STATISTICAL ANALYSIS PLAN

CLIENT: EA Pharma Co., Ltd

Protocol Number: E6011-ET2

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

Version Date: 30 SEP 2022

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Revision History

Version Number	Date	Reason for Change
Draft 0.1	21SEP2018	Initial version
Draft 0.2	19OCT2018	Updated according to comments done to Draft 0.1.
Draft 0.3	08NOV2018	Updated according to comments done to Draft 0.2.
Final 1.0	14NOV2018	Updated according to comments done to Draft 0.3.
Draft 1.1	18DEC2019	Amendment: Updated according to comments done to TLF draft 0.2. Updated template to L-BP-SOP-010 26MAR2019.
Draft 1.2	28FEB2020	Updated according to comments done to SAP Draft 1.1 and TLF draft 0.3
Draft 1.3	25MAY2020	Updated according to comments done to SAP Draft 1.2 and protocol amendment English version 5 03APR2020
Draft 1.4	6APR2022	Updated according to protocol amendment English version 11, dated 18APR2022
Draft 1.5	31MAY2022	Updated according to comments done to Draft 1.4
Draft 1.6	6JUL2022	Updated according to comments done to Draft 1.5
Draft 1.7	26JUL2022	Updated according to comments done to Draft 1.6
Final 2.0	15SEP2022	Updated according to comments done to Draft 1.7
Final 3.0	30SEP2022	Chain initial values for the algorithm of primary endpoint simulated by a Beta (0.5, 0.5) in order to improve the efficiency of the Bayesian model

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1. PROTOCOL SYNOPSIS

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 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 design Multinational, multicenter, randomized, 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]

Dose levels	**Route of Administration**
10 mg/kg E6011 dosing solution (approximately 100 mL) and matching placebo	Intravenous infusion pump
Duration of Treatment	**Period of Evaluation**
Maximum 64 weeks per subject (52 weeks for responders to the remission-induction)	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

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 centralized 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).

(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.

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 clinical 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 tumor, 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 cannot 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.

<u>Analysis of primary endpoint</u>

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 analyzed 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 analyzed 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 analyzed 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 analyzed 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 Mar 2022

Treatment: October 2018 to April 2022

Follow-up: Jun 2021 to April 2024

Close-out: May 2024

2. LIST OF ABBREVIATIONS

Abbreviations	Unabbreviated Terms (English)
BMI	Body mass index
CI	Confidence Interval
CDAI	Crohn's disease activity index
CRP	C-reactive protein
CV	Coefficient of variation
eCRF	electronic Case Report Form
FAS	full analysis set
FKN	Fractalkine
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigation Medical Product (or Placebo)
JCV	JC virus
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
MCMC	Markov chain Monte Carlo
MedDRA	medical dictionary for regulatory activities
MI	Multiple Imputation
OC	Observed Case
PD	Pharmacodynamics
PK	Pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PPS	Per Protocol Set
PT	preferred term
SAP	Statistical Analysis Plan
SES-CD	simple endoscopic score for Crohn's disease
SD	Standard deviation
SOC	system organ class
TEAE	treatment emergent adverse events
WHO DD	world health organization drug dictionary

3. INTRODUCTION

This analysis plan gives a detailed description of the statistical methodologies, data listings, summary tables, and figures planned in the analyses of the data in the Early phase 2 clinical trial of E6011 in patients with active Crohn's disease study. The statistical data analyses, described in this document, is intended to provide unbiased and valid conclusions concerning the objectives of the study.

3.1 Study Population

Patients with Crohn's disease ranging from moderate to severe aged 18 or over and under 65 on the date of consent, diagnosed with small intestine-type, small and large intestine-type, or large intestine-type Crohn's disease at least 12 weeks before giving consent and that meet the rest of the inclusion/exclusion criteria

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.

3.2 Planned Study Design

This is a multinational, multicenter, randomized, 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 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.

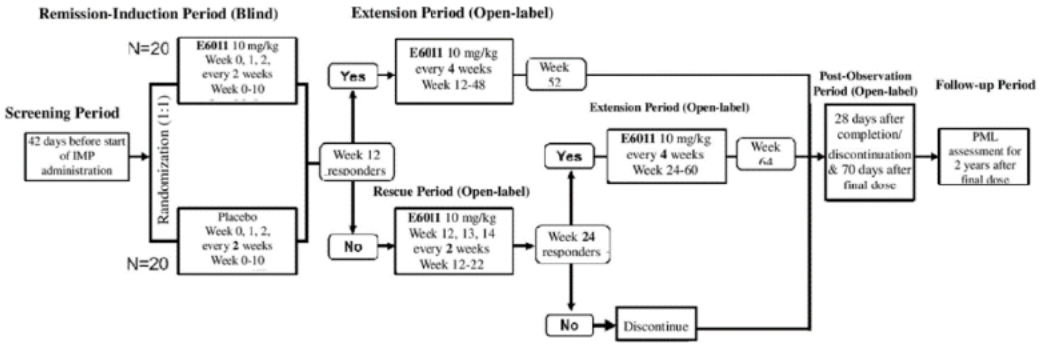
Subjects with less than 70 reduction on the CDAI (non-responders) at evaluation in Week 12 are to move on to the rescue period. The rescue period is to last 12 weeks, with additional administrations of 10 mg/kg of E6011 in Week 12, Week 13, Week 14 and every two subsequent weeks up to Week 22. Subjects 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.

Table 1 to 3 shows the schedule for this clinical trial.

Table 1 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 centralized 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. Randomization 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 Extension period.
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).

Table 2 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 3 Study Schedule (Non-responders)

	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		○	○		○		○	○

	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	○	○	○	○	○	○	○	○	○	○	○			

3.3 Study Objectives

3.3.1 Primary Objectives

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

3.3.2 Secondary objectives

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

3.3.3 Exploratory objectives

CCI [redacted]

4 ANALYSIS ENDPOINTS

4.1 Baseline Definition

As a rule, baseline values are defined as the last available value prior to the first injection of E6011 for all longitudinal endpoints unless explicitly stated otherwise in this document. As defined per protocol all assessments are performed before the IMP administration.

Change from baseline values are defined as:

$$Value\ measured\ after\ first\ dosing - Baseline\ value$$

4.2 Demographic and baseline characteristics

Demographic variables are detailed below:

- Sex: Male/Female
- Age (in years), defined as:

$$(year\ of\ informed\ consent - year\ of\ birth)$$

- Age (in years) <35, 35-<50 , ≥50
- Race: Asian (Japanese/Other Asian), White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander
- Race: Japanese/Non-Japanese
- Ethnicity: Hispanic or Latino, Non-Hispanic or Latino.
- Weight (kg)

- Height (cm)
- BMI (kg/m^2)
- Baseline CDAI: ≤330; > 330.
- Baseline PRO2: ≤24; > 24.
- Baseline SES-CD: ≤15; > 15.
- Proclivity to hypohepatia: Yes, No
  Having a proclivity to hypohepatia is defined as having at least one baseline AST or baseline ALT value greater than the upper lab limit of the corresponding parameter.
- Baseline eGFR: (mL/min/1.73m^2), defined as:

  for males:

  $$194 * serum\ creatinine^{-1.094} * age^{-0.287}$$

  for females:

  $$194 * serum\ creatinine^{-1.094} * age^{-0.287} * 0.739$$

- Baseline eGFR: (mL/min/1.73m^2) <30, 30-<60, 60-<90, ≥90

Variables related with history of Crohn's disease presented below will be descriptively summarized by treatment group:

- Type of Crohn's disease: Small intestine-type, Small and large intestine-type, Large intestine-type, Other.
- Site of lesions: Gastroduodenum, Jejunum, Ileum, Cecum, Ascending colon, Transverse colon, Descending colon, Sigmoid colon, Rectum, Anus/perianal.
- Duration of Crohn Disease's (in years), defined as:

$$\frac{(Informed\ consent\ date - Crohn's\ disease\ onset\ date + 1)}{365.25}$$

- Duration of Crohn Disease's (in years): ≤5 years; > 5 years.
- Crohn Disease's related Surgical procedure (Yes/No)
- Type of surgical procedure: Endoscopic dilatation, Strictureplasty, Ileocolic side-to-side anastomosis, End-to-end anastomosis, Ileocolic segmental resection, Drainage Seton, Ilco pouch-anal anastomosis, Other.
- Surgical site: Gastroduodenum, Jejunum, Ileum, Cecum, Ascending colon, Transverse colon, Descending colon, Sigmoid colon, Rectum, Anus/perianal, Other.

Medical history defined as any comorbidities or Crohn's Disease's complications at the time of Informed Consent will be also analyzed. This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Linical at the time of database lock.

4.3 Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version in use at the time of the DBL.

Prior medications are those the patient used before the first investigational medicinal product (IMP) intake. Prior medications can discontinue before first administration or can be ongoing during treatment phase.

Prior biologic treatment of Crohn's disease will be analyzed separately. Patients will be categorized depending on the prior biologic treatment used of Crohn`s disease:

- Previous biologics: Yes; No.
- Prior biologic treatment used of Crohn`s disease: Biologic naïve (no prior biologic treatment reported), 1 prior biologic failure (one prior biologic treatment reported), 2 prior biologic failures (2 prior biologic treatments reported), ≥3 prior biologics failures (3 or more prior biologic treatments reported)

Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the first IMP intake to the end of treatment + 14 days. A given medication can be classified both as a prior medication and as a concomitant medication.

The following medications will be analyzed:

- Corticosteroids concomitant before randomization: Yes; No.
- Immunomodulators concomitant before randomization : Yes; No.
- Enteral nutrition concomitant before randomization : Yes; No.

4.4 Extent of investigational medicinal product exposure and compliance

Duration of IMP exposure is defined as date and time of last IMP administration – date and time of first double-blind IMP administration + 14 days, regardless of unplanned intermittent discontinuations. Duration will be presented in days.

4.5 Efficacy endpoints

4.5.1 Primary Endpoints for Efficacy

- CR100 response rate at Week 12, defined as ratio of patients who had CDAI reductions of at least 100 points from baseline to Week 12. CDAI score will be considered as collected in the eCRF by the investigator.

4.5.2 Secondary Endpoints for Efficacy

- 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 concomitantly taking adrenocorticosteroid at remission induction period, 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 concomitantly taking adrenocorticosteroid at remission induction period, dosage (mg/day), change and percent change of adrenocorticosteroid from baseline.

4.6 Safety endpoints

Assessment items for safety evaluation include the following:

- Adverse events
- Laboratory test values
- Vital signs, weight, physical examination
- Standard 12-lead ECG examinations, neurological symptoms
- Blood $CD4^+$ cell count

4.7 Quality of Life or other Patient Report Outcomes endpoints

ePRO of "4.5.2 Secondary Endpoints for Efficacy" is applicable.

4.8 Pharmacokinetic Parameters endpoints

Individual serum concentration values of E6011 will be summarized as follows:

- Pharmacokinetics and serum E6011 concentration

  - Individual serum concentration values of E6011 will be listed and summarized using descriptive statistics (n, mean, standard deviation, geometric mean, CV, geometric CV, median, Q1,Q3, minimum and maximum) and nominal time point. The data of time points in subject with interruption will not be included on calculation of summary statistics after the interruption.

  - Actual sampling time and serum concentrations of E6011 for each subject will be listed.

  - The individual serum E6011 concentration–time profile will be displayed in linear and semi–log scales using actual sampling times in the same graph.

  - The mean serum concentrations of E6011 will be displayed using nominal blood sampling times with standard deviation in linear and semi–log scales in the same graph.

4.9 Immunogenicity endpoints

Individual serum concentration values of anti-E6011 antibody will be summarized as follows:

- Actual sampling time and serum concentrations of anti-E6011 antibody for each subject will be listed.

- The frequency and rate of serum anti-E6011 antibody and E6011-induced anti-E6011 antibody expression at each evaluation time will be calculated for each treatment group. If anti-E6011 antibodies and E6011-induced anti-E6011 antibody are confirmed, the frequency and ratio of their neutralizing activity (if present) and isotypes are to be calculated.

4.10 Biomarker endpoints

Individual serum concentration values of serum total fractalkine concentration (FKN), faecal calprotectin and serum CRP will be summarized as follows:

- Individual serum concentration values of fractalkine concentration (FKN), faecal calprotectin and serum CRP will be listed and summarized using descriptive statistics (n, mean, standard deviation, geometric mean, CV, geometric CV, median, Q1,Q3, minimum and maximum) and nominal time point. The data of time points in subject with interruption will not be included on calculation of summary statistics after the interruption.

- Actual sampling time and serum concentrations of fractalkine concentration (FKN), faecal calprotectin and serum CRP for each subject will be listed.

5 ANALYSIS POPULATIONS

5.1 Efficacy Populations

FAS (full analysis set) is a set of subjects to whom the IMP has been administered after randomization, and who had 1 or more evaluable, post-IMP administration primary efficacy endpoint (i.e., to have an evaluable CDAI value at baseline and any other post baseline).

PPS (per protocol set) is a set of subjects who has been randomized and satisfactorily ended the remission induction treatment period, subjects that fulfill all inclusion /exclusion criteria and have no major or critical protocol violations.

Patients in the efficacy populations will be analyzed according to the treatment group allocated by the randomization even if not treated with the correct treatment assigned.

5.2 Safety Population

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 points. Safety endpoints include adverse events, laboratory values, vital signs, weight, physical examination, standard 12-lead ECG, neurological symptoms and blood $CD4^+$ cell count. Patients in the safety population will be analyzed according to the treatment actually received at remission-induction period.

5.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will be defined as all available data on patients who took the active treatment and who had 1 or more evaluable, post-IMP serum E6011 concentration data points.

5.4 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set will be defined as all available data on patients who took the active treatment and who had 1 or more evaluable, post-IMP PD biomarker data points.

5.5 Immunogenicity Analysis Set

The immunogenicity will be analyzed using the safety analysis set.

6 STATISTICAL METHODOLOGY

This analysis plan gives a detailed description of the statistical methodologies, data listings, summary tables, and figures planned in the analyses of the data in the E6011-ET2 study.

This section describes the statistical analyses of the study based on the statistical section of the English protocol v10 17SEP2021. Any differences with the protocol will be identified and documented.

The statistical data analyses, described in this document, are intended to provide unbiased and valid conclusions concerning the objectives of the study.

This SAP describes only the analyses for the study objectives not involving the pharmacokinetic objectives. These will be described in a separate analysis plan.

6.1 General Methods

The analysis of the present study will be exploratory and primarily make use of descriptive statistical methods. In addition, exploratory statistical testing and modelling will be used to highlight interesting aspects of the data.

The continuous variables will be summarized using the following descriptive statistics:

- Number of patients (Number)
- Mean
- Standard deviation (SD)
- Median
- Minimum (min)
- Maximum (Max)
- Quartile 1 (Q1)
- Quartile 3 (Q3)
- Number of missing data (Missing)

Changes from baseline will be presented with its 95% confidence intervals.

For categorical variables including binary variables, the absolute (n) and relative frequency (%) will be summarized for each category at each scheduled visit.

All tables will be summarized by Japanese race.

Additionally, when appropriate, tables of efficacy endpoints (CDAI, PRO2 and SES-CD) in the remission-induction period will be summarized by:

- Sex: Male; Female
- Age: <35, 35-<50 , ≥50
- Previous biologics: Yes; No.
- Prior biologic treatment used of Crohn`s disease: Biologic naïve; 1 prior biologic failure; 2 prior biologic failures; ≥3 prior biologic failures
- CD-Type: Small intestine-type; Large intestine-type; Small and large intestine-type.
- CD duration: ≤5 years; > 5 years.
- CD-related surgery: Yes; No.
- Corticosteroids concomitant before randomization : Yes; No.
- Immunomodulators concomitant before randomization : Yes; No.
- Enteral nutrition concomitant before randomization : Yes; No.
- Baseline CDAI: ≤330; > 330.
- Baseline PRO2: ≤24; > 24.
- Baseline SES-CD: ≤15; > 15.

If one of the subgroups above has less than 5 patients, no results will be displayed.

Tables for adverse events in the remission-induction period will be summarized by:

- Sex: Male; Female
- Proclivity to hypohepatia: Yes, No
- Baseline eGFR: <30, 30-<60, 60-<90, ≥90

Five periods are defined in the study:

1) Remission-Induction Period (blind): comprises from day 0 to week 12. 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.

2) Rescue Period (Open label): comprises from week 12 to week 24 for non-responders. 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.

3) Extension Period (Open label): comprises from week 12 to week 52 for responders at week12 and from week 24 to week 64 for non-responders at week12. 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(responders) or Week 60(non-responders).

4) 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 and 70 days after the last administration of the IMP.

5) 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.

Four analysis periods are defined:

1) Remission-induction period: as defined above.

2) Rescue period: as defined above. This period will be used only for adverse events endpoints.

3) Entire administration period comprises the remission-induction period, the rescue period, the extension period and the post-observation period as defined above.

4) Follow-up period: as defined above.

Analyses of the remission-induction period will be performed after the remission-induction period is completed. Analyses of the entire administration period (remission-induction period, rescue period, extension period and post-observation period) will be performed after the post-observation period is completed. Analysis of the follow-up period will be performed after the follow-up period is completed.

In all TFLs that are displayed by treatment groups they will refer to the remission-induction treatments.

6.2 Missing Data Handling

6.2.1 Handling of adverse event missing/partial dates

Imputation of adverse events dates will be performed only for classification purposes.

If an adverse event date is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or post-treatment and any derivation that includes dates (e.g., period determination).

The algorithm for imputing start date will be conservative and will cover the following scenarios:

- If only day is missing, the day will be set to the first day of the month
- If the month and day are missing, the day and the month will be set to 1 Jan
- If the year, month and day are missing, no imputation will be performed

If the date does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent.

The algorithm for imputing end date will be conservative and will cover the following scenarios:

- If only day is missing, the day will be set to the last day of the month
- If the month and day are missing, the day and the month will be set to 31 Dec
- If the year, month and day are missing, no imputation will be performed

These data imputations are for categorization purpose only and will not be used in listings.

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events.

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events. These data imputations are for categorization purpose only and will not be used in listings.

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences the maximal severity will be imputed to “Severe”. These data imputations are for categorization purpose only and will not be used in listings.

6.2.2 Handling of any partial date required to calculate corresponding durations

For Crohn disease duration, partial dates will be imputed. If only the day is missing, the day will be replaced by the half-month-day. If the month is missing, the month will be replaced by June. No imputation of years will be done.

6.2.3 Handling of medication missing/partial dates

Imputation of medications dates will be performed only for classification purposes.

If a medication date is incomplete, an imputation algorithm will be used to classify the medication as prior or concomitant.

The algorithm for imputing start date will be conservative and will cover the following scenarios:

- If only day is missing, the day will be set to the first day of the month
- If the month and day are missing, the day and the month will be set to 1 Jan
- If the year, month and day are missing, no imputation will be performed

The algorithm for imputing end date will be conservative and will cover the following scenarios:

- If only day is missing, the day will be set to the last day of the month
- If the month and day are missing, the day and the month will be set to 31 Dec
- If the year, month and day are missing, no imputation will be performed

These data imputations are for categorization purpose only and will not be used in listings.

6.3 Patient Disposition

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as all patients who originally signed the informed consent.

Randomized patients consist of all screened patients with a treatment group allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not.

For the patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients
- Screen failure patients and reason for screen failure
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation

- Status at last study contact: Information collected will be compiled from the patient status panel and information of lost-to-follow-up status from the end of study (EOS) module of the eCRF which was defined as below.

Reason for study discontinuation will be described:

- Progression of the primary disease
- An adverse event unrelated to progression of the primary disease
- An inclusion criterion has turned out to be not met
- An exclusion criterion has turned out to be met
- The patient used prohibited drug(s) or drug(s) with restricted use
- The subject´s pregnancy has been confirmed
- Insufficient therapeutic effect (including less than 70 points decrease in CDAI after Rescue Phase)
- The subject requires a surgical operation
- Withdrawal of consent by the subject
- Lost to follow-up
- Discontinuation of the entire Study by the Sponsor
- Other reason by which the Study Treatment is not appropriate as judged by the Sponsor/Investigator

For all categories of patients (except for the screened and non-randomized categories), percentages will be calculated using the number of randomized patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. This summary will be provided by treatment group.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of patients with deviations by treatment group. The deviations will be defined and listed in the Protocol Deviation Document.

Additionally, the analysis populations for safety, efficacy will be summarized in a table by number of patients on the randomized population:

- Efficacy populations: FAS population, PPS population
- Safety population

6.3.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

- A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized twice

OR

- A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a non-randomized patient is treated with IMP reserved for randomized patients.
- Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages)

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Patient switched to another site

6.4 Demographics and Baseline Characteristics

Demographics and baseline variables (described in section 4.2) will be descriptively summarized.

6.5 Other Subject Characteristics

Anti-JC virus antibody test

Anti-JCV antibody test result (positive or negative) is judged according to the results of screen assay and inhibition assay. The results will be descriptively analyzed in the corresponding visit for each of the three analysis periods.

6.6 Study Windows

Week of evaluation for analysis will be defined in table 1 (similar approach as used in the E6011-J081-101 study).

See Table 1 Study Windows below for reference days:

Table 1 Study Windows

Analysis Visit Number	Analysis Visit	Target	Window	
			Lower	Upper
2	Baseline	1	-	-
3	Week 1	8	5	11
4	Week 2	15	12	18
5	Week 4	29	22	35
6	Week 6	43	36	49
7	Week 8	57	50	63
8	Week 10	71	64	77
9	Week 12	85	78	91
10	Week 13	92	-	95
11	Week 14	99	96	102
12	Week 16	113	106	119
13	Week 18	127	120	133
14	Week 20	141	134	147
15	Week 22	155	148	161
16	Week 24	169	162	175
17	Week 28	197	190	203
18	Week 32	225	218	231
19	Week 36	253	246	259
20	Week 40	281	274	287
21	Week 44	309	302	315
22	Week 48	337	330	343
23	Week 52	365	358	371
24*	Week 56	393	386	399
25*	Week 60	421	414	427
26*	Week 64	449	442	455

*Only for non-responders at week 12

The window for the post observational visit (28 days after completion/discontinuation of the treatment):

- For patients that discontinue treatment, the target day will be 28 days after the discontinuation date and the window will be [discontinuation date+1 , 58].
- For patients that complete the extension period or complete the rescue period but because of a lack of efficacy do not continue to the extension period, the target day will be 28 days after end of extension/rescue period date and the window will be [extension/rescue period end date +1 , 58].

Observation that has the most recent date-time on base date-time is adopted if plural observations exist in the time window.

In case that two or more assessments falling in the same window, the closest in absolute value to the target will be chosen. In case of a tie, the earliest assessment will be considered.

Pre-dose pharmacokinetic blood samples should be collected prior to dosing, no time window is advised for this sample. Post dose pharmacokinetic blood samples should be collected within a 10-minute time window starting from the end of the E6011 infusion.

Biomarker/pharmacogenomic samples should be collected during the following time windows specified below;

- During the remission induction period (all subjects), blood samples should be collected within ± 1 day during Week 1, and within ± 3 days during Weeks 2 to 12.
- During the extension period (responders), blood samples should be collected within ± 7 days during Weeks 16 to 52.
- During the rescue period (non-responders), blood samples should be collected within ± 1 day during Week 13, and within ± 3 days during Weeks 14 to 24.
- During the extension period (non-responders), blood samples should be collected within ± 7 days during Weeks 28 to 64.

6.6.1 Pharmacokinetic Sampling

Blood samples for the determination of serum E6011 concentrations are to be collected pre-dose and post the end of the infusion (within 10 minutes of the end of the infusion from week 0 to week 10). Blood samples will be collected as follows;

For all subjects during the remission-induction period blood samples will be collected during weeks 0, 1, 2, 4, 6, 8, 10, 12 and upon discontinuation.

During the extension period (responders) blood samples will be collected during weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and upon discontinuation.

During the rescue period (non-responders) blood samples will be collected during weeks 13, 14, 16, 18, 20, 22, 24 and upon discontinuation.

During the extension period (non-responders) blood samples will be collected during weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and upon discontinuation.

6.6.2 Biomarker Sampling

Blood samples for the determination of serum total FKN concentrations are to be collected as follows;

For All subjects during the remission-induction period blood samples will be collected during weeks 0, 1, 2, 4, 6, 8, 10, 12 and upon discontinuation.

Faecal samples for the determination of faecal calprotectin concentrations are to be collected as follows;

For All subjects during the remission-induction period faecal samples will be collected during weeks 0, 2, 4, 8, 12 and upon discontinuation.

During the extension period (responders) faecal samples will be collected during weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and upon discontinuation.

During the rescue period (non-responders) faecal samples will be collected during weeks 14, 16, 20, 24 and upon discontinuation.

During the extension period (non-responders) faecal samples will be collected during weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and upon discontinuation.

Blood samples for the determination of serum CRP concentrations are to be collected as follows;

For All subjects during the remission-induction period blood samples will be collected during weeks 0, 1, 2, 4, 6, 8, 10, 12 and upon discontinuation.

During the extension period (responders) blood samples will be collected during weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and upon discontinuation.

During the rescue period (non – responders) blood samples will be collected during weeks 13, 14, 16, 18, 20, 22, 24 and upon discontinuation.

During the extension period (non-responders) blood samples will be collected during weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and upon discontinuation.

6.6.3 Immunogenicity Sampling

Blood samples for the determination of Anti-E6011 antibodies are to be collected as follows;

For All subjects during the remission-induction period blood samples will be collected during weeks 0, 2, 4, 8, 12 and upon discontinuation.

During the extension period (responders) blood samples will be collected during weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and upon discontinuation.

During the rescue period (non-responders) blood samples will be collected during weeks 14, 16, 20, 24 and upon discontinuation.

During the extension period (non-responders) blood samples will be collected during weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and upon discontinuation.

6.7 Study Medication

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

Prohibited concomitant drugs	Generic name	ATC Code	Administration route
Biologics	Adalimumab	L04AB	
	Infliximab	L04AB	
	Ustekinumab	L04AC	
	Certolizumab pegol	L04AB	
	Natalizumab	L04AA	
	Vedolizumab	L04AA	
Adrenocorticosteroids injection/enema preparation	Dexamethasone	C05AA H02AB	Intravenous drip Intravenous bonus Subcutaneous Intramuscular Rectal
	Triamcinolone	C05AA H02AB	Intravenous drip Intravenous bonus Subcutaneous Intramuscular Rectal
	Hydrocortisone	A07EA C05AA H02AB	Intravenous drip Intravenous bonus Subcutaneous Intramuscular Rectal
	Prednisolone	H02AB H02BX	Intravenous drip Intravenous bonus

		A07EA C05AA	Subcutaneous Intramuscular Rectal
	Batamethasone	A07EA C05AA H02AB	Intravenous drip Intravenous bonus Subcutaneous Intramuscular Rectal
	Methylprednisolone	H02AB H02BX	Intravenous drip Intravenous bonus Subcutaneous Intramuscular Rectal
	Budesonide	A07EA	Intravenous drip Intravenous bonus Subcutaneous Intramuscular Rectal
Adrenocorticosteroids suppository	Diflucortolone	D07XC D07AC D07BC For diflucortolone there are only entries for ATC D (dermatological treatment)	Rectal
	Hydrocortisone	A07EA C05AA H02AB	Rectal
	Batamethasone	A07EA C05AA H02AB	Rectal
Immunomodulators (Except for topical use)	Cyclosporin	L04AD	Oral Sublingual Intravenous drip Intravenous bonus Subcutaneous Intramuscular Rectal Respiratory (Inhalation) Transdermal
	Tacrolimus hydrate	L04AD	Oral Sublingual Intravenous drip Intravenous bonus Subcutaneous Intramuscular Rectal Respiratory (Inhalation)

			Transdermal
	Mycophenolate mofetil	L04AA	Oral Sublingual Intravenous drip Intravenous bonus Subcutaneous Intramuscular Rectal Respiratory (Inhalation) Transdermal
Immunoglobulin products (Immunoglobulin preparations: J06B) or blood products	(Whole blood products)	B05A (blood and related products)	
	(Blood component products)	B05AA (blood substitutes and plasma protein fractions) B02BD (blood coagulation factors)	
	(Blood plasma fraction products)	B05AA B05AX	
Live vaccines	(Yellow fever)	J07BL	
	(Mumps)	J07BE J07BJ J07BD	
	(Tuberculosis)	J07AN	
	(Chicken pox)	J07BX	
	(Rubella)	J07BJ J07BD	
	(Measles)	J07BD	
	(Measles-rubella combination)	J07BD	
	(Rotavirus)	J07BH	
Investigational drug	(All investigational drugs)		

Extent of investigational medicinal product exposure and compliance.

Duration of IMP exposure is defined as date and time of last IMP administration – date and time of first double-blind IMP administration + 14 days, regardless of unplanned intermittent discontinuations. Duration will be presented in days.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and

cumulatively according to these categories: ≤ 1 week, (1 week, 4 weeks], (4 weeks, 8 weeks], (8 weeks, 12 weeks], (12 weeks, 22 weeks], (22 weeks, 48 weeks], (48 weeks, 60 weeks], >60 weeks.

Compliance:

A given administration will be considered non-compliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data. The percentage of noncompliant administrations will be descriptively summarized by treatment. Percentage of noncompliant administrations is defined as number of non-compliant administrations divided by the number of total administrations.

Treatment compliance (%) by period is defined as the actual number of IMP administration divided to the planned number of administrations.

Treatment compliance will be summarized by descriptive statistics for the FAS populations by treatment and study period. In addition, the percentage of patients per compliance level will be also summarized: ≤60%, (60%, 80%], (80% , 100%].

6.8 Efficacy Analysis

Efficacy analysis will be based in the FAS and PPS populations. Primary analysis will be produced in the FAS population. Primary analysis will be repeated in the PPS population as a sensitivity analysis.

Efficacy analysis will be done for the remission-induction period and the entire administration period.

6.8.1 Primary Efficacy analysis

Primary analysis aims to determine if the treatment effect in CR100 response rate at Week 12 is expected to be higher for patients treated with E6011 than for patients treated with placebo.

The Bayesian posterior distribution of the difference in the CR100 rate at Week 12 between E6011 (p1) and placebo (p2) is obtained as p1-p2 posterior distributions. Non-informative prior (Jeffreys) Beta (1/2, 1/2) distributions described by (Oleksandr Sverdlov, Yevgen Ryeznik, & Sheng Wu, January 1, 2015) will be used to calculate p1 and p2 posterior distributions.

A MCMC algorithm will be performed using the following parameters:

- Number of chains = 3
- Initial values for the algorithm in every chain= 3 starting values simulated by a Beta (0.5, 0.5)
- Number of Burn-in = 100000

- Number of Iterations = 200000

Diagnostic for the MCMC convergence will be checked though the Geweke Diagnostics test, Raftery-Lewis Diagnostics, Gelman-Rubin convergence and the autocorrelation efficiency. In case of any issue due to an autocorrelation or non-convergence of the algorithm, the size of the burn-in, the number of iterations and a possible thinning will be evaluated.

Efficacy of E6011 will be confirmed if there was a 50% or more probability of the difference between both groups being 25% according to the posterior distribution.

Probability of the difference between groups being greater than zero will be also calculated.

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

Primary analysis will be performed in the FAS population, and in the PPS population as a supportive analysis.

Two sensitivity analysis will be performed a Last Observation Carried Forward (LOCF) and an Observed Case (OC) imputation for CDAI at week 12 will be used instead of NRI.

Another supportive analysis will be performed following the same logistic regression model (randomization strata and treatment group as fixed factor) used in the secondary analysis.

6.8.2 Secondary Efficacy analysis

a. CDAI response rate (CR70) and remission rate at week 12 will be analyzed using logistic regression model considering randomization strata (Japanese/Non-Japanese and Male/Female) and treatment group as fixed factor. This model will estimate the Odds Ratio between the treatment arms.
   Also, the CDAI response rate (CR70, CR100) and remission rate are also to be described by treatment group week 2, week 4, week 8 and week 12.
   And finally, CDAI, change and percentage change from baseline will be descriptively analyzed too by treatment group at baseline, week 2, week 4, week 8 and week 12.

b. PRO2 response rate (PRO2-CR5, PRO2-CR8) and remission rate at week 12 will be analyzed using logistic regression model considering randomization strata (Japanese/Non-Japanese and Male/Female) and treatment group as fixed factor. This model will estimate the Odds Ratio between the treatment arms.
   Also, the PRO2 response rate (PRO2-CR5, PRO2-CR8) and remission rate are also to be described by treatment group week 2, week 4, week 8 and week 12.

And finally, PRO2, change and percentage change from baseline will be descriptively analyzed too by treatment group at baseline, week 2, week 4, week 8 and week 12.

c. SES-CD endoscopic response rate and endoscopic remission rate at week 12 will be analyzed using logistic regression model considering randomization strata (Japanese/Non-Japanese and Male/Female) and treatment group as fixed factor.
Also, the SES-CD endoscopic response rate and remission rate are also to be described by treatment group week 2, week 4, week 8 and week 12.
And finally, SES-CD endoscopic, change and percentage change from baseline will be descriptively analyzed too by treatment group at baseline, week 2, week 4, week 8 and week 12.

d. Steroid-free CDAI response rate (CR70, CR100) and remission rate will be described by treatment group at week 2, week 4, week 8 and week 12.

e. Steroid-free PRO2 response rate (PRO2-CR5, PRO2-CR8) and remission rate will be described by treatment group at week 2, week 4, week 8 and week 12.

f. The dose of adrenocorticosteroids related to Crohn's disease will be described using the change and percentage change from baseline by treatment group at baseline, week 2, week 4, week 8 and week 12.

The dose at baseline is calculated as the sum of doses in mg/day of all adrenocorticosteroids that are taken the baseline day. Doses at every visit are calculated as the sum of all adrenocorticosteroids taken from previous time point to the current visit date, for example, dose at week 2 is the sum of all doses taken from baseline to week 2 date.

Adrenocorticosteroids related to Crohn's disease will be identify as any concomitant corticosteroid at remission induction period in the database that has reported in the eCRF an indication to primary disease (Crohn's disease).Steroid free patients will be identified as patients that are taking any adrenocorticosteroid related to Crohn's disease at baseline and they stop taking them before week 12.

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 modeling of the endpoints.

Secondary analysis will be performed in the FAS population and in the PPS population.

6.8.3 Multiplicity considerations

No multiplicity issues are expected as the analysis will be mainly descriptive.

6.8.4 Other efficacy analysis

NA.

6.9 Safety Analysis

Safety will be evaluated in the Safety Population.

Adverse events and safety evaluations occurring during the four analysis periods (see section 6.1 for reference) will be analyzed. During the Follow-Up period only, adverse events categorized as PML will be collected.

6.9.1 Adverse Events

Treatment-emergent adverse events are adverse events that developed or worsened during the treatment-emergent adverse event period (from first date of IMP until last date of IMP +70 days).

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Post-treatment PML events will be described in a separate table, as well as pre-treatment, treatment emergent and post-treatment deaths.

Adverse events will be considered only in the period in which it starts.

The following summaries will be generated for the safety population.

a. Overview of adverse events during all study and by analysis period, summarizing number (%) of patients with any
   - Adverse event
   - Treatment-emergent adverse event
   - Serious treatment-emergent adverse event
   - Non-serious treatment-emergent adverse event
   - Treatment-emergent adverse event leading to death
   - Treatment-emergent adverse event leading to permanent treatment discontinuation
   - Treatment-emergent adverse event related to study drug

b. All adverse events during all study by primary SOC and PT, showing number (n) and percentage (%) of patients with at least 1 adverse event sorted by the SOC internationally agreed order. The other level (PT) will be presented in alphabetical order

c. All treatment-emergent adverse events by analysis period and by primary SOC and PT, showing number (n) and percentage (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other level (PT) will be presented in alphabetical order

d. All treatment-emergent adverse events related to IMP by analysis period and by primary SOC and PT, showing the number (n) and percentage (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other level (PT) will be presented in alphabetical order

e. All treatment-emergent adverse events by analysis period and by maximal severity, presented by primary SOC and PT, showing the number (n) and percentage (%) of patients with at least 1 treatment-emergent adverse event by severity (i.e., mild, moderate, or severe), sorted by the sorting order defined above.

f. All treatment-emergent serious adverse events by analysis period and by primary SOC and PT, showing the number (n) and percentage (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order.

g. All treatment-emergent non-serious adverse events by analysis period and by primary SOC and PT, showing the number (n) and percentage (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order.

h. All treatment-emergent serious adverse events related to IMP by analysis period and by primary SOC and PT, showing the number (n) and percentage (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other level (PT) will be presented in alphabetical order.

i. All treatment-emergent non-serious adverse events related to IMP by analysis period and by primary SOC and PT, showing the number (n) and percentage (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other level (PT) will be presented in alphabetical order.

j. All treatment-emergent adverse events leading to treatment discontinuation by analysis period and by primary SOC and PT, showing the number (n) and percentage (%) of patients sorted by the internationally agreed SOC order. The other level (PT) will be presented in alphabetical order. Information will be presented in two columns separately for all and related TEAEs leading to treatment discontinuation.

k. All treatment-emergent adverse events leading to death by analysis period and by primary SOC and PT, showing the number (n) and percentage (%) of patients sorted by the internationally agreed SOC order. Information will be presented in two columns separately for all and related TEAEs leading to death.

l. Number (n) and percentage (%) of patients who died by study period (pre-treatment, treatment-emergent, post-treatment).

m. All PML events during follow up by primary SOC and PT, showing number (n) and percentage (%) of patients with at least 1 one PML event sorted by the SOC internationally agreed order. The other level (PT) will be presented in alphabetical order

6.9.2 Laboratory

Laboratory parameters will be descriptively summarized by treatment and time point, see Table 2 for further reference.

Table 2 Laboratory Parameters

Category	Items
Haematology testing	White blood cell count (Leukocytes), red blood cell count (Erythrocytes), hemoglobin, hematocrit, platelet count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Blood biochemistry testing	
Liver function tests	Total bilirubin, ALP, AST, ALT, g GTP
Renal function tests	BUN, creatinine
Other tests	Plasma glucose, serum 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 (U/g creat), amylase (U/L)

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 categorized 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 at each visit.

In case that the total cell count of neutrophils, lymphocytes, monocytes, eosinophils, basophils is not given, and the percentage of them to the total white blood cell count is given, the total cell count of them can be derived as:

$$Total\ cell\ count\ of\ a\ specific\ white\ cell = \frac{Percentage\ of\ a\ specific\ white\ cell}{100} * Total\ WBC$$

In case that the percentage of cell count of neutrophils, lymphocytes, monocytes, eosinophils, basophils relative to total white cell count is not given, and the total count of them is given, the percentage of a specific white cell can be derived as:

$$Percentage\ of\ a\ specific\ white\ cell = \frac{Total\ cell\ count\ of\ a\ specific\ white\ cell}{Total\ WBC} * 100$$

6.9.3 Vital signs

Blood pressure (systolic, diastolic: mmHg), pulse rate (bpm), temperature (°C)], height (cm), and weight (kg) will be descriptively summarized by treatment and visit in the three analysis periods (see section 5.1 for further reference)

6.9.4 Standard 12-lead ECG examinations, neurological symptoms

Percentage of patients with any clinical finding (abnormal) along the first 12 weeks will be descriptively summarized by treatment group.

6.9.5 Blood CD4 positive cell count.

The number of CD4 (U/μL) will be summarized descriptively as quantitative variable by treatment and time point.

6.10 Other Analyses

6.10.1 Pharmacokinetic data handling

Lower Limit of Quantification (LLOQ) of Serum E6011 Concentration

The LLOQ of serum E6011 concentration is 0.1 μg/mL.

BLQ Handling for Calculation of PK Parameters

Not Applicable.

BLQ Handling for Developing Concentration–Time Profiles

When developing individual concentration–time profiles, BLQ values are replaced with

a. zero for time points prior to the first non–zero concentration following first dosing in a linear plot
b. "missing" for time points after the first non–zero concentration following first dosing in a linear plot
c. "missing" for all BLQ values in a semi–logarithmic plot.

When calculating the mean (or median) value for the concentration at a given time point, all BLQ values will be assigned as zero. If the proportion of values reported as BLQ is more than 50% or the calculated mean (or median) value is less than LLOQ at a time point, the value of mean (or median) is treated as:

a. zero for time points prior to the first non–zero mean (or median) concentration following first dosing in a linear plot
b. "missing" for time points after the first non–zero mean (or median) concentration following first dosing in a linear plot
c. "missing" for all BLQ values in a semi–logarithmic plot.

BLQ Handling for Developing Tables

BLQs are handled with same manner as the one in a linear plot for mean or median concentration profiles (see section 16.2.3)

Handling of anomalous concentration values

Anomalous values are those that are inconsistent with known or expected PK behavior of the drug, but are not defined on the basis of statistical tests for outliers. Individual concentrations deemed to be anomalous can be excluded from the PK analysis and median and mean profiles; such anomalous values will be identified in the report. Clear justification must be provided in the report for exclusion of any data.

General rules for presentation of drug concentrations and PK parameters

To show the presentation of individual/raw (raw, hereafter) values and summary statistics, the following rule should be applied: for drug concentrations, all of summary statistics (mean, median, and standard deviation (SD), raw minimum and maximum) have 3 significant digits.

Typical Variable	Standard Unit	N	Digit rule	Raw Minimum Maximum	Mean Median	SD
E6011 concentration	µg/mL	x	Significant digits	3	3	3

6.10.2 Pharmacokinetic Parameters

Serum concentrations of E6011 will be summarized using the pharmacokinetic analysis set. Summary statistics for serum E6011 concentrations are to be calculated for each specified sampling timepoint and treatment group.

Serum E6011 concentration-time profiles are also to be created.

6.10.3 Biomarker and Pharmacogenomic Parameters

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 levels, change and % 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. and blood $CD16^+$ monocytes etc. genetic markers are to be reported in a separately created report, and not included in the Clinical Study Report

6.10.4 Immunogenicity Analysis

The 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.

6.10.5 PK-PD Relationships

PK-PD relationships will be explored graphically, the geometric mean serum E6011 concentration time profile and PD biomarker time profile will displayed in the same graph on linear and semi log scales by dose. These plots will be generated by race (all patients, and by Japanese and non-Japanese patients).

Different endpoints and the corresponding PD biomarker will be displayed as a scatter plot and correlation coefficients should be calculated:

- E6011 concentrations
- CDAI
- PRO2
- SES-CD

These plots will be generated by race (all patients, and by Japanese and non-Japanese patients).

6.11 Modifications from the Statistical Section in the Protocol

There are no modifications from the statistical section in the protocol.

7 INTERIM ANALYSES

NA

8 SAMPLE SIZE AND POWER CALCULATIONS

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%.

9 STATISTICAL SOFTWARE

All statistical analyses, listing, tabulations and figures will be producing using SAS® Version 9.4 or later through fully validated and 21 CFR Part 11 compliant SAS Drug Development V3.3 interface.

10 GENERAL FORMAT OF TABLES, FIGURES AND SUBJECT DATA

Tables and listings will be produced in accordance with the principles outlined by the ICH E3 guideline. All summary tables will be presented by treatment group and race (all, Japanese and non-Japanese).

The design of the tables will be clear and concise so that comparative reading is easily possible.

All descriptive variables will be tabulated. Quantitative variables will be described showing their number of available and missing observations, mean and its CI (95% level), median, standard deviation, the range (minimum and maximum) and the first and third quartiles. Frequency and percentage will describe qualitative variables.

Missing values will be tabulated with their frequency but will not be included in the calculation of percentages. Analysis will be based on observed cases, i.e., no replacement of missing data is planned in general except otherwise planned in the appropriate statistical methodology section (section 11, section 12 or 14).

Pharmacokinetic data (E6011 serum concentrations) will be summarized by treatment group and race (All, Japanese and Non-Japanese) and evaluation time, including the number of sample results, minimum, medium, maximum, mean, standard deviation and coefficient of variation (CV). In addition, geometric means and geometric CV will be also shown.

Serum E6011 concentration vs time curves will be prepared. A serum concentration profile will be prepared for each subject and shown individually on a single plot per patient. A plot showing all serum profiles generated per treatment group will be prepared.

Summary serum E6011 concentration vs time profiles will also be prepared. A geometric mean serum profile will be shown by treatment group individually and grouped by treatment.

Pharmacodynamic data (serum total FKN concentrations, faecal calprotectin and serum CRP concentration measured values, change and % change from baseline) will be summarized by treatment group, evaluation time and race (all, Japanese and non-Japanese), including the number of sample results, minimum, medium, maximum, mean, standard deviation and coefficient of variation (CV). In addition, geometric means and geometric CV will be also shown.

Immunogenicity data (will be summarized by treatment group, evaluation time and race (all, Japanese and non-Japanese)) incidence and ratio of serum anti-E6011 antibodies are to be calculated by treatment group and evaluation time, and summarized including the number of sample results, minimum, medium, maximum, mean, standard deviation and coefficient of variation (CV). In addition, geometric means and geometric CV will be also shown.

11 REFERENCES

Oleksandr Sverdlov, P., Yevgen Ryeznik, M., & Sheng Wu, M. (January 1, 2015). Exact Bayesian Inference Comparing Binomial Proportions, with Application to Proof-of-Concept Clinical Trials. Therapeutics Innovation & Regulatory Science, Volume: 49 issue: 2, page(s): 163-174.