within 4 weeks prior to the start of IMP administration", or "oral treatment of antibiotics (including antiviral drugs) within 2 weeks prior to the start of IMP administration"

Furthermore, with regard to the novel coronavirus infection (COVID-19), patients who required any one of the following treatments; “hospitalization within 4 weeks prior to the start of IMP administration”, “any intravenous treatment within 4 weeks prior to the start of IMP administration” or “any oral treatment within 2 weeks prior to the start of IMP administration”.

(21) Patients who received total parenteral nutrition (TPN), peripheral parenteral nutrition (PPN), or enteral nutrition exceeding 1200 kcal/day within 4 weeks prior to the start of the IMP administration.

(22) Patients who received ≥30 mg/day of oral prednisolone (or an equivalent adrenocorticosteroid), adrenocorticosteroid injection, enema or suppository within 4 weeks prior to the start of the IMP administration.

(23) Patients who received cyclosporine, mycophenolate mofetil, or tacrolimus within 8 weeks prior to the start of the IMP administration (excluding topical use).

(24) Patients who received adalimumab, infliximab, certolizumab pegol, vedolizumab or ustekinumab (including biosimilars) within 8 weeks prior to the start of the IMP administration.

(25) Patients vaccinated with live vaccines within 12 weeks prior to the start of the IMP administration or patients who received a vaccine that is considered to have a risk of infection, such as a virus vector vaccine that uses a virus that retains its ability to proliferate within 12 weeks prior to the start of the IMP administration

(26) Patients who received an immunoglobulin preparation or a blood product within 24 weeks prior to the start of the IMP administration.

(27) Patients who have received natalizumab or E6011 in the past

(28) Patients with a history of a malignant tumour, lymphoma, leukemia, or lymphoproliferative disorders, or with complications thereof. However, this does not include completely resected skin cancers (epithelial cell cancers or basal cell cancers) and cervical cancers with no metastasis or recurrence observed for 5 more years at the time of giving consent.

(29) Patients with immunodeficiency or a history of HIV infection.

(30) Patients with a history of severe allergy (shock, anaphylaxis-like symptoms).

(31) Patients currently taking part in another clinical trial (including the post-observation period), or patients who were participating in another trial using an IMP or investigational medical device within 28 days (or within five times the length of the half-life period of the IMP, whichever is longer) prior to giving consent.

(32) Patients who received a faecal microbiota transplant (FMT), mesenchymal stem cell, etc. within 24 weeks prior to giving consent.

(33) Female patients of childbearing potential who had a positive result on the pregnancy test at screening or baseline, as well as lactating patients.

(34) Female patients of childbearing potential who:

- have not been on a highly effective method of contraception within 28 days prior to the start of IMP administration. The following are highly effective contraception methods:
  - Sexual abstinence (if preferred by subjects as their regular lifestyle)
  - Use of intrauterine device (IUD)

– Contraceptive implant
– Use of oral contraceptives
(The same oral contraceptive is to be used at a set dose for more than 28 days prior to the start of the IMP administration, and continued throughout the clinical trial and for 70 days after the last administration of the IMP)
– The male partner has undergone vasectomy and azoospermia has been confirmed

- Patients who do not agree to continue using one of the highly effective contraception methods described above throughout the clinical trial and for 70 days after the last administration of the IMP
- If the use of the aforementioned contraception methods is not appropriate or not allowed, the patients are required to consent to use another medically appropriate contraception method, i.e. a double-barrier method (combined use of a condom and contraceptive diaphragm, or a spermicide-containing cervical/vault cap, etc.)
- All females are deemed to have childbearing potential. However, postmenopausal women (menopausal age patients who have not menstruated for at least 12 consecutive months, which has been confirmed not to be due to other factors, or is not suspected to be due to other factors) and women who have undergone surgical sterilization (patients who have undergone bilateral tubal ligation, hysterectomy, or bilateral oophorectomy more than one month prior to the IMP administration) are excluded from this rule.

(35) Potential male patients with female partners of childbearing potential:

- that have not undergone proper vasectomy (azoospermia can not be confirmed) who (or whose partners) do not agree to use contraception employing one of the methods listed in the exclusion criteria (34) during the clinical trial and for 70 days after the last administration of the IMP (however, if the female partner does is not of childbearing potential, the subject can participate in the trial).
- patients whose female partner is pregnant and do not agree to use latex or synthetic condoms during the clinical trial and for 70 days after the last administration of the IMP.
- the patients must not donate sperm during the clinical trial and for 70 days after the last administration of the IMP.

(36) Patients who were judged to be unsuitable for participation in this clinical trial by the Principal Investigator or Sub-investigator.

Main Criteria for Evaluation and Analysis

Efficacy analysis will be performed using the FAS as the primary analysis set, while the PPS will be used as a supplementary analysis set.

Analysis of primary endpoint

For Week 12 CR100 rate, the Bayesian posterior distribution of the difference in the CR100 rate at Week 12 between the E6011 group and the placebo group is to be calculated. If there was a 50% or more probability of the difference between both groups being 25% or more, the efficacy of E6011 is confirmed.

Noninformative prior distribution is to be used for both the E6011 group and the placebo group.

Subjects with missing primary endpoint data by Week 12 after administration due to premature discontinuation or other reasons are treated as treatment failures (non-responder imputation [NRI]).

Analysis of secondary endpoints

- CDAI response rate (CR70, CR100 (excluding Week 12)) and remission rate are to be calculated by treatment group and evaluation time. Summary statistics for CDAI value, change and percent change from baseline are also to be calculated by treatment group and evaluation time.
- PRO2 response rate (PRO2-CR5, PRO2-CR8) and remission rate are to be calculated by treatment group and evaluation time. Summary statistics for PRO2 value, change and percent change from baseline are also to be calculated by treatment group and evaluation time.
- SES-CD endoscopic response rate and endoscopic remission rate are to be tabulated by treatment group and evaluation time. Summary statistics for SES-CD value, change and percent change from baseline are also to be calculated by treatment group and evaluation time.
- Steroid-free remission rate and steroid-free response rate in subjects concomitantly using adrenocorticosteroids is to be tabulated by treatment group and evaluation time. Summary statistics for steroid dosage, change and percent change from baseline are also to be calculated for each treatment group and evaluation time.

Pharmacokinetics

Drug concentration is to be analysed using the drug concentration analysis set. Summary statistics for serum E6011 concentration are to be calculated for each specified time. Serum E6011 concentration-time profile is also to be created.

Biomarkers, pharmacogenomics/pharmacogenetics

Biomarkers, pharmacogenomics/pharmacogenetics are to be analysed using the pharmacodynamic analysis set. Summary statistics for serum total FKN concentration, faecal calprotectin and serum CRP concentration measured values, change and percent change from baseline are to be calculated by treatment group and evaluation time. CCI [redacted] Details and results of the analysis of blood $CD16^+$ monocytes, etc., blood $CD16^+$ monocyte, etc. genetic markers and blood biomarkers (comprehensive proteome analysis) using the residual serum collected for this study are to be recorded in a separately created report, and not included in the Clinical Study Report.

Immunogenicity

Immunogenicity is to be analysed using the safety analysis set. Incidence and ratio of serum anti-E6011 antibodies are to be calculated by treatment group and evaluation time. If anti-E6011 antibodies are confirmed, frequency and ratio of their neutralizing activity (if present) and isotypes are to be calculated.

Safety

Safety is to be analysed using the safety analysis set. Summary statistics related to safety data (sample size, mean value, standard deviation, median value, minimum and maximum as continuous variables; sample size

and ratio as categorical variables) are to be calculated by each treatment group based on the treatment that was administered. Safety endpoints include adverse events, clinical examination values, vital signs, weight, physical examination, standard 12-lead ECG tests, neurological symptoms and blood $CD4^+$ cell count.

- Incidence rate of adverse events that occurred after the IMP administration is to be calculated by treatment group.
- Summary statistics for measured clinical examination values, vital signs and $CD4^+$ cell count, as well as their change from baseline, are to be calculated by treatment group.
- For standard 12-lead ECG test findings and neurological symptoms, the numbers and rates are shown in the shift table by each treatment group and by normal and abnormal findings.

Interim analysis

No interim analysis is planned in this clinical trial.

Sample size Justification

The number of subjects in this clinical trial was determined considering operating characteristics pertaining to a simulation efficacy evaluation, with reference to efficacy performance in the E6011-J081-101 study, as well as efficacy performance of similar drugs. With 20 subjects allotted to each group, if the actual difference in CR100 response rate between the E6011 group and placebo group is 40% or more, the probability of confirming the efficacy of E6011 is above 80%.

Study schedule and anticipated date of completion

Recruitment: September 2018 to October 2021

Treatment: October 2018 to April 2022

Follow-up: Jun 2021 to April 2024

Close-out: May 2024

3. Table of Contents

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4. List of Abbreviations

Abbreviations	Unabbreviated Terms (English)
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
5-ASA	5-amino salicylic acid
AST	aspartate aminotransferase (SGOT)
ATC	anatomical therapeutic chemical
AZP	azathioprine
BUN	blood urea nitrogen
CDAI	Crohn's disease activity index
CK	creatine kinase
CR	Clinical response
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
CX3CR1	CX3C motif chemokine receptor 1 (receptor of fractalkine)
DNA	deoxyribonucleic acid
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ECCO	European Crohn's and Colitis Organization
FAS	full analysis set
FKN	fractalkine
FMT	faecal microbiota transplantation
GCP	good clinical practice
GCAP	granulocytapheresis
γ GTP	γ -glutamyl transpeptidase
HBc	hepatitis B virus core
HBs	hepatitis B virus surface
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTLV-1	human T cell lymphotropic virus-1
IBD	inflammatory bowel disease
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL-12/23	Interleukin 12/23
IRB	Institutional Review Board

IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
JCV	JC virus
LDH	lactate dehydrogenase
LLT	lowest level term
LNH	low normal high
MedDRA	medical dictionary for regulatory activities
6-MP	6-mercaptopurine
MRI	magnetic resonance imaging system
MS	multiple sclerosis
MTX	methotrexate
NRI	Non-Responder Imputation
PD	pharmacodynamics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
POC	proof of concept
PPN	peripheral parenteral nutrition
PPS	per protocol set
PRO2	patient reported outcome 2
PT	preferred term
QOL	quality of life
QTcF	average time-matched QT corrected by the Fridericia formula
SC	subcutaneous
SES-CD	simple endoscopic score for Crohn’s disease
SI	Le Systeme international d'uniyes
SOC	system organ class
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment emergent adverse events
TNFα	tumour necrosis factor α
TPN	total parenteral nutrition
URL	uniform resource locator
WHO DD	world health organization drug dictionary

5. Ethics

5.1 IRB/IEC

The protocol, informed consent form and other related documents must be reviewed and approved by an IRB/Independent Ethics Committee (IEC) established and operated in accordance with the ICH GCP (Section 3) and regulations applicable in each respective region. In order to revise the protocol or change the informed consent form, it is necessary to undergo another review by the IRB/IEC and obtain approval (however, this excludes changes in administrative items such as change of the monitor or telephone number). A document certifying compliance with the ICH GCP and regulations applicable in each region in establishing, reviewing and operating the IRB/IEC is to be submitted to the Sponsor.

The Principal Investigator (or, in accordance with the regulations of each region, the head of Clinical Trial Centre) is to obtain an approval document from the chairperson of the IRB/IEC before starting the clinical trial. The Sponsor (or its representative) is to obtain said document before delivering the IMP to the Clinical Trial Centre (ICH GCP, Section 4.4). Should the IRB/IEC decide to suspend or discontinue the clinical trial, the Principal Investigator (or, in accordance with the regulations of each region, head of Clinical Trial Centre) is to promptly report this to the Sponsor.

The Principal Investigator or the Sponsor (depending on the regulations of each region), is to report to the IRB/IEC once a year (or in accordance with the regulations) on the clinical trial implementation status. When the Principal Investigator is required to report to the IRB/IEC, in addition to sending the report to the IRB/IEC, he/she shall submit a copy of the report to the Sponsor. The Principal Investigator or the Sponsor, in addition to making periodic reports as stipulated by the regulations of each region, shall report to the IRB/IEC (according to the regulations of each region, the report is made either via the head of the Clinical Trial Centre after notifying the Principal Investigator and the head of the Clinical Trial Centre, or directly to the IRB/IEC) all reportable adverse events according to the ICH GCP and the IRB/IEC procedure manual. Moreover, the Principal Investigator is to report to the IRB/IEC and the Sponsor through the head of Clinical Trial Centre a summary of the clinical trial results upon completion of the clinical trial.

In Europe, the Principal Investigator is to report to the IEC a summary of the clinical trial results upon completion of the clinical trial. The Sponsor is to notify the IEC and competent authority of the clinical trial completion within 90 days from the completion. Clinical trial completion shall be marked by the date of the last follow-up visit of the last subject in this clinical trial. The Sponsor is to report to the IRB/IECthe summary of the clinical trial results as well.

If the clinical trial is prematurely discontinued or temporarily suspended, the Principal Investigator is to notify the IRB/IEC and competent authority of this fact within 15 days. A detailed explanation of the reason for the discontinuation or suspension is to be provided in writing.

5.2 Ethical implementation of the clinical trial

This clinical trial is to be carried out in compliance with the Sponsor's (or its representative's) SOP that was created in accordance with the following guidelines, etc.

- Ethical principles based on the WMA Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects)
- ICH GCP (CPMP/ICH/135/95)
- All clinical trials carried out in European countries shall adhere to European Good Clinical Practice Directive 2005/28/EC and European Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) are to be reported to competent authorities of involved European countries in accordance with the regulations

5.3 Information provided to subjects and informed consent

The Principal Investigator, in accordance with the ICH GCP (Section 4) and regulations of each region, shall create an informed consent form with the help of the Sponsor and obtain approval of the IRB/IEC.

The Principal Investigator or the Sub-investigator is required to explain to each subject (or representative) the clinical trial content, purpose, procedures, scheduled participation period, anticipated clinical benefits, risks and inconveniences, whether there are other treatment methods available to the subject, and the fact that the subject's confidentiality will be protected. The Principal Investigator or the Sub-investigator shall also explain that the subject's participation in the clinical trial is voluntary, that the subject may refuse to participate or withdraw from the trial at any time, and that the refusal or withdrawal will not adversely affect the subject's subsequent medical treatment or relationship with the doctor. A document written in a non-specialised language shall be used in the above informed consent explanation.

Before participation in the trial, the subject is to sign his/her name and date the informed consent form that has been approved by the IRB/IEC/IEC. The informed consent form must also be signed and dated by the Principal Investigator or authorized Sub-investigator who conducted the informed consent discussion. The subject needs to understand the explanation before writing his/her signature and date on the form. The subject is to receive a copy of the signed informed consent form and subject information sheet. If the subject is unable to read the informed consent form, an impartial witness needs to be present throughout the entire informed consent explanation process. The witness is to read out and explain to the subject the informed consent form and other information for the subject contained in documents. Afterwards, the subject is to give a verbal consent to participate in the study. Then, the witness is to write his/her signature and date on the consent form after the subject, if he/she is able to, has written his/her signature and date on the form. Before carrying out any assessments and evaluations related to this clinical trial, it is necessary to confirm whether the subject has signed the informed consent form. The subject may not be enrolled in the clinical trial before signing his/her informed consent.

The original of all signed informed consent form are to be stored at the Clinical Trial Centre, and this is to be verified by the Sponsor.

If any information that might affect the subject's willingness to continue participation in this clinical trial becomes available, the information is to be promptly provided to the subject, and the fact of its

provision is to be recorded in writing.

In cases where the consent of a legally acceptable representative is required, if the subject understands the fact of his/her participation in the clinical trial, the Principal Investigator or Sub-investigator shall use the informed consent form to explain about the clinical trial to the subject in the same way he did to the legally acceptable representative, and obtain the subject's signature. Subjects who are unable to sign the consent form are to verbally confirm their willingness to participate, which is to be recorded in the consent form.

6. Principal Investigators and the Clinical Research Associates

This clinical trial will be conducted at 18 Clinical Trial sites (anticipated) in Japan, Europe and Russia by Principal Investigators selected by the Sponsor (Attachment 1).

The name and contact information (telephone number and FAX number) of the Sponsor and Contract Research Organization (CRO) are listed in Attachment 2.

7. Introduction

Crohn's disease is one of inflammatory bowel diseases (IBD) that causes longitudinal ulcers in the small and large intestine, which leads to abdominal pain, diarrhoea, fever, melena and weight loss. The disease commonly occurs in people in their 10s and 20s. The patients experience repeated recurrences that cause a progressive destruction of the gastrointestinal tract tissue[1] , which ultimately necessitates a resection. The cause of Crohn's disease is not known, but it is thought to be a multifactorial disease caused by an intricate combination of genetic factors, environmental factors such as diet, and increased inflammatory cytokines such as tumour necrosis factor (TNFα) associated with immunological abnormality[2] . The number of Crohn's disease patients in Japan has been growing each year, with approximately 41,000 patients as of present (2014, number of medical care certificate holders). This disease is especially prevalent in Europe and America, where the incidence rate is high.

At present, there is no cure for Crohn's disease, and the goal of the treatment is to prevent recurrence, control disease activity and maintain clinical remission. Biologics such as anti-TNF α antibody products have greatly changed the therapeutic system, as they were found to be effective in Crohn's disease patients who did not derive sufficient benefits from existing therapeutic drugs, including steroids or immunomodulators. However, there are also patients who do not respond to such biologics, patients for whom the therapeutic efficacy decreases[3] , and patients for whom administration cannot be continued due to allergic reactions. As such, it cannot be said that biologics sufficiently meet medical needs. Consequently, there is a strong demand for development of drugs with new mechanisms of action that are highly effective and safe.

E6011 is the world's first humanised anti-fractalkine (FKN) monoclonal antibody created by Eisai's KAN Research Institute, Inc. FKN has a dual effect of modulating leukocyte migration and acting as an adhesion molecule, and plays an important role in leukocyte infiltration in the inflamed tissue[4] . From the fact that anti-FKN antibody suppressed damage to large intestine in mouse models of T cell transfer colitis and oxazolone-induced colitis, it has been suggested that FKN plays a role in intestinal inflammation [5] . In

addition, FKN expression and FKN receptor (CX3CR1) positive cells are increased in Crohn's disease patients' peripheral blood and inflamed gastrointestinal tract tissue, which points out to a relationship between the pathology of Crohn's disease and FKN[6,7,8,9]. Based on the above, it is expected that E6011, by inhibiting FKN function, will suppress migration and infiltration of lymphocytes and monocytes into inflammatory sites, thus reducing inflammatory lesions in the gastrointestinal tract of Crohn's disease patients.

At present, a phase 1 study of single intravenous (IV) E6011 administration in Japanese healthy adult subjects (E6011-J081-001, hereinafter "Study 001") and a phase 1 study of single subcutaneous administration (SC) in healthy Japanese adult subjects (E6011-J081-002, hereinafter "Study 002") have been completed. No adverse events that raise concerns in terms of safety and tolerability were observed with the dosages used in Study 001 (IV: 0.0006 to 10 mg/kg) and Study 002 (SC: 50 to 400 mg).

In a phase 1/2 study of repeated intravenous E6011 administration in Japanese subjects with Crohn's disease (E6011-J081-101, hereinafter "Study 101"), safety and tolerability upon administering 2 mg/kg, 5 mg/kg, 10 mg/kg and 15 mg/kg of E6011 were evaluated as primary objectives. Analysis of the 12-week administration has been completed, and there were no safety or tolerability problems concerning Crohn's disease with the 2 to 15 mg/kg repeated administration. In addition, exploratory evaluation of efficacy showed a trend towards improvement in the clinical symptoms of Crohn's disease.

Based on the above results and in view of the present demand for a Crohn's disease drug with a new mechanism of action in terms of efficacy and safety, a double-blind, placebo-controlled, parallel-group clinical trial has been designed to evaluate the efficacy and safety of E6011, which is a new drug expected to benefit Crohn's disease patients. Due to the number of Crohn's disease patients being smaller in Japan compared to Europe and America, making it difficult to enrol subjects in Japan alone, and due to the fact that the next phase of the clinical trial is going to be focused on non-Japanese patients, this clinical trial has been designed as a multinational clinical trial with added participation of European countries.

8. Clinical trial objective

To perform the following evaluation after administering E6011 to patients with moderate to severe active Crohn's disease.

8.1 Primary objective

To examine the efficacy and safety of E6011 at 12 weeks after administration by means of double-blind placebo-controlled trial.

8.2 Secondary objective

- To examine the efficacy and safety of a long-term administration of E6011.
- To evaluate the pharmacokinetics and immunogenicity of E6011.

8.3 Exploratory objective

CCI [redacted]

9. Clinical trial plan

9.1 General clinical trial design and plan

This is a multinational, multicentre, randomised, double-blind, placebo-controlled, parallel-group, early phase 2 clinical trial. This clinical trial consists of a screening period, remission-induction period (double blind), rescue period (open-label), extension period (open-label), post-observation period and follow-up period. Administration of the IMP is to start after confirming eligibility at baseline (at week 0 before the start of the IMP administration) upon having carried out the screening test within 42 days prior to the start of the IMP administration after obtaining consent.

Patients with moderate to severe active Crohn's disease are to be randomly allocated to an E6011 10mg/kg group and a placebo group (1:1) using stratified allocation in which race (Japanese/non-Japanese) and history of previous use of biologics (yes/no) are used as allocation factors. The administration volume (about 100 mL) is to be prepared based on the weight of the subject by diluting E6011 with a physiological saline solution, and infused intravenously over approximately 30 minutes. The physiological saline solution used to dilute E6011 is to be used as a placebo. The remission-induction period is to last 12 weeks, with E6011 or placebo administered in a double-blind method on Week 0, Week 1, Week 2, and once every two subsequent weeks up to Week 10, and the efficacy of E6011 is to be evaluated in Week 12. Subjects with a reduction in the CDAI (Crohn's Disease Activity Index) of 70 or more (responders) compared to baseline at evaluation on Week 12 are to move on to the open-label extension period. The extension period is to last 40 weeks, with 10 mg/kg of E6011 administered every four weeks from Week 12 to Week 48 and E6011 efficacy is to be evaluated at Week 52.

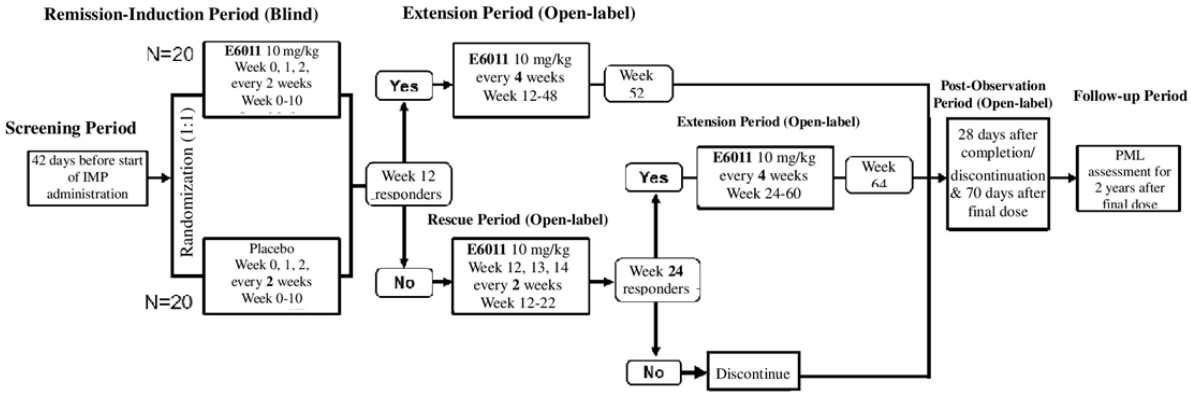
Subjects with less than 70 reduction in the CDAI (non-responders) at evaluation in Week 12 are to move on to the rescue period. The rescue period is to last 12 weeks, with additional administrations of 10 mg/kg of E6011 in Week 12, Week 13, Week 14 and every two subsequent weeks up to Week 22. Subjects with a reduction in the CDAI of 70 or more compared to baseline/Week 12 at evaluation in Week 24 of the rescue period are to move on to the open-label extension period. The extension period is to last 40 weeks, with 10 mg/kg of E6011 administered every four weeks from Week 24 to Week 60 and E6011 efficacy is to be evaluated at Week 64. Patients with less than 70 reduction in the CDAI compared to baseline and Week 12 at evaluation in Week 24 are to be discontinued.

The Principal Investigator or Sub-investigator is to confirm that the subjects' data as of Week 12 of the remission-induction period (double-blind) has been completely entered into the eCRF by the time the first evaluation in the rescue period or extension period takes place. Blinding in the double-blind period is to be maintained until a database in the double-blind study period is locked.

The post-observation period consists of an assessment in person 28 days after the completion or discontinuation of the extension period of the clinical trial, and an assessment in person or over the phone 70 days after the last administration of the IMP. The follow-up period entails contacting the patients over the phone, etc. every 6 months until 2 years have passed from the last administration of the IMP to inquire whether they have experienced progressive multifocal leukoencephalopathy (PML).

Figure 1 shows the design of the clinical trial.

Figure 1 Clinical trial design



Responders at CDAI evaluation on Week 12 of the remission-induction period are to move on to the extension period, in which E6011 is administered every four weeks. Non-responders are to move on to the rescue period, and if the CDAI has improved by Week 24, they are to move on to the extension period, in which E6011 administered every four weeks. Subjects whose CDAI has not improved by Week 24 are to be discontinued.

9.1.1 Screening period

After the clinical trial has been sufficiently explained to each subject, a written consent is to be obtained from each subject before carrying out any assessments and evaluations related to this clinical trial. Section5.3 describes procedures related to obtaining consent.

Patients who signed consent are to undergo screening period tests in between 42 days and one day before the start of the IMP administration. The Principal Investigator or Sub-investigator is to confirm whether each subject meets all inclusion criteria and does not fall under any of the exclusion criteria.

Screening results are to be recorded in the case report form. If a subject is deemed not eligible to participate in this clinical trial, the reason is to be recorded in the case report form.

Because subjects deemed to require prophylactic administrations of isoniazid as a result of tuberculosis check-up in the screening period will start receiving the IMP after more than 21 days of prophylactic administration, the screening period may be extended until 21 days have passed from starting isoniazid (Prophylactic treatment should be given in accordance with the local guidelines).

9.1.2 Remission-induction period

Subjects who were deemed eligible to participate in the screening period and at baseline are to be allocated to the E6011 10 mg/kg group and placebo group at the ratio of 1:1 using stratified allocation in which race and history of previous use of biologics are used as allocation factors. E6011 or placebo is to be administered to allocated subjects in a double-blind method on Week 0, Week 1, Week 2, and every two subsequent weeks until Week 10.

9.1.3 Rescue period

Subjects with a reduction in the CDAI of less than 70 compared to baseline after finishing evaluation in Week 12 of the remission-induction period are to move on to the rescue period. The rescue period is to last 12 weeks, with 10 mg/kg of E6011 administered in an unblinded manner on Week 12, Week 13, Week 14 and every two subsequent weeks until Week 22.

The Principal Investigator or Sub-investigator is to confirm before the first evaluation in the rescue period is carried out that non-responders' data up to Week 12 of the remission-induction period (double-blind period) has been entered in the case report form. Blinding of each subject's treatment group is to be maintained until the database of the remission-induction period is locked.

Subjects with a reduction in the CDAI of 70 or more compared to baseline or Week 12 at evaluation in Week 24 are to move on to the extension period. Subjects with less than 70 reduction in the CDAI compared to baseline and Week 12 are to be discontinued.

9.1.4 Extension period

Subjects who finished evaluation at Week 12 of the remission-induction period and had a CDAI response of 70 or more, and subjects who moved on to the rescue period and finished evaluation at Week 24 with a CDAI response of 70 or more are to move on to their respective extension period. The extension period is to last 40 weeks, with 10 mg/kg E6011 administered in an unblinded manner every four weeks up to Week 48 or Week 60.

The Principal Investigator or Sub-investigator is to confirm before the first evaluation in the extension period is carried out that responders' data up to Week 12 of the remission-induction period (double-blind period) has been entered in the case report form. Blinding of each subject's treatment group is to be maintained until the database of the remission-induction period is locked.

9.1.5 Post-observation period

After the extension period of the clinical trial has been finished or discontinued, examinations are to be carried out 28 days after the completion or discontinuation of the extension period (in the hospital) and 70 days after the last administration of the IMP (in the hospital or over a telephone call).

9.1.6 Follow-up period

PML onset is to be investigated over the phone, etc. every 6 months in the two-year follow-up period after the last IMP administration.

9.2 Discussion of the clinical trial design, including control group selection

This is a multinational, multicenter, randomised, double-blind, placebo-controlled, parallel-group, clinical trial with the primary objective of evaluating the efficacy and safety of E6011 in patients with moderate to severe active Crohn's disease.

In Japan's Crohn's disease treatment guidelines, oral adrenocorticosteroids (including budesonide), nutritional therapy and immunomodulators are used as remission-induction therapy in moderate to severe

active Crohn's disease. Antibacterial drugs and apheresis are sometimes used as concomitant therapies. If oral adrenocorticosteroids and nutritional therapy are not effective, the use of anti-TNFα antibody biologics is recommended[10]. On the other hand, ECCO guidelines suggest using vedolizumab, an anti-α4β7 integrin antibody, as well as anti-TNFα antibody as biologics for the treatment of active Crohn's disease[11]. Recently, ustekinumab, an anti-IL-12/23 antibody, is beginning to be used as a drug indicated for Crohn's disease. As such, this clinical trial will be conducted to evaluate the efficacy of E6011 administration in patients with moderate to severe active Crohn's disease who were not deriving satisfactory benefits from the use of existing drugs (adrenocorticosteroids, immunomodulative drugs, or biologics).

In this clinical trial, randomisation is to take place to eliminate bias in allocating subjects to treatment groups, to maintain balance in subject characteristics between the groups, and in order to improve validity of statistical comparison of the groups. Further, stratified allocation is to be performed in which race and history of biologic use, which might influence the efficacy evaluation, are used as allocation factors. In order to minimise the possibility of bias in data collection and endpoint evaluation, treatment groups are to be blinded.

EMA's Guidelines on the development of new medicinal products for Crohn's disease state that "it is desirable that clinical symptoms in the active disease period improve within 12 weeks". [12] As the results of Study 101 suggested that E6011 may be effective when administered for 12 weeks, evaluation period in the remission-induction period of this clinical trial was set to 12 weeks, with the primary endpoint as the ratio of subjects who had CDAI reductions of at least 100 points from basline at Week 12 (CR100 response rate).

Due to the fact that the subjects of this clinical trial were patients that did not derive sufficient benefits from treatment with existing drugs, an extension period of 40 weeks maximum was designed for subjects whose CDAI improve after the end of the 12-week remission-induction period (responders). A rescue period was also designed for subjects who do not show improvement in CDAI in the remission-induction period (non-responders) so that they would be able to receive E6011 in the same form and dosage as in the remission-induction period. The design is such that those subjects whose CDAI improve in the rescue period will move on to the extension period. It was decided that a design allowing both responders and non-responders to receive E6011 after the 12-week remission-induction period would be beneficial for the patients.

The post-observation period was set as 70 days after the last administration of the IMP, because of approximately five times the length of the longest observed half-life period of E6011. A follow-up period was designed to entail checking for the onset of PML, which is an anticipated risk of E6011, for two years after the last administration of the IMP.

9.3 Selection of clinical trial population

Approximately 40 subjects will be included in this clinical trial.

- E6011 group 20 subjects: Placebo group 20 subjects
- 22 Japanese subjects: 18 Non-Japanese subjects (rough estimate)

・ 8 biologic-naive patients (rough estimate)

Subjects that meet all the following inclusion criteria and do not fall under any of the exclusion criteria shall receive the IMP.

9.3.1 Inclusion criteria

Subjects who meet all the following criteria are eligible to participate in this clinical trial.

(1) Crohn's disease patients aged 18 or over and under 65 on the date of consent.

(2) Patients diagnosed on basis of clinical findings, endoscopic findings, etc. with small intestine-type, small and large-intestine type, or large-intestine type Crohn's disease at least 12 weeks before giving consent.

(3) Patients with a baseline (at Week 0 before the start of IMP administration) disease severity ranging from moderate to severe. CDAI score between 220 and 450, and a PRO2 score between 14 and 34.

(4) Patients with a Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥7 (or for patients with isolated ileal disease, ≥4 in ileum segment) in the screening period, with one or more ulcers (in SES-CD score, ulcer presence subscore ≥ 1 in any segment) assessed by colonoscopy and confirmed by a centralised review.

(5) Patients who received adrenocorticosteroids or immunomodulators in the past, but showed no therapeutic response (insufficient response) or the drugs were not tolerated (intolerance). Alternatively, patients who cannot taper adrenocorticosteroids (dependence). Alternatively, patients who showed no therapeutic response after administering biologic(s) (primary nonresponse), patients who initially showed therapeutic response but it lessened or disappeared afterwards (secondary nonresponse), or patients who did not tolerate the drug (intolerance). (Detailed criteria are described in Attachment 7 and Attachment 8).

(6) If the patients are taking 1,200 kcal/day or less enteral nutrition, the dosage and administration have not changed for at least 4 weeks prior to the start of the IMP administration.

(7) If the patients are taking aminosalicylic acid (5-ASA), salazosulfapyridine, or antibiotics for the treatment of Crohn's disease (metronidazole, ciprofloxacin, etc.), the dosage and administration have not changed for at least 4 weeks prior to the start of the IMP administration.

(8) If the patients are taking under 30 mg/day of oral prednisolone (or equivalent adrenocorticosteroid) or 9 mg/day or less of oral budesonide, the dosage and administration have not changed for at least 4 weeks prior to the start of the IMP administration.

(9) If the patients are taking azathioprine (AZP), 6-mercaptopurine (6-MP) or methotrexate (MTX), the dosage and administration have not changed for at least 8 weeks prior to the start of the IMP administration.

(10) Patients who have received a sufficient explanation about the compliance rules of this clinical trial, who are willing to comply with them, and who are able to do so.

(11) Patients who voluntarily gave a written consent to participate in this clinical trial.

9.3.2 Exclusion criteria:

Patients who meet any of the following criteria shall be excluded from this clinical trial.

(1) Patients diagnosed with ulcerative colitis or indeterminate colitis (refers to cases in which there is a difficulty distinguishing between Crohn's disease and ulcerative colitis, intermediate colitis).
(2) Patients diagnosed with gastrointestinal epithelial dysplasia.
(3) Patients who have an abscess or are suspected to have one (however, patients with perianal abscess whose symptoms are stable with treatment, such as drug treatment or drainage, are not excluded).
(4) Patients with an artificial anus, ileo-anal pouch or fistula (however, patients with anal fistula whose symptoms are stable with treatment, such as drug treatment or drainage, are not excluded).
(5) Patients with symptomatic or high-grade gastrointestinal stenosis (patients who require expansion by endoscopy or who require have SES-CD score stenosis sub-score of 3, etc.).
(6) Patients who, after undergoing small bowel resection, have been diagnosed with a short bowel syndrome, which makes maintaining caloric intake difficult.
(7) Patients who have newly started seton drainage treatment within 12 weeks prior to the start of the IMP administration.
(8) Patients who have undergone bowel resection or a gastrointestinal surgery within 24 weeks prior to the start of the IMP administration.
(9) Patients who tested positive for *C. difficile* toxin test in the screening period.
(10) Patients who tested positive for HIV, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis B virus DNA (HBV-DNA), hepatitis C virus antibody (anti-HCV), or human T cell leukemia virus type 1 antibody (anti-HTLV-1) in the screening period (however, this excludes patients who tested positive only for anti-HBs, clearly shown to be due to hepatitis B vaccination). Patients who tested negative for HBsAg and quantitative HBV-DNA and positive for anti-HBc antibody and/or anti-HBs antibody may participate in the clinical trial as long as the Principal Investigator or Sub-investigator takes proper measures such as monitoring HBV-DNA based on (not restricted to the following)
    - For Japan: Guidelines for measures against hepatitis B arising due to immunosuppression or chemotherapy
    - For Poland: Recommendations for the treatment of chronic viral hepatitis B in 2018 by Polish Group of Experts for HBV
    - For Hungary: Diagnosis and treatment of chronic hepatitis B and D. Hungarian national consensus guideline
    - For Czech Republic: EASL (European Association for the Study of the Liver) 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection
    - For Russian Federation: Order of Ministry of Health of Russian Federation #786н "On approval of the standard of specialized medical care for chronic viral hepatitis B" dd. 09.11.2012

    In addition, patients who tested positive for HCV antibody and who were at least 24 weeks post-treatment may participate in the clinital trial as long as negative HCV-RNA is confirmed during the screening period.

(11) Patients with positive or repeated indeterminate (inconclusive) results on the TB test (QuantiFERON ® -TB Gold test or T-SPOT ® TB test). However, patients with indeterminate (inconclusive) results on repeated tests may be included in this clinical trial if they are started on prophylactic isoniazid least 21 days prior to the start of IMP administration. (The dose is generally 300 mg/day. If the patient has a low body weight, the dose is to be 5 mg/kg a day. The drug is administered for approximately 9 months.) Prophylactic treatment should be given in accordance with the local guidelines.

(12) Patients with findings showing a history of tuberculosis on a chest X-ray test in the screening period.

(13) Patients with findings of neurological symptoms such as motor impairment, cognitive disorder, language disorder or dysphagia in the evaluations during the screening period.

(14) Patients with a WBC count of less than 3,000/μL or blood $CD4^+$ cell count under 200/μL in the screening period tests.

(15) Patients with a medical history of clinically significant vasculitis.

(16) Acute myocardial infarction, unstable angina pectoris, cerebral infarction, and symptomatic cerebral haemorrhage patients.

(17) Patients whose AST or ALT was more than three times the upper normal limit in the screening period tests or patients whose serum creatinine level was more than 1.5 times the upper normal limit in the screening period tests.

(18) Patients with a QTcF exceeding 450 ms repeatedly in standard 12-lead ECG tests in the screening period tests.

(19) Patients who have undergone cytoapheresis (granulocytapheresis; GCAP) within 2 weeks prior to the start of the IMP administration.

(20) Patients who required any one of the following treatments of infection; "hospitalization within 4 weeks prior to the start of IMP administration", "intravenous treatment of antibiotics (including antiviral drugs) within 4 weeks prior to the start of IMP administration", or "oral treatment of antibiotics (including antiviral drugs) within 2 weeks prior to the start of IMP administration".

Furthermore, with regard to the novel coronavirus infection (COVID-19), patients who required any one of the following treatments; “hospitalization within 4 weeks prior to the start of IMP administration”, “any intravenous treatment within 4 weeks prior to the start of IMP administration” or “any oral treatment within 2 weeks prior to the start of IMP administration”.

(21) Patients who received total parenteral nutrition (TPN), peripheral parenteral nutrition (PPN), or enteral nutrition exceeding 1200 kcal/day within 4 weeks prior to the start of the IMP administration.

(22) Patients who received ≥30 mg/day of oral prednisolone (or an equivalent adrenocorticosteroid), adrenocorticosteroid injection, enema or suppository within 4 weeks prior to the start of the IMP administration.

(23) Patients who received cyclosporine, mycophenolate mofetil, or tacrolimus within 8 weeks prior to the start of the IMP administration (excluding topical use).

(24) Patients who received adalimumab, infliximab, certolizumab pegol, vedolizumab or ustekinumab

(including biosimilars) within 8 weeks prior to the start of the IMP administration.

(25) Patients vaccinated with live vaccines within 12 weeks prior to the start of the IMP administration or patients who received a vaccine that is considered to have a risk of infection, such as a virus vector vaccine that uses a virus that retains its ability to proliferatewithin 12 weeks prior to the start of the IMP administration

(26) Patients who received an immunoglobulin preparation or a blood product within 24 weeks prior to the start of the IMP administration.

(27) Patients who have received natalizumab or E6011 in the past.

(28) Patients with a history of a malignant tumour, lymphoma, leukemia, or lymphoproliferative disorders, or with complications thereof. However, this does not include completely resected skin cancers (epithelial cell cancers or basal cell cancers) and cervical cancers with no metastasis or recurrence observed for 5 more years at the time of giving consent.

(29) Patients with immunodeficiency or a history of HIV infection.

(30) Patients with a history of severe allergy (shock, anaphylaxis-like symptoms).

(31) Patients currently taking part in another clinical trial (including the post-observation period), or patients who were participating in another trial using an IMP or investigational medical device within 28 days (or within five times the length of the half-life period of the IMP, whichever is longer) prior to giving consent.

(32) Patients who received a faecal microbiota transplant (FMT), mesenchymal stem cell, etc. within 24 weeks prior to giving consent.

(33) Female patients of childbearing potential who had a positive result on the pregnancy test at screening or baseline, as well as lactating patients.

(34) Female patients of childbearing potential who:

- have not been on a highly effective method of contraception within 28 days prior to the start of IMP administration. The following are highly effective contraception methods:
  - Sexual abstinence (if preferred by subjects as their regular lifestyle)
  - Use of intrauterine device (IUD)
  - Contraceptive implant
  - Use of oral contraceptives
  - (The same oral contraceptive is to be used at a set dose for more than 28 days prior to the start of the IMP administration, and continued throughout the clinical trial and for 70 days after the last administration of the IMP)
  - The male partner has undergone vasectomy and azoospermia has been confirmed.
- Patients who do not agree to continue using one of the highly effective contraception methods described above throughout the clinical trial and for 70 days after the last administration of the IMP
- If the use of the aforementioned contraception methods is not appropriate or not allowed, the patients are required to consent to use another medically appropriate contraception method, i.e. a double-barrier method (combined use of a condom and contraceptive diaphragm, or a

spermicide-containing cervical/vault cap, etc.)

- All females are deemed to have childbearing potential. However, postmenopausal women (menopausal age patients who have not menstruated for at least 12 consecutive months, which has been confirmed not to be due to other factors, or is not suspected to be due to other factors) and women who have undergone surgical sterilization (patients who have undergone bilateral tubal ligation, hysterectomy, or bilateral oophorectomy more than one month prior to the IMP administration) are excluded from this rule.

(35) Potential male patients with female partners of childbearing potential:

- that have not undergone proper vasectomy (azoospermia can not be confirmed) who (or whose partners) do not agree to use contraception employing one of the methods listed in the exclusion criteria (34) during the clinical trial and for 70 days after the last administration of the IMP (however, if the female partner does is not of childbearing potential, the subject can participate in the trial)
- patients whose female partner is pregnant and do not agree to use latex or synthetic condoms during the clinical trial and for 70 days after the last administration of the IMP
- The patients must not donate sperm during the clinical trial and for 70 days after the last administration of the IMP

(36) Patients who were judged to be unsuitable for participation in this clinical trial by the Principal Investigator or Sub-investigator.

9.3.3 Termination of subject treatment or evaluation

The Principal Investigator or Sub-investigator may terminate the subjects' participation in the clinical trial at any time for safety reasons or reasons related to the conduct of the clinical trial. The subjects themselves may request discontinuation of the IMP administration or participation in the clinical trial at any time without providing explanation.

All subjects who discontinue the clinical trial after the start of the IMP administration are to undergo assessments at discontinuation outlined in the study schedule (Table 4) (see "9.5.5 Subject completion and withdrawal ").

Note that if any of the following applies to the subject, he or she is to be discontinued.

(1) The subject has experienced adverse events which make continuation difficult.
(2) The subject's pregnancy has been confirmed.
(3) The subject has been deemed to be ineligible to participate in the clinical trial.
(4) It has become difficult for the subject to continue to use a concomitant drug/concomitant therapy as instructed.
(5) The subject requires a surgical operation.
(6) The subject has been diagnosed with gastrointestinal epithelial dysplasia.
(7) The subject has been diagnosed with a malignant tumour.
(8) The subject has less than 70 reduction in the CDAI at Week 24 (rescue period) compared to baseline and Week 12.

9.4 Treatment method

9.4.1 IMP administration method

The dose of E6011 corresponding to the subject's weight is to be diluted with a physiological saline solution to prepare a 10 mg/kg E6011 dosing solution (approximately 100 mL). The physiological saline solution used to dilute E6011 is to be used as a placebo. The weight measurements used in the weight-dosage conversion to establish dosage (full dose) are to be the measurements taken on Week 0, Week 12, Week 24, Week 36 and Week 48 (only subjects moving on the rescue period), and the conversion dosage (full dose) may not change even if the patient gains or loses weight in between the measurements. IMP preparation procedure details are listed in Attachment 4.

The IMP is to be infused intravenously through an in-line filter (pore size: 0.2 μm) using an infusion pump over approximately 30 minutes (including saline flush). If drug hypersensitivity thought to be related to the IMP administration is observed, the subsequent infusion rate can be reduced, and the patient may be prophylactically premedicated with antihistamines and antipyretics.

The IMP is to be administered after all investigations scheduled for that day, excluding post-administration blood collection for the purpose of measuring serum E6011 concentration, have been completed.

The subject is to stay in the hospital for 60 minutes after the first and second administration in the remission-induction period and the rescue period, and is allowed to leave after safety has been confirmed.

The IMP is to be administered in the following periods (Table 1).

- Remission-induction period: E6011 or placebo is to be administered with repeat IV dosing to the E6011 10 mg/kg group or placebo group in Week 0, Week 1, Week 2, and every 2 subsequent weeks until Week 10.
- Rescue period: 10 mg/kg of E6011 is to be administered with repeat IV dosing in Week 12, Week 13, Week 14, and every 2 subsequent weeks until Week 22.
- Extension period: 10 mg/kg of E6011 is to be administered with repeat IV dosing every 4 weeks from Week 12 to Week 48 to remission-induction period responders, and from Week 24 to Week 60 after the completion of the rescue period to remission-induction period non-responders.

Table 1 IMP administration method

IMP	Dosage	Dosage form	Administration method	Administration period
E6011	10 mg/kg	Aqueous solution	10 mg/kg of E6011 dosing solution (approximately 100 mL) is to be infused intravenously over the period of approximately 30 minutes.	Remission-induction period: 12 weeks Rescue period: 12 weeks Extension period: 40 weeks
Placebo	N/A	Aqueous solution	The physiological saline solution (approximately 100 mL) is to be infused intravenously over the period of approximately 30	Remission-induction period: 12 weeks Rescue period: No administration

			minutes.	Extension period: No administration

N/A: Not applicable

The Principal Investigator shall appoint the Clinical Trial Centre's pharmacist or a person with appropriate qualifications as the unblinded trial staff (unblinded trial pharmacist, unblinded trial doctor, or unblinded trial coordinator). Until maintaining the blinding is no longer necessary, such as at code break, only the unblinded trial pharmacist or unblinded trial doctor can prepare the IMP. The unblinded trial pharmacist or unblinded trial doctor, upon confirming the subject's allocation group and the subject's weight, is to prepare an E6011 dosing solution. The unblinded trial pharmacist or unblinded trial doctor is to create an IMP preparation record and deliver prepared IMP to the IMP administration trial staff, maintaining the blinding. Only an IMP administration trial staff who has undergone a proper training can administer the IMP. In the double-blind period, the unblinded trial pharmacist or unblinded trial doctor is to dispense the IMP after placing a semi-transparent or non-transparent concealing cover on the intravenous drip bottle sealed using a sticker, and after the IMP administration has been completed, the unblinded trial staff is to confirm that the seal sticker is still intact indicating that the concealing cover has not been taken off from the bottle until the end of administration, and that the blinding is thus maintained.

9.4.2 IMP identification

The IMP used in this clinical trial is shown in Table 2.

E6011 is to be stored in a labelled, dedicated box and supplied by the Sponsor. Each box is to contain 10 vials of E6011. Details concerning the IMP label and packaging are listed in Attachment 5.

Table 2 IMP

Type	Dosage form and content	Manufacturer
E6011	Aqueous solution containing 100 mg of E6011 in 1 vial (1 mL)	Eisai Co., Ltd.

9.4.2.1 E6011 chemical name, structural formula, etc.

- Test drug code: E6011
- Generic name: Undetermined
- Chemical name: IgG2
- Molecular weight: 147kDa
- Structural formula: Glycoprotein of an immunoglobulin structure comprising two light chains each consisting of 214 amino acid residues and two heavy chains each consisting of 445 amino acid residues connected by a disulfide bond

9.4.2.2 Control drug

Placebo

9.4.2.3 IMP label

E6011 label is to follow applicable regulations of the participating countries and be written in the languages required by each of the participating countries.

Details concerning the IMP label and packaging are listed in Attachment 5.

9.4.2.4 Storage conditions

The IMP is to be stored according to prescribed storage conditions. The trial pharmacist (or his/her representative) shall monitor the temperature of the storage location and make sure that the IMP is being stored at the prescribed temperature range. The Principal Investigator (or his/her representative) (or, in accordance with the regulations of each region, the head of Clinical Trial Centre) shall be responsible for ensuring that the storage location temperature is being monitored throughout the period of the clinical trial, and that the records thereof are being stored. When recording temperatures, a temperature data collection system and automatic temperature recording devices validated at each respective Clinical Trial Centre, handwriting, or other methods are to be used. Further, it is required that the monitoring method enable to check the lowest and highest temperature recorded and managed over a given period if necessary.

9.4.3 Method of allocating subjects to treatment groups

A screening test is to take place within 42 days prior to the start on IMP administration, and patients whose eligibility has been confirmed are to be allocated to the E6011 10 mg/kg group or placebo group at a ratio of 1:1 using stratified allocation in which race and history of previous use of biologic medications are used as allocation factors.

Randomisation is to be performed by a central allocation method using an Interactive Web Response System (IWRS). At Week 0, the Principal Investigator (or his/her representative) is to enter the subjects' information into the IWRS. After subject registration is complete in the IWRS, the confirmation of registration (not including the information on group allocation) are to be notified via an e-mail to the Principal Investigator (or his/her representative), unblinded staff and Sponsor. Access to IWRS is to be restricted so that information on group allocation can be only retrieved by the unblinded trial staff of the Clinical Trial Centre and the unblinded trial staff of the Sponsor. The Principal Investigator or Sub-investigator is to record the eligibility results in the screening log/enrolment log, and prescribe the IMP to subjects deemed eligible to participate at screening and baseline evaluation.

After confirming the prescription by the Principal Investigator or Sub-investigator, the unblinded trial staff is to validate the registration results and allocation groups in the IWRS, and the unblinded trial pharmacist or unblinded trial doctor is to prepare the IMP in accordance with the treatment group allotment indicated by IWRS.

9.4.4 Dosage selection in the clinical trial

In the 12-week period administration in Study 101, adverse events have been observed in 18 out of 28 subjects (64.3%). Of out these, adverse events observed in 2 or more subjects included nasopharingitis in 5 subjects (17.9%), and headache, nausea, anal abscess, and Crohn's disease in 2 subjects each (7.1%). Increase of E6011 dose-dependent incidence of side-effects and any concerning events were not observed,

and there were no safety or tolerability issues for Crohn's disease patients with the dosage range up to 15 mg/kg of IV E6011 administered biweekly. Concerning efficacy, although Study 101 is an open-label trial designed not to include a placebo group, evaluations up to Week 12 showed a trend towards improvement of clinical symptoms of Crohn's disease in each group (E6011 2 mg/kg group, 5 mg/kg group, 10 mg/kg group and 15 mg/kg group). Highest numbers of patients with improvement and patients who achieved remission were in the 10 mg/kg group.

By means of PK/PD analysis which used serum E6011 concentration and serum total FKN (the sum of free FKN and E6011-FKN complex) concentration in Study 001 and Study 002, a simulation of connectivity between E6011 used in Study 101 and its target, membrane-bound FKN, has been performed. Analysis showed that E6011 occupancy on membrane-bound FKN was approximately 99% with 10 mg/kg.

The above results showing that sufficient target occupancy and clinical symptom improvement can be expected with 10 mg/kg, it has been judged that in this clinical trial, which is a pivotal POC study, 10 mg/kg is the appropriate dosage to evaluate the efficacy of E6011 remission-induction. As in Study 101, dosing was set to take place in Week 0, Week 1, Week 2, and every 2 subsequent weeks.

As for the dosage and administration in the extension period, considering the fact that the subjects are patients who had experienced an improvement of their symptoms, as well as for subject convenience, 10 mg/kg, a dosage identical to the one used in the remission-induction period, was chosen to be administered intermittently at 4 week intervals.

9.4.5 Dosage selection for each subject and administration period

See section 9.4.1 IMP administration method.

The IMP can be administered regardless of meals.

The IMP is to be administered after completing all assesssments scheduled for that day (excluding blood sampling immediately after the end of administration to measure serum E6011 concentration).

9.4.6 Blinding

During the double-blind period, information on treatment groups must not be disclosed to subjects or any blinding staff involved in implementation and evaluation of the clinical trial. The randomised data is to be strictly controlled, and the Sponsor or CRO is to store it carefully. Further, until code break, the data must not be known to anyone besides the persons designated in the procedure manual.

Although the rescue period and extension period are open-label trials, the information on each subject's treatment group must not be disclosed to subjects or any blinding staff until the remission-induction period database is locked.

After code break, the institution measuring drug concentration and the institution measuring immunogenicity are to report each subject's measurement result to the Sponsor.

The colonoscopy image is to be sent to an imaging assessment professional, where it is to be evaluated in a blinded manner to maintain subject blinding.

The IMP supplier, IWRS and the Sponsor are to store the coding key listing treatment groups

corresponding to subject numbers in a sealed condition. When it is deemed necessary to learn about the IMP treatment group in case of medical emergencies, the data might be unblinded by following the IWRS code break procedure. Section9.5.4.5 describes the unblinding procedure. The Investigators are to, as soon as possible prior to code break, confirm with the Sponsor the necessity thereof.

9.4.6.1 Blinding method

Blinding is to be maintained for the subjects and the blinded staff in the following way.

- A physiological saline solution is to be used as control for the IMP.
- Blinding maintenance systems are to be put in place both at the Sponsor's and at the Clinical Trial Centre. Unblinded staff are to be designated on the task delegation log before the start of the clinical trial.
- Until it is no longer necessary to maintain blinding, such as at code break, the Sponsor's unblinded trial monitor is to be the person contacting the unblinded trial staff about the delivery (however, this excludes first delivery) in order to maintain blinding by not using any blinded staff as an intermediary.
- Until it is no longer necessary to maintain blinding, such as at code break, only the unblinded trial pharmacist or unblinded trial doctor can prepare the IMP. The unblinded trial pharmacist or unblinded trial doctor is to prepare the IMP in an environment closed off from blinded staff.
- The unblinded trial pharmacist or unblinded trial doctor is to create an IMP preparation record, and deliver the prepared IMP to the IMP administration staff while maintaining the blinding (the IMP used in the double-blind period is dispensed with a translucent concealing cover placed on the intravenous drip bottle).
- After the end of the IMP administration, the unblinded trial staff is to confirm that the concealing cover has not been taken off from the bottle until the end of administration, and that the blinding is thus maintained.

9.4.6.2 Maintenance of blinding

An emergency key is to be created by inserting the allocation number table into the subject registration system, and the key is to be stored by IWRS. Note that the emergency key cannot not be opened other than by a procedure determined in advance. (See section 9.5.4.5)

9.4.6.3 Reporting blinded item measurement results

In order to maintain blinding, results of the following laboratory tests are to be stored at each measuring institution until code break, and they may not be disclosed to the Principal Investigator, Sub-investigator, trial coordinator and Sponsor. If the Sponsor needs to obtain the laboratory test results before code break, the obtained information must be limited to a necessary minimum, and each measuring institution must re-blind subject information and submit a measurement report as means of maintaining the blinding of each subject.

- Serum E6011 concentration
- Serum anti-E6011 antibodies

- Serum total FKN concentration
- Blood $CD16^+$ monocytes, etc. (only collected by Japanese subjects)
- Blood $CD16^+$ monocytes, etc. genetic marker
- To explore blood biomarkers (comprehensive proteome analysis) using the residual serum collected for this study

9.4.7 Prior treatment and concomitant treatment

Prior treatment and concomitant drugs/treatment are to be as specified below.All drugs (including over-the-counter products) and concomitant therapies used from the time of obtaining consent to the end (or discontinuation) of the extension period are to be recorded in the case report form. If the Principal Investigator or Sub-investigator used any concomitant drugs and therapies as measures against adverse events, he is to record them in the case report form. Vaccines administered during the clinical trial are to be recorded in the case report form as concomitant therapies (concomitant use of live vaccinesand vaccines that are considered to be at risk of infection, such as virus vector vaccines using viruses that retain the ability to proliferate, are prohibited).

Drug name, administration route, administered amount, date of starting the administration, date of ending the administration, and reason for use are to be recorded in the case report form for all drugs. However, health foods such as vitamins, injection solutions, and drugs used in examinations and diagnostic imaging do not need to be recorded in the case report form.

If concomitant drugs and therapies were used for the treatment of subjects' medical symptoms observed at obtaining consent, the symptoms are to be recorded in the case report form as disease complications.

9.4.7.1 Prohibited concomitant therapies and concomitant drugs

9.4.7.1.1 Prohibited concomitant therapies and concomitant drugs

The concomitant use of the following drugs/treatments shall be prohibited until the end of the extension period (or discontinuation).

- Biologics (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab and natalizumab, including biosimilars)
- Adrenocorticosteroid injections, enemas and suppositories
- Cyclosporine, mycophenolate mofetil, tacrolimus (excluding topical use)
- Immunoglobulin preparations, blood products
- Cytoapheresis (GCAP)
- Total parenteral nutrition (TPN), peripheral parenteral nutrition (PPN)
- Faecal microbiota transplant, mesenchymal stem cell, etc.
- Live vaccine
- Vaccine with possible risk of infection such as virus vector vaccine using virus having proliferation capability
- Other IMPs/investigational medical devices

Attachment 6 shows a detailed list of prohibited concomitant drugs.

9.4.7.1.2 Restricted concomitant drugs

The following drugs may be used in combination with the IMP, but the dosage and administration may not be changed until Week 12 (or until discontinuation).

In principle, the dosage and administration may not be changed from Week 12 until the end of the extension period, but dosage reduction, discontinuation, increasing dosage after dosage reduction (up to the dosage used at the start of the IMP administration) or resuming administration after discontinuation is allowed. If the symptoms of subjects taking oral adrenocorticosteroids or receiving oral budesonide improve (CR100 achievement), the dosage is to be reduced in principle, using as reference the steroid dosage reduction schedule set forth in Attachment 9.

- Aminosalicylic acid (5-ASA)
- Salazosulfapyridine
- Antibiotic drugs for the treatment of Crohn's disease
- Oral administration of adrenocorticosteroids (less than 30 mg/day of prednisolone equivalent), oral budesonide (9 mg/day or less)
- Azathioprine (AZP)
- Mercaptopurine (6-MP)
- Methotrexate (MTX)
- Enteral nutrient preparation (1,200 kcal/day or less)

The SARS-CoV-2 vaccine may be used concomitantly, but it should not be administered within 7 days before or after the IMP administration.

Attachment 6 shows a detailed list of restricted concomitant drugs.

9.4.7.1.3 Restricted concomitant therapies

Seton drainage treatment may be concomitantly used with the IMP, but new seton placement is prohibited from 12 weeks prior to the start of IMP administration until the end of the extension period (or discontinuation).

9.4.8 Compliance with the treatment method

The Principal Investigator, Sub-investigator or trial coordinator is to record the date of the IMP administration, time of the start of administration, time of the end of administration, and administration conditions in the case report form. If the full dose of the IMP could not be administered, the reason thereof is to be recorded in the case report form. The monitor is to monitor the administration compliance status when visiting the Clinical Trial Centre.

Until it is no longer necessary to maintain blinding, such as at code break, the unblinded trial monitor is to check whether the IMP dosage is prepared correctly in each allocation group, and whether the IMP is being administered to the subjects, and record his/her observations at Clinical Trial Centre visits.

9.4.9 Supply and management of IMP

The Principal Investigator (or, in accordance with the regulations of each region, the head of Clinical Trial Centre, or his/her designated trial pharmacist or representative) is responsible for handling the IMP (use, storage, maintaining records) in accordance with the IMP handling procedure manual received from the Sponsor, GCP, local regulations or the regulations of each region.

Blinding maintenance systems are to be put in place both at the Sponsor's and at the Clinical Trial Centre in order to handle blinded information in the IMP delivery work in this clinical trial. The Principal Investigator (or, in accordance with the regulations of each region, the head of Clinical Trial Centre, or his/her designated trial pharmacist or representative) is to appoint a pharmacist or other qualified person of the Clinical Trial Centre as an unblinded trial staff that is different from the blinded staff. For the purpose of maintaining blinding at the Clinical Trial Centre, the Sponsor is to convey appropriate information to the unblinded trial staff of the Clinical Trial Centre and educate and instruct them how to store the IMP. Blinding maintenance system is to continue operating after the earliest possible first delivery of the IMP until it is no longer necessary to maintain blinding, such as at code break. For details, see "Blinded data in E6011-ET2 handling manual".

The Sponsor is to deliver the IMP to the trial pharmacist upon conclusion of the clinical trial agreement between the Clinical Trial Centre and the Sponsor.

The Principal Investigator shall not use the IMP for purposes other than the conduct of this clinical trial. The Principal Investigator is also not allowed to provide the IMP to individuals who are not participating in this clinical trial.

The Clinical Trial Centre is to accurately record the quantity of received IMP, number of prescribed IMP, number of IMP prescribed but not administered to subjects (unused IMP-1), number of IMP that the Clinical Trial Centre received but not prescribed to subjects (unused IMP-2) and number of IMP returned to a storage warehouse designated by the Sponsor (sum of unused IMP-1 and unused IMP-2) (if any quantities of IMP were disposed of at the Clinical Trial Centre, this is also to be recorded). The data to be recorded includes, but is not limited to the following examples: (a) record of IMP recipient, (b) log of prescribed and returned IMP per subject, (c) IMP management log, (d) set of documents enclosed at IMP delivery, (e) record of IMP return, (f) if the IMP was disposed of at the Clinical Trial Centre, the record thereof. The Sponsor shall provide all the above forms. If the Clinical Trial Centre wishes to use other forms, it has to obtain permission of the Sponsor.

IMP management records must be viewable upon request when the monitor is carrying out investigation (if the investigation takes place before code break, the unblinded monitor is to be in charge) or when a regulatory authority personnel is performing an inspection. If the Sponsor has not defined rules of disposing of the IMP at the Clinical Trial Centre, the Principal Investigator (or, in accordance with the regulations of each region, the head of Clinical Trial Centre, or his/her designated trial pharmacist or representative) is to, during the clinical trial or after its completion, return all unused IMP (including empty boxes and unused IMP-2) to a storage warehouse designated by the Sponsor. The IMP may be disposed of at the Clinical Trial Centre only if, due to regulations or special circumstances surrounding the IMP used in this clinical trial, it is impossible to return the IMPs to a storage warehouse designated by the

Sponsor. When disposing of the IMP at the Clinical Trial Centre, it is necessary to obtain the Sponsor's permission before starting the disposal procedure. The trial pharmacist (or his/her representative) is to confirm the number of all unused IMP and after exchanging with the Sponsor a collection statement and return statement, return the IMP to a storage warehouse designated by the Sponsor. The IMP must be packaged in accordance with the regulations of each region and sent back to a storage warehouse designated by the Sponsor. Depending on the region, the IMP to be returned by the Clinical Trial Centre may be directly collected by the monitor, who will then deliver them to a storage warehouse designated by the Sponsor (if the IMP is collected before code break, the unblinded monitor is to be in charge). If the Sponsor has given permission to dispose of the IMP at the Clinical Trial Centre, the disposal is to follow the procedure stipulated by the Clinical Trial Centre, and a record thereof is to be submitted to the Sponsor.

The monitor is to monitor the IMP use status throughout the period of the clinical trial at Clinical Trial Centre visits, at the end of the clinical trial, etc.

9.5 Clinical trial methodology

9.5.1 Assessment items

The Principal Investigators, Sub-investigators or trial coordinator shall assess the following items in subjects who have given consent and record them in case report forms.

9.5.1.1 Demographic characteristics and assessment method

Each subject's demographic characteristics are to be assessed at the time of screening. Items include date of birth, sex, race and ethnicity. In addition to these items, the subject ID Code and the date of consent are also to be recorded in their case report form.

9.5.1.2 Assessment items and method during the screening period

9.5.1.2.1 History of Crohn's disease

To be assessed and recorded in case report forms during the screening period: Crohn's disease-related surgery, disease type (small intestine-type, small and large intestine-type, or large intestine-type), affected site (e.g., anus/perianus, rectum, duodenum, colon, jejunum, ileum), and the time of onset.

9.5.1.2.2 Prior treatment

Information to be recorded in case report forms regarding prior biologic treatment of Crohn's disease: drug name, route of administration, dosage, treatment start date (treatment start period), treatment end date, reason for the discontinuation, etc.

9.5.1.2.3 Past medical history/complications

To be assessed during the screening period: past medical history (including surgery unrelated to Crohn's disease) and complications (including intestinal and extraintestinal complications of Crohn's disease). Complications and past medical history (within 5 years prior to the time of giving consent) that the Principal Investigators or Sub-investigators judge to affect efficacy or safety are to be recorded in case report forms. Conditions that are ongoing at the time of consent but have resolved before IMP

administration (e.g., cold) are treated as complications.

9.5.1.2.4 Other items assessed during the screening period in this clinical trial or specific to the disease area

< *C. difficile* toxin test>

Subjects' stool samples are collected during the screening period and tested for *C. difficile* toxins. Assays are done at a lab facility and test results are recorded in the medical record of clinical trial centres. Samples are to be handled according to the procedures outlined separately.

<Viral test, tuberculosis test>

A viral test (for HIV, HBsAg, anti-HBs, anti-HBc, HBV-DNA, anti-HCV (and HCV-RNA as needed for anti-HCV positive patient), and anti-HTLV-1) and tuberculosis test (QuantiFERON® -TB Gold or T-SPOT® .TB test) are to be conducted. Assays are done at a lab facility (except for the QuantiFERON® -TB Gold test and the T-SPOT® .TB test if it is carried out at clinical trial centres) and test results are treated as source data at clinical trial centres. Samples are to be handled according to the procedures outlined separately.

<Chest X-ray test>

Chest X-ray tests in two directions of transverse and side views are conducted and the results of normal/abnormal assessment are to be recorded in case report forms. Additionally, if symptoms suggestive of tuberculosis are observed after the start of the IMP administration, examinations such as a chest X-ray should be performed to check for tuberculosis at the discretion of the Principal investigator or Sub-investigators.

9.5.1.3 Assessment items and method for efficacy evaluations

9.5.1.3.1 Evaluation of disease activity based on CDAI score and PRO2

<CDAI>

CDAI is to be calculated when indicated by the study schedule (Table 4).

Among the CDAI evaluations, the number of liquid or very soft stools and scores for abdominal pain and general well-being are evaluated by subjects themselves using the electronic patient reported outcomes and entered electronically.

The Principal Investigators, Sub-investigators or clinical trial coordinators shall contact the subjects the day before the start of a weekly evaluation to ensure that they properly enter the number of liquid or very soft stools and scores for abdominal pain and general well-being.

The Principal Investigators or Sub-investigators are to evaluate each subject's disease state and use, among others, the electronic patient reported outcomes and pertinent test results to evaluate the CDAI (Attachment 10). As a general rule, the CDAI evaluations should be performed by the same Principal Investigator or Sub-investigator at each clinical trial centre. Principal Investigators, Sub-investigators or trial coordinators shall record the results of CDAI evaluations in case report forms.

Evaluation day haematocrit (within the visit window) and weight values, and screening period height value should be used to calculate the CDAI. To eliminate the effect of colonoscopy on CDAI evaluations, the results from the most recent week, excluding the day before, the day of, and the day after colonoscopy should be used for electronic patient reported outcomes.

If any of the number of liquid or very soft stools and scores for abdominal pain and general well-being is missing for one day, the mean number of liquid or very soft stools over the other six days (rounded to the nearest integer) and the maximum abdominal pain and general status scores in the other six days are to be used as substitutes.

If any of the number of liquid or very soft stools and scores for abdominal pain and general well-being is missing for two days, the mean number of liquid or very soft stools over the other five days (rounded to the nearest integer) and the maximum abdominal pain and general status scores in the other five days are to be used substitutes. If information from three or more days is missing, it is treated as missing and CDAI is not calculated.

In the evaluation of disease activity level based on CDAI scores, CR70 and CR100 are defined as clinical response with a decrease of ≥ 70 points and ≥ 100 points from baseline, respectively, and remission is defined as CDAI < 150.

<PRO2>

PRO2 is to be calculated when indicated by the study schedule (Table 4).

In PRO2 evaluations, the number of liquid or very soft stools and abdominal pain score are evaluated by subjects themselves using the electronic patient reported outcomes and entered electronically.

The Principal Investigators, Sub-investigators or clinical trial coordinators shall contact the subjects the day before the start of a weekly evaluation to ensure that they properly enter the number of liquid or very soft stools and scores for abdominal pain and general well-being.

Principal investigators or sub-investigators are to evaluate PRO2 based on the electronic data on electronic patient reported outcomes (Attachment 11).

To eliminate the effect of colonoscopy test on PRO2 evaluations, the results from the most recent week, excluding the day before, the day of, and the day after colonoscopy should be used for electronic patient reported outcomes.

If any of the number of liquid or very soft stools and abdominal pain score is missing for one day, the mean number of liquid or very soft stools over the other six days (rounded to the nearest integer) and the maximum abdominal pain score in the other six days are to be used substitutes. If any of the number of liquid or very soft stools and abdominal pain score is missing for two days, the mean number of liquid or very soft stools over the other five days (rounded to the nearest integer) and the maximum abdominal pain score in the other five days are to be used as substitutes. If information from three or more days is missing, it is treated as missing and PRO2 is not calculated.

In the evaluation of disease activity level based on PRO2, PRO2-CR5 (equivalent to CR70) and PRO2-CR8 (equivalent to CR100) are defined as clinical response with a decrease of 5 or more points from baseline, and 8 or more points from baseline, respectively, and PRO2-remission is defined as PRO2

less than 8 points. [13]

With regards to electronic patient information outcomes, to prevent influencing self-evaluations, subjects are to perform their evaluations prior to all tests/evaluations in the applicable evaluation period conducted by Principal Investigators or Sub-investigators, except at the time of discontinuation. To ensure accuracy and completeness of subject entries, if data entered the previous day is incomplete, Principal Investigators, Sub-investigators or trial coordinators are to contact the subject and instruct him/her to enter the missing data before the end of the day. These evaluations are made at each evaluation point and will not be compared to the past evaluations.

9.5.1.3.2 Endoscopic evaluation of GI disorder by SES-CD

Endoscopy is to be performed and the SES-CD score calculated when indicated by the study schedule (Table 4).

Principal Investigators or Sub-investigators are to make colonoscopic video recording of the colon to ileum and send the video data to a third-party image reading institution that conducts central reviews. Graphic data is to be processed to ensure that individual patients cannot be identified. Colonoscopic video recording and graphic data are to be sent following separately outlined procedures. Principal Investigators or Sub-investigators are to determine the eligibility of each subject based on the results of central review graphic data reading during the screening period.

SES-CD scores are calculated by totalling the points for 1. size of ulcers, 2. ulcerated surface, 3. affected surface, and 4. presence of stenosis, graded on a 4-point scale (0-3) in each of the five segments: Rectum, left colon, transverse colon, right colon, and terminal ileum (Attachment 12).

Endoscopic response is defined as a decrease in SES-CD of at least 50% from baseline and endoscopic remission is defined as 2 or less points [14, 15].

9.5.1.3.3 Evaluation of corticosteroid dose reduction

Steroid dose is to be reduced, in principle, using as reference the steroid dose reduction schedule outlined in Attachment 9 in subjects who are on concomintant adrenocorticosteroids (including concomintant budesonide) and achieve CR100 response.

Steroid-free remission is defined as clinical remission (CDAI remission or PRO2-remission) in subjects who have become steroid free through steroid reduction. Similarly, steroid-free clinical response is defined as clinical response (CR70 response, CR100 response, PRO2-CR5 response and PRO2-CR8 response) in subjects who have become steroid free through steroid reduction.

9.5.1.4 Assessment items and method for pharmacokinetic, immunogenicity, biomarker and pharmacogenomic/pharmacogenetic evaluations

9.5.1.4.1 Drug concentration assays

<Serum E6011 concentration>

Blood samples for assaying serum E6011 concentration are to be collected when indicated by the study schedule (Table 4). When collecting blood immediately after IMP administration, it should be drawn from the opposite side of IMP administration. A validated, specific and selective assay method shall be used to

measure serum E6011 concentration at a drug lab. Table 5 and Table 6 show the total amount of blood sampled. Samples are to be handled according to the procedures outlined separately.

9.5.1.4.2 Immunogenicity assessment items and method

<Serum anti-E6011 antibodies>

Blood samples for assaying serum anti-E6011 antibodies are to be collected when indicated by the study schedule (Table 4). A validated, specific and selective assay method shall be used to determine the presence or absence of serum anti-E6011 antibodies at an immunogenicity lab. In addition, when anti-E6011 antibody production is confirmed, the neutralizing activity and isotypes of the anti-E6011 antibodies shall be evaluated. Table 5 and Table 6 show the total amount of blood sampled. Samples are to be handled according to the procedures outlined separately.

9.5.1.4.3 Assessment items and method for biomarker and pharmacogenomic/pharmacogenetic evaluations

<Total serum FKN concentration>

Blood samples for assaying total serum FKN concentration are to be collected when indicated by the study schedule (Table 4). Table 5 and Table 6 show the total amount of blood sampled. Samples are to be handled according to the procedures outlined separately. Assays are performed by a biomarker lab.

<Serum CRP concentration>

Blood samples for assaying serum CRP concentration are to be collected when indicated by the study schedule (Table 4). Table 5 and Table 6 show the total amount of blood sampled. Samples are to be handled according to the procedures outlined separately. Assays are performed by the central laboratory.

<Faecal calprotectin concentration>

Samples for assaying faecal calprotectin concentration are to be collected when indicated by the study schedule (Table 4). Samples are to be handled according to the procedures outlined separately. Assays are performed by the central laboratory.

<Blood $CD16^+$ monocytes, etc.>

Samples for an exploratory measurement of the ratios of blood $CD16^+$ monocytes, etc. are to be collected when indicated by the study schedule (Table 4). Flow cytometric subset analysis of peripheral blood mononuclear cells, etc. is to be carried out. Note that this assay is only carried out for Japanese subjects. Table 5 and Table 6 show the total amount of blood sampled. Samples are to be handled according to the procedures outlined separately. Assays are performed by the biomarker measurement site.

<Blood $CD16^+$ monocyte genetic markers >

Samples for an exploratory assay of blood $CD16^+$ monocyte, etc. genetic markers are to be collected when indicated by the study schedule (Table 4). DNAs of $CD16^+$ monocytes, etc. extracted from blood

samples are to be used to analyse DNA methylation status. Table 5 and Table 6 show the total amount of blood sampled. Samples are to be handled according to the procedures outlined separately. Assays are performed by the biomarker measurement site.

<To explore Blood biomarkers>

Comprehensive proteome analysis is performed using the residual serum (collected for total serum FKN concentration, serum E6011 concentration and serum anti-E6011 antibody tests). This analysis is performed at the proteome analysis organization. Additional exploratory biomarker studies (e.g. comprehensive metabolome analysis, lipidome analysis and analysis by single/multiplex experimental system, etc.) may be added CCI [redacted]. Genetic tests are not to be carried out.

Note that this evaluation and analysis indicated above in this subsection for subjects who enrolled this study in accordance with previous version of study protocol (version 6 or earlier) is to be performed only when this subject's concent obtained.

9.5.1.5 Assessment items and method for safety evaluation

Assessment items for safety evaluation include the following, as listed in the study schedule (Table 4).

Adverse events, laboratory test values, vital signs, weight, physical findings, standard 12-lead ECG examinations, neurological symptoms and blood $CD4^+$ cell count.

9.5.1.5.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject. An AE does not necessarily have a causal relationship with an IMP. In the present trial, IMP refers to E6011 and the placebo.

In this clinical trial, an AE is defined as follows.

- Any undesirable or unintended sign (including an abnormal laboratory value), symptom, or illness that emerges after signing informed consent, whether or not it has a causal relationship with the IMP. When an illness is diagnosed based on signs and symptoms, the illness, rather than individual signs/symptoms, is treated as an AE.
- An illness that emerges or aggravation of a pre-existing illness.
- A laboratory value or worsening of a test (e.g., ECG, X-rays) indicative of some symptom (including tests not prescribed by the protocol).
- A laboratory value or worsening of a test (e.g., ECG, X-rays) that results in a change of treatment method or discontinuation of the clinical trial (including tests not specified in the protocol).
- Recurrence of an episodic medical condition (e.g., headaches) that was not present at the time of signing informed consent.
- An abnormal laboratory value that requires some form of intervention, or discontinuation or interruption of treatment with the IMP, whether or not it is identified in the protocol.

Note that worsening of the underlying disease (Crohn's disease) is not treated as an AE (minor fluctuations in CDAI and SES-CD scores are accounted for in efficacy evaluations but are not regarded as

AEs), except when it worsens beyond expectations (e.g., requiring hospitalization or surgery).

All AEs that emerge after signing of informed consent and up to 70 days after the final dose of the IMP are to be compiled and recorded in case report forms, whether or not they have a causal relationship with the IMP or study procedures. For screening failure subjects whose reason for failure is the onset of an AE, the name and seriousness of the AE are to be documented in their case report forms.

All abnormal laboratory values judged to be AEs are to be documented in case report forms. Abnormal laboratory values do not need to be separately recorded if they are considered to be part of the clinical symptoms that have been reported as AEs. It is the responsibility of Principal Investigators and Sub-investigators to check every laboratory value and judge whether it is considered an AE. They are to judge medically and scientifically whether an abnormal laboratory value should be regarded as an independent AE.

Every AE must be followed up until it resolves or 70 days after the final dose of the IMP (whichever occurs sooner). Serious AEs are to be followed up until they have resolved or until their symptoms have stabilised if they are not likely to resolve.

Principal Investigators or Sub-investigators are to use all means necessary to classify each AE by its severity and relationship with the IMP.

Severity evaluation of adverse events

AEs are evaluated based on three levels of severity (mild, moderate, severe) and documented in case report forms. The three levels are defined as follows.

Mild	Causes discomfort but not to the extent that it interferes with normal daily activities
Moderate	Causes discomfort to the extent that it interferes with normal daily activities
Severe	Incapacitated or unable to carry out normal daily activities

Evaluating the severity of AEs is different from evaluating the seriousness of AEs (see section 9.5.1.5.2).

Evaluation of causal relationship with the IMP

The following points are to be addressed when evaluating the causal relationship between an AE and the IMP.

- The temporal relationship between the timing of AE onset and the start of IMP administration
- The course of the AE and particularly the effect of the IMP if the treatment was discontinued or resumed
- Whether or not the AE is known to occur with this IMP or similar drugs
- Any risk factors in the target population that increase the likelihood of the AE
- Any confounding factors related to the onset of the AE but unrelated to the IMP

Classification of causal relationship with the IMP

Unrelated	No reasonable causal relationship exists between the IMP and AE
Related	A reasonable causal relationship possibly exists between the IMP and AE

9.5.1.5.2 Serious adverse events and other important occurrence

A serious adverse event (SAE) is any untoward medical occurrence in a subject that at any IMP dose:

- Results in death
- Is life-threatening (where "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe, or if the administration of the IMP continued)
- Requires hospitalisation or prolongation of hospitalisation
- Results in persistent or significant disability/dysfunction, or
- Causes a congenital anomaly/birth defect (in the child of the subject who received the IMP).

Other medically important events, i.e., a significant medical event that is not immediately life-threatening or results in death or hospitalization, but may jeopardise the subject and may require intervention to prevent one of the above stated outcomes is regarded as serious. In such circumstances, whether emergency reporting is warranted is judged based on medical and scientific grounds.

Pregnancy and breastfeeding shall also be reported using the same procedures as SAEs. AEs resulting from overdose, misuse, abuse, and dosing errors shall also be reported using the same procedures as SAEs (see section 9.5.4.2 and section 9.5.4.3). Such events are to be treated as SAEs only if they fit the above definitions. Note that these AEs, whether or not they fit the definitions of SAEs described above, are all to be documented in case report forms.

SAEs are to be followed up until they have resolved or until their symptoms have stabilised if they are not likely to resolve.

Hospitalization without an AE, such as those described below, are not treated as SAEs.

- Hospitalization for temporary treatment of conditions other than AEs
- Hospitalization that is specified in the protocol in advance
- Hospitalization that was scheduled before signing of informed consent (for a condition that required hospitalization before administration of the IMP and did change after administration)
- Hospitalization for IMP administration or for a procedure to gain access to the IMP administration route
- Hospitalization for routine procedures to maintain medical devices that have been in use before IMP administration (e.g. battery replacement)

9.5.1.5.3 Laboratory tests

Table 3 and Table 4 show laboratory tests (blood, urine) and sample collection timing in this clinical trial.

Haematology tests are to be processed in clinical trial centres and other tests are processed by the

central laboratory. Results of haematology tests are to be included in case report forms. The Sponsor and clinical trial centres will receive results of other tests from the testing laboratory. Test results reported to clinical trial centres are to be retained as source data. Samples for the tests conducted by the central laboratory are to be handled according to the procedures outlined separately.

If abnormal laboratory values matches the definitions of AE described in the protocol (section9.5.1.5.1), they are to be documented in case report forms.

If an abnormal laboratory value matches one of the definitions of SAE described in the protocol (section 9.5.1.5.2) the Principal Investigator is to send a SAE Report to the Sponsor by FAX or other means (eCRF can also be used for reporting) (section9.5.4.1 Reporting of SAEs).

Table 3 Laboratory Tests

Category	Items
Haematology testing	White blood cell count, red blood cell count, haemoglobin, haematocrit, platelet count, differential white blood cell count (neutrophils, lymphocytes, monocytes, acidophils, basophils)
Blood biochemistry testing	
Liver function tests	Total bilirubin, ALP, AST, ALT, γ GTP
Renal function tests	BUN, creatinine
Other tests	Glucose, albumin, total cholesterol, triglyceride, amylase, inorganic phosphate, LDH, CK, total protein, uric acid, Na, K, Cl, Ca, CRP
Urinalysis	pH, protein, glucose, urobilinogen, ketone bodies, occult blood, specific gravity, amylase

9.5.1.5.4 Vital signs and weight measurement

During the visits specified in the study schedule (Table 4), vital signs [blood pressure (sytolic, diastolic: mmHg), pulse rate (bpm), temperature (°C)], height (cm), and weight (kg) are to be measured using prescribed methods and documented in case report forms. Blood pressure and pulse rate should be measured in the seated or supine position after resting for at least 5 minutes. Blood pressure should generally be measured on the same arm each time and, if possible, by the same person. Temperature should be taken under the armpit.

If vital sign measurement is scheduled after blood collection on the same day, there should be at least a 30-minute gap between the blood collection and vital sign measurement.

9.5.1.5.5 Physical findings

A physical examination is to be conducted during the visits specified in the study schedule (Table 4). Results of the examination are to be documented in the records of clinical trial centres. Any changes from screening that fit the definition of AE are to be documented in case report forms.

9.5.1.5.6 ECG

Standard 12-lead ECG tests are to be conducted when indicated by the study schedule (Table 4).

ECGs are performed after 10 minutes of resting while maintaining the resting supine position. The results of normal/abnormal assessment made by principal investigators or sub-investigators are to be recorded in case report forms. If blood collection is scheduled before ECG on the same day as ECG, there should be at least a 30-minute gap between the blood collection and ECG so as to ensure that the blood collection does not affect the ECG. Any abnormal ECGs that fit the definition of AE described in the protocol (section9.5.1.5.1) are to be documented in case report forms as AEs.

9.5.1.5.7 Other assessment items for safety evaluations

<Pregnancy test>

Female subjects of childbearing potential are to undergo urine pregnancy test (qualitative, in clinical trial centres) when indicated by the study schedule (Table 4), and the test results are to be recorded in case report forms.

<Neurological symptoms>

Subjects are to be assessed for the presence or absence of neurological symptoms using the neurological symptoms checklist (Attachment 13) when indicated by the study schedule (Table 4), and the results are to be recorded in case report forms. Also, if a neurological symptom is suspected whenever subjects are examined outside of specified assessment times, a neurological assessment must be performed using the neurological symptoms checklist. Any abnormalities that are found after IMP administration must be reported to the Sponsor using the "Neurological Symptoms Report (Attachment 14)" sent by FAX, etc. and examined by a neurologist or other specialists. Additionally, brain MRI (T1-weighted, FLAIR and diffusion-weighted imaging) is to be performed within two weeks and the MRI images submitted to the Sponsor. The Sponsor shall immediately forward the information to a PML evaluator and seek advice on whether the subject should continue the IMP administration. The IMP administration is to be put on hold until the evaluation is completed by the PML evaluator. Such events are to be documented in case report forms as AEs.

< Blood $CD4^+$ cell count >

Blood samples for blood $CD4^+$ cell counting are to be collected when indicated by the study schedule (Table 4). Table 5 and Table 6 show the total amount of blood sampled. The assay is performed at a lab facility and the Sponsor and clinical trial centres will receive results of tests from the lab. Test results reported to clinical trial centres are to be retained as source document. Samples are to be handled according to the procedures outlined separately.

<PML assessment>

Starting from 70 days after the last administration of the IMP, the onset of PML is to be assessed every six months after the last administration of E6011 for two years. Non-PML AEs are not subject to assessment. The onset of PML is to be assessed every six months and the results recorded in case report forms. A confirmed onset of PML is to be documented as a SAE in case report forms. In this case, a "Serious Adverse Event Report" must be submitted to the sponsor. The following details are to be included in the "Serious Adverse Event Report" prepared upon confirmation of PML onset.

Findings related to the definitive diagnosis of PML [such as clinical features, brain MRI findings, genetic testing for detection of JC virus (JCV) DNA cerebrospinal fluid, and relevant laboratory results], the course from onset to definitive diagnosis, history of treatment for the underlying disease after the end of IMP administration, the status of steroid and immunosuppressant use after the end of IMP administration, etc.

9.5.1.6 Other assessment items

<Anti-JC virus antibody test>

Anti-JCV antibody testing is to be conducted when indicated by the study schedule (Table 4). If discontinuing at Week 24 for a lack of CDAI response, the test is to be conducted during the Week 24 visit or 28 days after discontinuation. Samples are to be handled according to the procedures outlined separately.

9.5.2 Observation/assessment items and the study schedule

9.5.2.1 Study schedule

Table 4 shows the schedule for this clinical trial.

Observations and assessments conducted after the start of IMP administration are scheduled beginning from the start date (Day 1) of IMP administration. If observations/assessments need to be rescheduled for whatever reason during the remission-induction period, they must be conducted within plus or minus 1 day of the scheduled date in Week 1 and thereafter plus or minus 3 days of the scheduled dates up to Week 12. During the rescue period, they must be conducted within plus or minus 1 day of the scheduled date in Week 13 and thereafter plus or minus 3 days of the scheduled dates up to Week 24. During the extension period and post-observation period, they must be conducted within plus or minus 7 days of the scheduled dates (“within plus 7 days” of “70 days after the last IMP administration”).

Assessments during the follow-up period are to be scheduled using calendar days counting from the date of the last IMP administration. From the last IMP administration to 2 years thereafter, they must be conducted within plus or minus 1 month of the scheduled dates (example: if the last IMP is administered on 1 November 2019, the scheduled date follow-up would be 1 May 2020; the window in this case would be between 1 April 2020 and 1 June 2020).

Table 4 E6011-ET2 Study Schedule (All Subjects)

	Screening period	Remission-induction period (double-blind)								
Visit	1	2	3	4	5	6	7	8	9	-
Test/Observation Time	Days -42 to -1 days	Week 0 [i]	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Discontinuation [j]
Allowed deviations		—	± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	—
Signing of informed consent [a]	○									
Demographic characteristics, history of present illness	○									
Past medical history, complications	○									
Inclusion/exclusion criteria check	○	○								
Colonoscopy [b]	○								○	○
IMP administration [c]		○	○	○	○	○	○	○	○ [k]	
Prior treatment and concomitant drugs/therapies	◄	———	———	———	———	———	———	———	———	►
Physical findings	○	○	○	○	○	○	○	○	○	○
Height/weight [d]	○	○		○	○		○		○	○
Vital signs	○	○	○	○	○		○		○	○
Standard 12-lead ECG	○								○	○
Chest X-ray test	○									
Neurological symptoms [e]	○								○	○
Anti-JCV antibody test	○									○
Blood $CD4^+$ cell test	○								○	○
Viral test, tuberculosis test	○									
Pregnancy test [f]	○	○							○	○
C. difficile toxin test	○									
CDAI, PRO2		○[o]		○	○		○		○	○
Haematology test, blood biochemistry test, urinalysis	○	○	○	○	○	○	○	○	○	○
Adverse event	◄	———	———	———	———	———	———	———	———	►
Serum E6011 concentration [g, h]		○	○	○	○	○	○	○	○	○
Serum anti-E6011 antibodies [h]		○		○	○		○		○	○
Serum total FKN concentration [h]		○	○	○	○	○	○	○	○	○
Blood $CD16^+$ monocytes, etc. (FCM) [h]		○	○	○	○				○	○
Blood $CD16^+$ monocyte, etc. genetic markers [h]		○	○	○	○				○	○
Faecal calprotectin		○		○	○		○		○	○

a. A written consent of the subject is required prior to undergoing tests and medication washout as part of the requirements to participate in this clinical trial.
b. Endoscopic evaluations are performed by a centralised review.
c. The IMP is to be administered after completing all assessments scheduled for that day (excluding serum E6011 concentration immediately after the end of administration).
d. Height is measured during the screening period (on Visit 1) only.
e. If abnormal neurological symptoms are found after IMP administration, the patient must be examined by a neurologist and undergo brain MRI (T1-weighted, FLAIR and diffusion-weighted imaging) within two weeks.
f. Pregnancy test is conducted only in female subjects of childbearing potential.
g. Blood samples are collected before and immediately after (within 10 minutes of) IMP administration between Week 0 and Week 10.

h. Test results are to be retained by the testing laboratories and not to be shared with Principal Investigators, Sub-investigators and trial coordinators until code break. Blood CD16+ monocytes, etc. (FCM) is only conducted in Japanese subjects
i. Randomisation is to be performed at baseline (before the start of IMP administration in Week 0).
j. As many specified tests and evaluations as possible should be conducted for the assessment at discontinuation.
k. E6011 to be administered after the transition to the rescue period or Extensionperiod.
l. PML onset is to be investigated over the phone, etc. at six months, one year, one and a half years, and two years after the final IMP dose.
m. E6011 not to be administered when discontinuing at Week 24 for a lack of CDAI response.
n. To be conducted during the Week 24 visit or 28 days after discontinuation only when discontinuing at Week 24 for a lack of CDAI response.
o. The hematocrit value used to calculate the CDAI score at Week 0 or screening test (screening test value may also be used if this is within 7 days of the date of the CDAI assessment).

p. Table 4 E6011-ET2 Study Schedule (Responders)

	Extension period (open-label)											Post-observation period		Follow-up period
Visit	10	11	12	13	14	15	16	17	18	19	-	20	21	-
Test/Observation Time	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Discontinuation [j]	28 days after completion/ discontinuation	70 days after last dose administration	2 years after last dose administration [l]
Allowed deviations	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	-	± 7 days	+7 days	± 1 month
Signing of informed consent [a]														
Demographic characteristics, history of present illness														
Past medical history, complications														
Inclusion/exclusion criteria check														
Colonoscopy [b]										○	○			
IMP administration [c]	○	○	○	○	○	○	○	○	○					
Prior treatment and concomitant drugs/therapies	←										→			
Physical findings	○	○	○	○	○	○	○	○	○	○	○	○		
Height/weight [d]	○	○	○	○	○	○	○	○	○	○	○			
Vital signs	○	○	○	○	○	○	○	○	○	○	○	○		
Standard 12-lead ECG			○			○				○	○			
Chest X-ray test														
Neurological symptoms [e]			○			○				○	○			
Anti-JCV antibody test										○	○			
Blood $CD4^+$ cell test						○				○	○			
Viral test, tuberculosis test														
Pregnancy test [f]										○	○			
C. difficile toxin test														
CDAI, PRO2	○	○	○	○	○	○	○	○	○	○	○			
Haematology test, blood biochemistry test, urinalysis	○	○	○	○	○	○	○	○	○	○	○	○		
Adverse event	←										→			(PML)
Serum E6011 concentration [g, h]	○	○	○	○	○	○	○	○	○	○	○			
Serum anti-E6011 antibodies [h]	○	○	○	○	○	○	○	○	○	○	○			
Serum total FKN concentration [h]														
Blood $CD16^+$ monocytes, etc. (FCM)[h]			○							○	○			
Blood $CD16^+$ monocyte, etc. genetic markers[h]			○							○	○			
Faecal calprotectin	○	○	○	○	○	○	○	○	○	○	○			

Table 4 E6011-ET2 Study Schedule (Non-responders) 1/2

	Rescue period (open-label)							
Visit	10	11	12	13	14	15	16	-
Test/Observation Time	Week 13	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Discontinuation [j]
Allowed deviations	± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	--
Signing of informed consent [a]								
Demographic characteristics, history of present illness								
Past medical history, complications								
Inclusion/exclusion criteria check								
Colonoscopy [b]								
IMP administration [c]	○	○	○	○	○	○	(○)[m]	
Prior treatment and concomitant drugs/therapies	◄	―	―	―	―	―	―	►
Physical findings	○	○	○	○	○	○	○	○
Height/weight [d]		○	○		○		○	○
Vital signs	○	○	○		○		○	○
Standard 12-lead ECG							○	○
Chest X-ray test								
Neurological symptoms [e]							○	○
Anti-JCV antibody test							(○) [n]	○
Blood $CD4^+$ cell test							○	○
Viral test, tuberculosis test								
Pregnancy test [f]							○	○
C. difficile toxin test								
CDAI, PRO2		○	○		○		○	○
Haematology test, blood biochemistry test, urinalysis	○	○	○	○	○	○	○	○
Adverse event	◄	―	―	―	―	―	―	►
Serum E6011 concentration [g, h]	○	○	○	○	○	○	○	○
Serum anti-E6011 antibodies [h]		○	○		○		○	○
Serum total FKN concentration [h]								
Blood $CD16^+$ monocytes, etc. (FCM) [h]								
Blood $CD16^+$ monocyte, etc. genetic markers [h]								
Faecal calprotectin		○	○		○		○	○

Table 4 E6011-ET2 Study Schedule (Non-responders) 2/2

	Extension period (open-label)											Post-observation period		Follow-up period
Visit	17	18	19	20	21	22	23	24	25	26	-	27	28	
Test/Observation Time	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Discontinuation [j]	28 days after completion/discontinuation	70 days after last dose administration	2 years after last dose [l] administration
Allowed deviations	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	-	± 7 days	+7 days	± 1 month
Signing of informed consent [a]														
Demographic characteristics, history of present illness														
Past medical history, complications														
Inclusion/exclusion criteria check														
Colonoscopy [b]										○	○			
IMP administration [c]	○	○	○	○	○	○	○	○	○					
Prior treatment and concomitant drugs/therapies	◄										►			
Physical findings	○	○	○	○	○	○	○	○	○	○	○	○		
Height/weight [d]	○	○	○	○	○	○	○	○	○	○	○			
Vital signs	○	○	○	○	○	○	○	○	○	○	○	○		
Standard 12-lead ECG			○			○				○	○			
Chest X-ray test														
Neurological symptoms [e]			○			○				○	○			
Anti-JCV antibody test										○	○	(○) [n]		
Blood $CD4^+$ cell test						○				○	○			
Viral test, tuberculosis test														
Pregnancy test [f]										○	○			
C. difficile toxin test														
CDAI, PRO2	○	○	○	○	○	○	○	○	○	○	○			
Haematology test, blood biochemistry test, urinalysis	○	○	○	○	○	○	○	○	○	○	○	○		
Adverse event	◄										►			(PML)
Serum E6011 concentration [g, h]	○	○	○	○	○	○	○	○	○	○	○			
Serum anti-E6011 antibodies [h]	○	○	○	○	○	○	○	○	○	○	○			
Serum total FKN concentration [h]														
Blood $CD16^+$ monocytes, etc. (FCM) [h]														
Blood $CD16^+$ monocyte, etc. genetic markers [h]														
Faecal calprotectin	○	○	○	○	○	○	○	○	○	○	○			

9.5.2.2 Total amount of blood sampled

Table 5 and Table 6 show the number of blood sampling and the total amount of blood sampled throughout the trial period. More blood may be collected if a test value is outside the normal range or when a Principal Investigator or Sub-investigator decides it is necessary to confirm the safety of a subject.

Table 5 The total amount of blood sampled (Responders)

Item	Amount of blood sampled per collection	Screening period	Remission-induction period	Extension period	After administration Observation period
		Days -41 to -1	Weeks 0-12	Weeks 13-52	Weeks 53-56
Viral test, tuberculosis test	18 mL	1 sample			
Haematology testing *	(2 mL)	1 sample	8 samples	10 samples	1 sample
Blood biochemistry testing	5 mL	1 sample	8 samples	10 samples	1 sample
Blood $CD4^+$ cell count	5 mL	1 sample	1 sample	2 samples	
Anti-JCV antibodies	3.5 mL	1 sample	(Note 1)	1 sample	
Serum E6011 concentration (Before E6011 administration)	2 mL		8 samples	10 samples	
Serum anti-E6011 antibodies	5 mL		5 samples	10 samples	
Serum total FKN concentration	2 mL		8 samples		
Serum E6011 concentration (immediately after the end of E6011 administration (within 10 minutes))	2 mL		7 samples		
Blood $CD16^+$ monocytes, etc. (FCM) (Note 2)	5 mL		5 samples	2 samples	
Blood $CD16^+$ monocyte, etc. genetic marker	5 mL		5 samples	2 samples	
Amount of blood sampled		33.5 mL	185.5 mL	173.5 mL	7 mL
The total amount of blood sampled up to Week 12		219 mL			
The total amount of blood sampled up to Week 52		392.5 mL			
The total amount of blood sampled up to Week 56		399.5 mL			

*Haematology testing is done in clinical trial centre. The total amount of blood sampled is calculated by using 2 mL as the amount of blood required per collection.

Note 1: If a subject is discontinuing during the remission-induction period, one sample (3.5 mL) of blood is collected at discontinuation testing.

Note 2: Blood CD16+ monocytes, etc. (FCM) is only conducted in Japanese subjects.

Table 6 The total amount of blood sampled (Non-responders)

Item	Amount of blood sampled per collection	Screening period	Remission-induction period	Rescue period	Extension period	After administration Observation period
		Days -41 to -1	Weeks 0-12	Weeks 13-24	Weeks 25-64	Weeks 65-68
Viral test, tuberculosis test	18 mL	1 sample				
Haematology testing *	(2 mL)	1 sample	8 samples	7 samples	10 samples	1 sample
Blood biochemistry testing	5 mL	1 sample	8 samples	7 samples	10 samples	1 sample
Blood $CD4^+$ cell count	5 mL	1 sample	1 sample	1 sample	2 samples	
Anti-JCV antibodies	3.5 mL	1 sample	(Note 1)	(Note 2)	1 sample	(Note 2)
Serum E6011 concentration (Before E6011 administration)	2 mL		8 samples	7 samples	10 samples	
Serum anti-E6011 antibodies	5 mL		5 samples	4 samples	10 samples	
Serum total FKN concentration	2 mL		8 samples			
Serum E6011 concentration (immediately after the end of E6011 administration) (within 10 minutes))	2 mL		7 samples			
Blood $CD16^+$ monocytes, etc. (FCM) (Note 3)	5 mL		5 samples			
Blood $CD16^+$ monocyte, etc. genetic marker	5 mL		5 samples			
Amount of blood sampled		33.5 mL	185.5 mL	91.5 mL	153.5 mL	10.5 mL
The total amount of blood sampled up to Week 12		219 mL				
The total amount of blood sampled up to Week 24		310.5 mL				
The total amount of blood sampled up to Week 64		464 mL				
The total amount of blood sampled up to Week 68		474.5 mL				

*Haematology testing is done in clinical trial centre. The total amount of blood sampled is calculated by using 2 mL as the amount of blood required per collection.

Note 1: If a subject is discontinuing during the remission-induction period, one sample (3.5 mL) of blood is collected at discontinuation testing.

Note 2: One blood sample (3.5 mL) to be collected when discontinuing at Week 24 or 28 days after discontinuation for a lack of CDAI response.

Note 3: Blood CD16+ monocytes, etc. (FCM) is only conducted in Japanese subjects.

9.5.3 Suitability of assessment items

<Efficacy>

The proportion of subjects with CDAI reductions of at least 70 points from baseline (CR70 response rate), CR 100 response rate, and the proportion of subjects with CDAI below 150 points (CDAI remission rate) by using the CDAI score were chosen as the efficacy endpoints of this clinical trial. As the sample size was determined for this clinical trial based on the CR100 response rate used as an efficacy endpoint in the 101 trial, it was deemed appropriate to use the CDAI score that includes CR100 response rate. Meanwhile the EMA guidelines have pointed out problems with the CDAI score, suggesting that clinical symptoms and mucosal inflammation be independently evaluated. Accordingly, as secondary endpoints, clinical symptoms will be evaluated with PRO2 and mucosal inflammation with the SES-CD using colonoscopy. Likewise, based on the EMA guidelines, steroid-free remission rate and response rate will also be evaluated in subjects on concomitant corticosteroids.

<Safety>

For the evaluation of safety in this clinical trial, adverse events, laboratory test values, vital signs, weight, physical findings, 12-lead ECG, neurological symptoms and blood $CD4^+$ cell count will be used as indices for evaluating subjects' safety. Additionally, the following tests will be conducted

<The risk of PML>

The risk of PML has been reported as a rare side effect of natalizumab (humanised monoclonal antibody against α4-integrin), which is used in the treatment of Crohn's disease and multiple sclerosis [16]. The mechanism of onset remains unclear but has been linked to α4-integrin. There have been no findings that suggest PML in the previous clinical trials. However, the possibility of E6011 indirectly affecting α4-integrin cannot be ruled out completely because, although its mechanism of action is neutralizing FKN, the actions of integrins have been shown to increase due to the interaction of FKN and CX3CR1 [17]. For this reason, a PML risk-related exclusion criterion was established such that subjects with a $CD4^+$ cell count under 200/μL, WBC count under 3,000/μL, or with abnormal neurological symptoms are to be excluded. In addition, subjects are to be regularly assessed for neurological symptoms throughout the clinical trial and a system is to be put in place such that PML evaluators are available to provide their opinions on PML diagnosis and treatment (if abnormal neurological symptoms are found after IMP administration, the subject must be examined by a neurologist and undergo brain MRI within two weeks, and the IMP administration is to be put on hold until the evaluation is completed by a PML evaluator). Furthermore, although the mechanism of onset of PML is not completely understood, neurological disturbances are believed to be caused by reactivation of the latent JCV which becomes activated by reduced cellular immunity [18], Anti-JCV antibody testing is to be conducted and information is to be collected during screening period and at completion (discontinuation) of the IMP administration, and PML onset is to be investigated over the phone, etc. every 6 months in the two-year follow-up period after the last IMP administration..

9.5.4 Reporting of SAEs, pregnancy and other important AEs

9.5.4.1 Reporting of SAEs

Investigators are to report every serious adverse event, whether or not it has a causal relationship with the IMP, to the sponsor by sending a SAE Report by FAX, etc. (eCRF can also be used for reporting) as soon as possible (no later than 24 hours) upon receiving the information.

All SAEs that emerge up to 70 days after the last dose administration of the IMP are to be compiled, whether or not they have a causal relationship with the IMP or study procedures. All SAEs are to be followed up until they have resolved or until their symptoms have stabilised if they are not likely to resolve. Any SAEs for which causal relationship with the IMP (or procedures specified in the protocol) cannot be ruled out in the opinion of a principal investigators or sub-investigator are to be reported to the sponsor regardless of the amount of time that has passed after the end of clinical trial.

After the end of IMP administration, during the two-year follow-up period, only the onset of PML is to be assessed.

Safety-related Emergency Contact Details are provided in Attachment 2 1.4.1.

It is important that SAE Reports are as complete as possible at the time of initial reporting, including the principal investigator's or sub-investigator's evaluation of causal relationship with the IMP.

Whenever additional information on SAEs is received, the investigator is to contact the sponsor's representative within one day after the receipt. If the additional information changes the evaluation of causal relationship with the IMP, the change is to be described in the SAE Report (eCRF can also be used for reporting).

If the sponsor requests additional information regarding the details of a SAE Report, the clinical trial centre shall provide without delay detailed supplementary information, including copies of medical record, autopsy report, and other documents.

9.5.4.2 Reporting of pregnancy and breastfeeding

Any time when a pregnancy is estimated to have occurred in a female subject (or the female partner of a subject) prior to the last visit or within 70 days of the last dose administration of the IMP, or when a subject breastfeeds while receiving the IMP or within 70 days of the last dose administration of the IMP, it must be reported.

Poor pregnancy outcomes that are suspected to be causally related to the IMP must be reported regardless of the amount of time that has passed after IMP administration.

Miscarriages, abortions, congenital abnormalities, and still births are considered serious adverse events and to be reported with the same method and in the same time frame as SAEs (see section9.5.4.1 Reporting of SAEs).

Whenever information on a pregnancy or breastfeeding is received, the investigator is to report it to the sponsor by FAX or email without delay (within one day at the latest). The contact details for reporting a pregnancy or breastfeeding are the same as the Safety-related Emergency Contact Details described in section 9.5.4.1 . The Pregnancy-related Report (Attachment 15) is to be used. In addition, investigators are to confirm the pregnancy outcomes and report the information to the sponsor using the form for reporting

pregnancy-related information (Attachment 16: Pregnancy-related Report) without delay (within one day at the latest).

Subjects who have become pregnant are to be withdrawn from the clinical trial.

9.5.4.3 Reporting of other notable occurrences

9.5.4.3.1 Reporting of AEs resulting from overdose, misuse, abuse, and dosing errors

AEs resulting from overdose, misuse, abuse, and dosing errors are the AEs that occur when the IMP is administered (or ingested by the subject) differently than as specified by the protocol. The definitions of overdose, misuse, abuse, and dosing error are as follows.

Overdose	Accidental or intentional administration (or ingestion) of the IMP in quantities greater than that is specified in the protocol
Misuse	Administration (or ingestion) of the IMP intentionally or inappropriately not according to the method of administration specified in the protocol
Abuse	Intentional administration (or ingestion) of the IMP in excess quantities temporarily or continuously with adverse physical or mental effects.
Dosing error	Any accidental event that triggers or becomes a cause of inappropriate use of the IMP or adverse effects on a subject, despite the proper management of the IMP by the clinical trial centre or subject.

All AEs resulting from overdose, misuse, abuse, or a dosing error are to be documented in case report forms and reported according to the procedure specified in section9.5.4.1 Reporting of SAEs (including those that do not fit the definition of SAE). All cases of abuse are to be treated as AEs. While AEs resulting from overdose, misuse, abuse, and dosing errors that do not fit the definition of SAE are also to be reported according to the emergency reporting procedure using the SAE Report form, they are documented as non-serious AE in SAE Reports and case report forms (eCRF can also be used for reporting).

9.5.4.4 Emergency reporting

In accordance with regulations and emergency reporting procedure of the respective region (and within the region-specific time frame) the sponsor must report reportable AEs to principle investigators, directors of clinical trial centres, and regulatory authorities. For this reason, principal investigators or sub-investigators are to report all the information on the SAE Report form according to the procedure outlined in “Reporting of SAE” (section9.5.4.1).

9.5.4.5 Unblinding

In case of a medical emergency, investigators will be able to break the code of the applicable subject if it is necessary to know the subject’s IMP allocation for ensuring the subject’s treatment and safety. In such cases, the AEs that led to emergency code break are to be treated as SAEs and the procedure outlined in “Reporting of SAEs” (section9.5.4.1) is to be followed. All code breaks must be clearly documented with reason and justification. In addition, unblinding must immediately be reported to the sponsor.

The procedure for emergency code break is as follows.

[[Emergency code break procedure]]

(1) The requester of code break (investigators or the sponsor) enters necessary information (names of clinical trial centre/department, subject's ID code, date of birth, drug number, and reason for code brake) into the IWRS in order to perform an emergency code break for the applicable subject and places their signature.

(2)Upon completion of code break, the e-mail will be distributed to the sponsor.

9.5.4.6 Reporting of AEs to regulatory authorities

Adverse events are reported to regulatory authorities in accordance with local laws and laws of each region and with the guidance set forth by the sponsor or its third-party representative. Forms used for reporting are as per local regulations and regulations of each region.

All clinical trials carried out in European countries shall adhere to European Good Clinical Practice Directive 2005/28/EC and European Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) are to be reported to competent authorities of involved European countries in accordance with the regulations.

9.5.5 Subject completion and withdrawal

The subjects themselves may request to discontinue participating in the clinical trial at any time without providing explanation. All subjects who discontinue the clinical trial after the start of the IMP administration are to undergo assessments at discontinuation outlined in the study schedule (Table 4)

The principal investigator or sub-investigator shall promptly inform the subject of the discontinuation, provide appropriate medical care and take other necessary measures. If a subject fails to make hospital visits, follow-up assessments of the reason, medication status, AEs, the progression of signs and symptoms, among others, are to be made as much as possible through letters, phone calls, etc.

The main reason (one) among the list of reasons (onset of AE, lost to follow-up, personal reason, insufficient therapeutic effect, worsening of underlying disease, consent withdrawal, pregnancy, trial discontinuation by the sponsor, other reasons) is to be recorded in the case report forms of dropout subjects.

9.5.6 IMP abuse (or IMP diversion to non-subjects)

Not applicable.

9.5.7 Checks for medical care at another department/another hospital

Principal investigators, sub-investigators, and clinical research coordinators are to instruct subjects to contact them in advance when planning to receive medical care at another department or another hospital for the first time. In addition, principal investigators, sub-investigators, and clinical research coordinators are to check with subjects at each visit whether they have been seen at another department or another hospital since their last visit and if they plan to do so. If a subject has a plan to be seen at another department or another hospital, the principal investigator or sub-investigator is to inform the attending physician of the subject's trial participation with the subject's consent.

9.6 Quality assurance of the data

This clinical trial shall be conducted in compliance with the protocol, SOPs, operational manual, applicable guidelines and regulations. Auditors independent of the department conducting the clinical trial are to regularly audit clinical trial centres.

9.6.1 Data collection

Required data as specified by the protocol are to be collected using case report forms and the information is to be entered into data management systems that conform to regulations. As specified in ICH GOP, case report forms are printed records, readable records or electronic records, designed to collect all the protocol-specified information on each subject and report it to the sponsor.

Collecting data for case report form shall follow the manual for creating case report forms. Principal investigators are responsible for all the data collected in case report forms and reported. By placing their signatures, principal investigators must guarantee the accuracy, reliability and completeness of the data.

The sponsor has the ownership of the original case report forms containing the complete data. They must not be disclosed through any means, without a written permission of the sponsor, to a third party, except those clinical trial personnel designated by the sponsor and representatives from the regulatory authorities of each region.

9.6.2 Management of clinical trial data

The sponsor will collect data using a standard computer system and software. The system and software have been validated and in compliant with the regulations. Additionally, all data from case report forms and other external data (e.g., laboratory values) will be entered into the clinical trial database using the above-mentioned system.

9.7 Statistical method

For analysis, SAS ® or other validated statistical software will be used as needed. In this clinical trial, analysis of the remission-induction period is to begin once the remission-induction period database has been locked and unblinded. Analysis of the entire administration period is to be performed once the database for the entire dosing period (remission-induction period, rescue period, extension period, and follow-up post-observation period) has been locked. Analysis of the follow-up period is to begin after the follow-up period database has been locked.

Details are described in the statistical analysis plan. The analysis plan will be fixed before locking databases for each of the remission-induction period, the entire administration period and follow-up period.

9.7.1 Statistical and analysis plan

This section outlines the analysis of clinical trial data. From here to section 9.7.1.9 mainly describes the analysis of the remission-induction period, while section 9.7.1.10 and section 9.7.1.11 describe the analysis of the entire administration period and follow-up period.

9.7.1.1 Endpoints

9.7.1.1.1 Primary endpoint

<Primary endpoint>

CR100 response rate at Week 12

9.7.1.1.2 Secondary endpoints

<Secondary endpoints>

- CR70 response rate, CR100 response rate (excluding Week 12) and CDAI remission rate (proportion of subjects with below 150 points) at each evaluation time
- Proportion of subjects with at least 5-point reduction in PRO2 from baseline (PRO2-CR5 response rate), proportion of subjects with at least 8-point reduction from baseline (PRO2-CR8 response rate), and proportion of subjects with below 8 points (PRO2-resmission rate) at each evaluation time
- Proportion of subjects with at least 50% improvement in SES-CD score from prior to IMP administration (endoscopic response rate) and proportion of subjects with 2 or less in SES-CD score (endoscopic remission rate) at Week 12
- Change and percent change in CDAI score from baseline at each evaluation time
- Change and percent change in PRO2 from baseline at each evaluation time
- Change and percent change in SES-CD score from baseline at Week 12
- In subjects who were concomintantly taking adrenocorticosteroid, proportion of subjects who achieved steroid-free maintenance (steroid-free remission rate, steroid-free improvement rate) through steroid dose reduction and clinical remission (CDAI remission or PRO2 remission) or clinical improvement (CR70 response, CR100 response, PRO2-CR5 response or PRO2-CR8 response)
- In subjects who were concomintantly taking adrenocorticosteroid, dosage, change and percent change of adrenocorticosteroid from baseline

9.7.1.2 Definition of the analysis population

FAS (full analysis set) is a set of subjects to whom the IMP has been administered after randomisation, and who had 1 or more evaluable, post-IMP administration primary efficacy endpoint data points.

PPS (per protocol set) is a set of subjects who satisfactorily complied with the Protocol. Detailed

criteria deemed to match present analysis sets are to be decided upon before the database is locked and unblinded, and they are to be specified in the analysis plan.

Safety analysis set is a set of subjects to whom the IMP has been administered, and who had 1 or more evaluable, post-IMP administration safety data.

Pharmacokinetic analysis set is a set of subjects to whom the IMP has been administered, and who had 1 or more evaluable, post-IMP administration serum E6011 concentration data points.

Pharmacodynamic analysis set is a set of subjects to whom the IMP has been administered, and who had 1 or more evaluable, post-IMP administration biomarker data points.

9.7.1.3 Breakdown of subjects

Consented subjects and screening failure subjects with reason for screening failure are to be summarised. Additionally, randomised subjects, untreated subjects (after randomization), treated subjects, completed subjects, discontinued subjects with reason for discontinuation are to be summarised by allocated treatment group.

9.7.1.4 Characteristics of demographic and pre-treatment values

Characteristics of demographic and other pre-treatment values are to be presented for the FAS and safety analysis set. Continuous variables include age, weight, height, and biomarkers. Categorical variables include sex and race.

9.7.1.5 Prior treatment and concomitant treatment

Drugs recoded in case report forms should be listed using the 11-character drug codes of the World Health Organization Drug Dictionary (WHO DD). The number of subjects (percentage) receiving prior treatment drugs and concomitant drugs is to be calculated for each treatment group using the FAS. Furthermore, it is to be calculated for each Anatomical Therapeutic Chemical (ATC) classification (if classified into applicable ATC classes, such as the anatomical class, therapeutic class, pharmacologic class, and chemical class) and WHO DD preferred term. A prior treatment drug is defined as a drug discontinued prior to the start of IMP administration. A concomitant drug is defined as “when a drug that was started prior to IMP administration continues to be used at the start of IMP administration” or “a drug that was started during the IMP administration period and used before the end of the extension period (or discontinuation)”. Prior treatments and concomitant treatments are to be categorised into “drugs” or “non-drug therapies” and presented in a table.

9.7.1.6 Efficacy analysis

Efficacy analysis will be performed using the FAS as the primary analysis set, while the PPS will be used as a supplementary analysis set.

9.7.1.6.1 Analysis of primary efficacy endpoint

For Week 12 CR100 response rate, the Bayesian posterior distribution of the difference in the CR100 rate at Week 12 between the E6011 group and the placebo group is to be calculated. If there was a 50% or

more probability of the difference between both groups being 25% or more, the efficacy of E6011 is confirmed. Noninformative prior distribution is to be used for both the E6011 group and the placebo group.

Subjects with missing primary endpoint data due to premature discontinuation before 12 weeks after administration or other reasons are treated as non-responders - non-responder imputation (NRI).

9.7.1.6.2 Analysis of secondary efficacy endpoints

- CDAI response rate [CR70, CR100 (excluding Week 12)] and remission rate are to be calculated by treatment group and evaluation time. Summary statistics for CDAI value, change and percent change from baseline are also to be calculated by treatment group and evaluation time.
- PRO2 response rate (PRO2-CR5, PRO2-CR8) and remission rate are to be calculated by treatment group and evaluation time. Summary statistics for PRO2 value, change and percent change from baseline are also to be calculated by treatment group and evaluation time.
- SES-CD endoscopic response rate and endoscopic remission rate are to be calculated by treatment group and evaluation time. Summary statistics for SES-CD value, change and percent change from baseline are also to be calculated by treatment group and evaluation time.
- Steroid-free remission rate and steroid-free response rate in subjects concomitantly using adrenocorticosteroids is to be tabulated by treatment group and evaluation time. Summary statistics for steroid dosage, change and percent change from baseline are also to be calculated for each treatment group and evaluation time.

Subjects with missing secondary endpoint data due to premature discontinuation before 12 weeks after administration or other reasons are treated as non-responders (NRI) in the analysis of secondary endpoints.

9.7.1.7 Analysis of pharmacokinetics, pharmacodynamics, pharmacogenomics/pharmacogenetics and other biomarker evaluations

9.7.1.7.1 Pharmacokinetic analysis

Serum E6011 concentration is to be summarised using the pharmacokinetic analysis set. Summary statistics for serum E6011 concentration are to be calculated for each specified time. Serum E6011 concentration-time profile is also to be created.

9.7.1.7.2 Analysis of pharmacodynamics, pharmacogenomics/pharmacogenetics and other biomarkers

Exploratory biomarker and pharmacogenomic analyses are to be performed using the pharmacodynamic analysis set. Summary statistics for serum total FKN concentration, measured faecal calprotectin and serum CRP values, change and percent change from baseline are to be calculated by treatment group and evaluation time. CCI

Details and results of the analysis of blood $CD16^+$ monocytes, etc., genetic marker for $CD16^+$ monocytes, etc. and blood biomarkers (comprehensive proteome analysis) using the residual serum

collected for this study will be provided in a separate report and will not be included in the Clinical Study Report.

9.7.1.8 Safety analysis

Safety is to be analysed using the safety analysis set. Summary statistics related to safety data (sample size, mean, standard deviation, median, minimum and maximum for continuous variables; sample size and ratio for categorical variables) are to be calculated by treatment group based on the actual treatment received. Safety endpoints include adverse events, laboratory values, vital signs, weight, physical examination, standard 12-lead ECG, neurological symptoms and blood $CD4^+$ cell count. In safety analysis, Day 1 is the start date of IMP administration.

9.7.1.8.1 Exposure status

Summary statistics for the numbers of subjects who received the IMP, the exposure period, and dose are to be presented by treatment group.

9.7.1.8.2 Adverse event

Adverse events in case report forms are to be reworded using the ICH medical terminology (MedDRA). Using MedDRA (Version 21.0 or later), terms used in case report forms are reworded the closest Lowest Level Term (LLT). In addition, Preferred Terms (PT) and System Organ Classes (SOC) will also be entered into databases.

A treatment emergent adverse event (TEAE) is an adverse event that was not present prior to but emerges after IMP treatment. This includes the following:

- An event already present prior to IMP treatment that, after having been absent immediately prior to IMP treatment, re-emerges during IMP treatment
- An adverse event already present prior to IMP treatment that worsens in severity during IMP treatment compared to before treatment.

TEAE will be used for analysis. All adverse events including non-TEAEs are to be presented in a table.

TEAEs are to be tabulated by treatment group. The number (percentage) of subjects with TEAEs is to be tabulated by SOC and PT. A single adverse event reworded to a MedDRA term is occasionally reported multiple times in one subject. In such cases, the subject is counted as one when tabulating the number of subjects with the particular adverse event. Additionally, the number (percentage) of subjects with TEAEs is to be tabulated by the highest severity (mild, moderate or severe).

Furthermore, the number (percentage) of subjects with TEAEs is to be tabulated by causal relationship (related, not related).

9.7.1.8.3 Laboratory test values

Laboratory values are to be tabulated using the SI units.

Summary statistics for continuous variables are to be calculated for measurements at each Visit and their change from baseline by treatment group. For sequential categorical variables, laboratory values are to be categorised into under normal range (L), within normal range (N), or over normal range (H). Then,

the number of subjects and percentage by LNH categories are presented in a shift table (baseline vs each visit post-dose). In addition, post-dose maximum and minimum values are to be similarly presented in a shift table.

9.7.1.8.4 Vital signs

Summary statistics for vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature and weight) and their change from baseline at each evaluation time are to be calculated for each evaluation time and for each treatment group.

9.7.1.8.5 ECG

The numbers of subjects having normal and abnormal standard 12-lead ECG and their percentages are to be presented in a shift table for each treatment group.

9.7.1.8.6 Immunogenicity

Immunogenicity analysis is to be conducted using the safety analysis target set. The frequency and rate of serum anti-E6011 antibody expression at each evaluation time are to be calculated for each treatment group. If anti-E6011 antibodies are confirmed, frequency and ratio of their neutralizing activity (if present) and isotypes are to be calculated.

9.7.1.8.7 Other special tests

<Neurological symptoms>

The numbers of subjects having a normal and an abnormal result and their percentages are to be presented in a shift table for each treatment group.

< Blood $CD4^+$ cell count >

Summary statistics for $CD4^+$ cell count and change from baseline at each evaluation time are to be calculated for each treatment group and evaluation time. Additionally, values are to be categorised into under normal range (L), within normal range (N), and over normal range (H) and presented for each treatment group in a shift table.

9.7.1.9 Other analyses

<Anti-JCV antibodies>

Specific analytical methods are described in the statistical analysis plan.

9.7.1.10 Analysis of the entire dosing period

The same efficacy, pharmacokinetic, biomarker, immunogenicity, and safety analyses performed for the remission-induction period are to be performed.

9.7.1.11 Analysis of the follow-up period

The numbers of subjects with and without PML and their percentages are to be presented in a shift

table for each treatment group. The same safety analysis performed for the remission-induction period is to be performed.

9.7.2 Target sample size

The number of subjects in this clinical trial was determined considering stimulation-generated operating characteristics relating to efficacy assessment, based on efficacy outcomes of the 101 trial and of similar drugs. With 20 subjects allotted to each group, if the actual difference in CR100 response rate between the E6011 group and placebo group is 40% or more, the probability of confirming the efficacy of E6011 is above 80%.

The number of enrolled subjects was 25 at the end of the recruitment. Therefore, the sample size will be reduced to 25 subjects, but the analysis plan will remain unchanged and performed in accordance with section 9.7 Statistical method.

9.7.3 Interim analysis

No interim analysis is planned in this clinical trial.

9.7.4 Other key statistical and analytical considerations

Not applicable.

9.7.5 Changes to the analysis plan

If the analysis plan needs to be changed after the start of the clinical trial, the Sponsor shall determine the effect the change(s) will have on the clinical trial and the method of applying the change(s). Details of the change are to be outlined in the Clinical Study Report.

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11. Procedures and instructions (action plan)

11.1 Changes in the clinical trial protocol

Principal Investigators or Sub-investigators must not make any changes to the protocol without the Sponsor's prior written agreement.

Changes relating to the safety of subjects, scope of assessments, or scientific quality of the clinical trial require notification to the public health authority or regulatory authorities, and the approval of every IRB/IEC involved in this clinical trial. Provided, however, that this shall not apply to cases where such changes in the clinical trial protocol arise under medically unavoidable circumstances, such as to avoid urgent risk to the subject. In the event the protocol was not followed for safety reasons, the Principal Investigator or a Sub-investigator shall give prompt notice of the fact to the Sponsor and the clinical trial centre's IRB/IEC. The Sponsor will report the incident to regulatory authorities in accordance with the regulations of the region.

Revisions that are strictly administrative changes do not necessarily require notification to the public health authority or regulatory authorities, and the approval of every IRB/IEC involved in this clinical trial. Provided, however, that the Sponsor shall notify the IRB/IEC and regulatory authorities (or, in accordance with the regulations of the region, the head of the clinical trial centre) as necessary using a document containing the details of such changes.

11.2 Conformity to the clinical trial protocol

Principal Investigators and Sub-investigators shall conduct this clinical in compliance with the clinical trial protocol (see ICH GCP, Section 4.5).

11.3 Monitoring procedures

In addition to visiting clinical trial centres, monitors shall communicate with Principal Investigators, Sub-investigators, and other designated trial personnel by phone, mail, or email. Monitors are to visit clinical trial centres in accordance with the monitoring procedures. Principal Investigators (or the directors of clinical trial centres as required by regulations of each region) shall accept monitors' actual visits to check the status of compliance with ICH GCP and regional regulations. Furthermore, case report forms and medical records (source documents) of the corresponding subjects must be readily available to be verified by Sponsor's representatives. Source data verification is to be performed in accordance with regulations of each region to confirm protocol compliance status and data accuracy. All records at clinical trial centres are subject to audit by regulatory authority of each region and the IRB/IEC.

Based on ICH GCP (Section 1.52), source documents include, but are not limited to, the following:

- Medical records of examining rooms, administrative offices, and hospitals
- Certified copies or transcriptions of documents recorded by healthcare professionals
- Records of auto-recording devices [e.g., Interactive Voice/Web Response System (IVRS/IWRS), X-rays, ultrasound tests, CTs, MRIs, radiographic images, ECGs, EEGs, sleep polygraphs, lung capacity tests, as well as microfiches and photographic negatives regardless of the preservation method]

- Questionnaires on pain, QOL, and medical history filled out by subjects
- Telephone communication records
- Patient Diaries or self-evaluation checklist
- Records of IMP provided and quantity checks retained by the Pharmacy Department or study personnel
- Laboratory test results and other forms of lab test-related result (e.g., a result of urine pregnancy test and an urine soaked dipstick)
- Records of communication between physicians or with the IRB/IEC regarding trial subject's treatment
- A part of data recorded in case report forms that was directly entered by subjects (e.g., questionnaires)
- Electronic patient reported outcomes entered by subjects

11.4 Data recording

Suitable and authorised individuals shall create a case report form for each subject who gave consent. All data contained in case report forms must be consistent with the source documents, except when data directly recorded in case report forms is regarded as the source data. When correcting data in case report forms, change history must be left clearly with the date of correction, and the person making the correction, the reason for correction, and the data before the correction must remain legible. Only the required data as specified in the protocol shall be recorded in case report forms.

Once signed, the Principal Investigator shall submit case report forms to the Sponsor and retain their copies.

For the number of liquid or very soft stools, degree of abdominal pain, and subjective general status among the CDAI assessment items and PRO2, the data entered by subjects in the electronic patient reported outcomes are to be used for evaluations. These data cover various health aspects that are evaluated and directly given by subjects; as such, they will not be interpreted by Principal Investigators or Sub-investigators.

11.5 Source data specification

All data contained in case report forms must be consistent with the source documents. If the following items not recorded in medical records, including charts then case report forms constitute source data for these items.

- IMP administration status (e.g., reason for discontinued administration or dosage change)
- Reason for prior treatments and concomitant treatments (including drug and non-drug therapies)
- Discontinuation-related information (e.g., subject stopped coming in for visits)
- AE-related information (e.g., seriousness, causal relationship with the IMP)
- CDAI
- PRO2

11.6 Retention of records

It is Principal Investigators' (or, in accordance with regulations of each region, the heads of clinical trial centres or persons designated by them) responsibility to retain, even if the trial has ended or been discontinued, all trial-related documents including but not limited to: the clinical trial protocol, copies of case report form data, investigator's brochure, documents submitted to regulatory authorities (e.g., the informed consent form, records of communication with IRB/IEC). Additionally, once trial databases are locked, the Sponsor is to provide Principal Investigators the list showing each subject's treatment group. Clinical trial centres shall retain trial-related documents for at least two years after the final approval in ICH regions and until such time that the application is no longer under review in ICH regions; or until three years have passed after the development of the test drug is officially discontinued.

As the documents may need to be retained even after the above retention period has elapsed, Principal Investigators shall discuss with the Sponsor whether or not to destroy the documents. Principal Investigators, even if they were to retire or resign from their positions, shall discuss with the Sponsor ways to retain the documents.

The test drug is expected to receive the biological product designation. For retrospective study-purposes, clinical trial centres shall maintain and manage the documents identifying each "subject's name, address, and IMP administration dates/lot numbers" for at least 10 years from the date of the final dose.

11.7 Audit procedures and inspections

In addition to the regular monitoring procedures, the Sponsor's auditing staff will perform audits in accordance with the Sponsor's SOP to verify that ICH GCP and regulations of each region are being fully adhered to. Additionally, if the regulatory authority requests an inspection during or after the clinical trial, the Principal Investigator shall immediately notify the Sponsor of this fact.

11.8 IMP handling

The Sponsor is to provide the IMP to clinical trial pharmacists. The IMP provided must be kept in appropriate storage space (e.g. a locked cabinet) and stored under the specified conditions. Clinical trial pharmacists must accurately record the status of IMP delivery and use in the IMP Accountability Log. If requested, a copy of the IMP Accountability Log must be submitted to the Sponsor at the end of the clinical trial. An accurate record of the dates and quantities of IMP prescribed to each subject must be presentable at the time of investigation or inspection. After the IMP has been delivered to clinical trial centres, monitors are to verify the documents as well as all other trial-related documents as needed.

The IMP is provided for the clinical trial only and must not be used for any other purposes. Clinical trial pharmacists must dispose of unused portions of the IMP without the Sponsor's permission. At the end of the trial or as appropriate during the trial, clinical trial pharmacists shall return all unused bottles of the IMP and, if requested, provide a copy of the Drug Accountability Log containing complete information to the Sponsor (or predesignated person) (except when the Sponsor has approved of disposal at each clinical trial centre).

11.9 Public release of the clinical trial results

Any manuscripts, summaries and other documents based on the results of this clinical trial that are to be presented must first be reviewed and approved in writing by the Sponsor. This review is conducted in order to protect Sponsor's proprietary information that existed at the start of the clinical trial or arises during the clinical trial.

The details of necessary duties pertaining to public release of any data, documents based on the clinical trial results, and other information that arises or is created are to be outlined in the agreement made by and entered into between the Principal Investigator and the Sponsor or CRO.

11.10 Disclosure of information/results and confidentiality

Principal Investigators, Sub-investigators, trial coordinators and IRB/IEC members are obliged to keep confidentiality of the information contained in the clinical trial protocol and its revisions, as well as any results obtained during the trial. Full or partial disclosure must first be agreed to by the Sponsor in writing and only be used for reviewing or conducting the clinical trial. Data collected as part of this clinical trial may not be used in any literary work including publications without the Sponsor's written agreement. These duties related to non-disclosure and non-use must not reduce the duties stipulated in the non-disclosure agreement made between the Sponsor (or CRO) and the Principal Investigator/head of clinical trial centre.

Every member involved in the conduct of this clinical trial must adhere to these duties related to non-disclosure and non-use stipulated in the non-disclosure agreement made between the Sponsor (or CRO) and the Principal Investigator/head of clinical trial centre.

11.11 Discontinuation of clinical trial

The Sponsor may discontinue the clinical trial for medical reasons. The Sponsor also has the right to discontinue the clinical trial at any time for any reason. The Sponsor must promptly notify Principal Investigators/heads of clinical trial centres and regulatory authorities of discontinuation or suspension and the reason thereof. The Sponsor or Principal Investigators/heads of clinical trial centres must also promptly notify the IRB/IECs of discontinuation or suspension and the reason thereof in accordance with applicable regulations.

Principal Investigators may discontinue the clinical trial whenever they deem it necessary. If Principal Investigators discontinue or suspend the trial without the Sponsor's prior consent, they shall notify the heads of the clinical trial centres of this fact (if necessary) and Principal Investigators/heads of clinical trial centres shall promptly notify the IRB/IECs of this fact. Principal Investigators/heads of clinical trial centres shall provide the Sponsor and the IRB/IECs a detailed explanation of discontinuation or suspension in writing. Furthermore, trial-related documents must be saved in accordance with the stipulations of "Retention of records."

11.12 Compensation for health damages

The Sponsor shall be insured in accordance with guidelines and regulations of the country in which the clinical trial is conducted to cover the liability for subjects.

12. Appendix

Appendix 1 Collection, handling, use, storage and security of samples for pharmacodynamic, pharmarcogenomic, and biomarker evaluations and protection of subjects' privacy

Samples from subjects enrolled in this clinical trial will be collected to perform pharmacodynamic, pharmarcogenomic, and biomarker analyses. The collected samples will be used for assessments and validations and have an important role in identifying biomarkers that are useful in predicting results related to therapeutic response and/or safety, as well as the sequence of transcriptional regulatory regions of such gene expression biomarkers; they are also useful in developing diagnostic drugs.

The collection of samples used for pharmacodynamic, pharmarcogenomic, and biomarker evaluations shall be made conforming to the sample processing procedures outlined in the clinical trial protocol and, unless the collection and use of samples are prohibited by regulatory requirements, in accordance with the stipulations of the clinical trial protocol.

Sample collection and handling

Pharmacogenomic samples and biomarker samples shall be collected when indicated by the study schedule. If blood samples to be used for pharmacogenomic testing and biomarker testing cannot be collected when indicated by the study schedule for practical or medical reasons, they may be collected during other hospital visits based on the judgement of the Principal Investigator or clinical trial centre staff.

Security, use and storage of samples

DNA extraction and other sample processing and DNA methylation are to be done at testing centres according to the Sponsor's instructions. Samples are to be processed, analysed and stored at appropriate testing centres to ensure data reliability and protection of subject privacy.

The use of samples is restricted within the scope specified in the clinical trial protocol. Testing centres have no authority to go beyond the scope required to conduct the prescribed analyses or the right to hand over the samples. The Sponsor will never hand over the samples to a third party.

The samples will be stored for no more longer than three years after the end of the clinical trial. At the end of the storage period, samples will be destroyed. When regulatory authorities (or medical product approval bodies) have inquiries about this clinical trial, the samples may be stored for a longer period. Under such special circumstances, the samples are to be stored until such time that the inquires have been properly addressed.

The advancement of research and technology can potentially lead to identification of gene mutations of interest or unanticipated alternative genetic analysis techniques. It is impossible to predefine all potential analyses that may be conducted in the future. Accordingly, all collected (according to ICH E18 draft guidelines) samples will be single-coded or double-coded to protect the privacy of the subjects.

Right to withdraw consent

Whenever subjects wish to withdraw their consent to participating in the evaluation during the sample

storage period, the Sponsor will destroy their samples. Provided however, all the results of analysis performed up to the point of consent withdrawal will be used as needed to maintain the integrity of the evaluation project.

Subject privacy and data disclosure

Samples will be single-coded or double-coded and will not carry personal identifiers (e.g., initials, date of birth, public ID number). Double-coding refers to labelling initially with one code (subject ID), then with the second code. It is possible to identify the individual subject with the use of both coding keys. These coding keys are typically maintained by different managers. Coding keys that link sample IDs to subject IDs will be stored separately from the samples. At this point, samples become double-coded and the initial code becomes the subject ID. Testing centre operators who conduct genetic testing will never access the coding keys. Clinical data collected as part of the clinical trial does not contain information that can identify the individual subject. Clinical data can be linked by using sample ID coding keys.

The Sponsor will ensure data protection and take as many steps as possible to maintain confidentiality. The data on subjects enrolled in the clinical trial may be analysed in all global regions, regardless of where their samples were collected.

The Sponsor and their representatives and agents may share coded data with the following organizations and their members that conduct the evaluations and audits:

- Clinical trial centres
- CRO under contract with the Sponsor
- IRB/IECs/IECs involved in the evaluations
- Regulatory authorities or relevant public agencies

After the completion of the analysis, the results will be documented in a separate report, and partial or complete coded data will be included in lists or tables. Other publications (e.g., peer-reviewed scientific journals) and public presentations of the clinical trial results may contain summaries of the study population, but will never release any results that may be able to identify the individual subjects.

Considering the nature of evaluation of pharmacodynamic, pharmarcogenomic, and biomarker analysis results, it is not possible to disclose the individual subject data to a given subject. It is unlikely that any results obtained in the analysis would have an immediate clinical significance to the subjects (patients) or their family. For this reason, the results obtained in the analysis will not be disclosed to the subjects (patients) or their attending physicians.

13. Attachments

Attachment 1 Clinical trial centres and Principal Investigators (Applicable to Japan, separate document outside the protocol for Europe)

Attachment 2 Clinical trial framework

Attachment 3 Reference criteria for determining severity levels of laboratory values

Attachment 4 IMP preparation procedure

Attachment 5 IMP types, packaging and labelling (Labelling applicable to Japan, separate document outside the protocol for Europe)

Attachment 6 List of prohibited/restricted concomitant drugs

Attachment 7 Criteria for insufficient therapeutic response with the existing drugs (steroids and immunomodulators) pertaining to inclusion criterion 5

Attachment 8 Criteria for primary nonresponse, secondary nonresponse and intolerance with biologics pertaining to inclusion criterion 5

Attachment 9 Criteria for steroid dosage reduction schedule

Attachment 10 CDAI Score Sheet

Attachment 11 Evaluation of disease activity by PRO2

Attachment 12 Endoscopic evaluation by SES-CD

Attachment 13 Neurological symptoms check list

Attachment 14 Abnormal neurological symptoms report

Attachment 15 Pregnancy report

Attachment 16 Pregnancy outcome

Attachment 17 Information on medical devices (blood-collecting tubes, etc.) not approved in Japan (Applicable to Japan)

Attachment 18 Report of defective medical devices not approved in Japan (Applicable to Japan)