NOVARTIS

Translational Sciences

AIN457

Protocol No. CAIN457A2202

A multicenter, randomized, double-blind, placebo-controlled, parallel-group proof-of-concept study to assess the efficacy, safety and tolerability of two single iv infusions of AIN457 10 mg/kg (anti IL-17 monoclonal antibody) in patients with moderate to severe active Crohn's disease

Property of Novartis
It may not be used, divulged, published or otherwise disclosed
without the consent of Novartis

Study synopsis and assessment schedule

AIN457

Title of study: A multicenter, randomized, double-blind, placebo-controlled, parallel-group proof-of-concept study to assess the efficacy, safety and tolerability of two single iv infusions of AIN457 10 mg/kg (anti IL-17 monoclonal antibody) in patients with moderate to severe active Crohn's disease

Objectives:

Primary objective(s)

- Efficacy of AIN457 on mean Crohn's Disease Activity Index (CDAI) at 6 weeks

Secondary objective(s)

- Percentage of subjects achieving remission and/or response, as defined by CDAI <150 or a decrease of at least 70 points from baseline
- Percentage of subjects achieving remission, as defined by CDAI <150
- Percentage of subjects achieving response, as defined by a reduction in CDAI of at least 70 points
- Effect of AIN457 on mean CDAI at 2 and 4 weeks
- Area under CDAI score curve from week 4 to week 10
- Maintenance of remission and/or response during the follow-up period and at the end of study
- Pharmacokinetics of AIN457
- Safety and tolerability of AIN457

Exploratory Objective(s)

- Biomarker profile in moderate to severe active Crohn's disease
- Effect of AIN457 on biomarkers in Crohn's disease
- Concentration of IL-17 in blood
- Evaluation of individual (objective and subjective) parameters of CDAI
- Quality of life using Inflammatory Bowel Disease Questionnaire (IBDQ) at 6 weeks and end of study

The results from the exploratory objectives will be presented in the clinical study report as required.

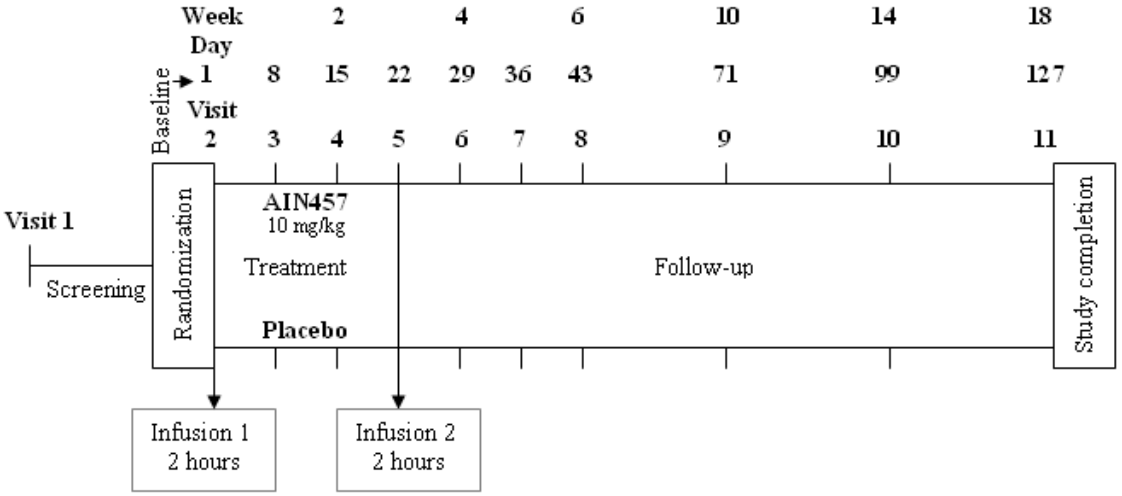
Design:

Proof-of-concept study to evaluate efficacy, safety and tolerability of AIN457 in moderate to severe active Crohn's disease.

Study consists of three periods: a screening period of maximum 28 days; a treatment period of 3 weeks and a follow-up period of 15 weeks.

Subjects who meet the inclusion/exclusion criteria at screening will undergo baseline evaluations and assessment of CDAI. All baseline safety results must be available prior to randomization and dosing.

Figure 0-1 Study design



Subjects with moderate to severe active Crohn's disease (CDAI ≥220 and ≤450), whose disease is not controlled on corticosteroids, immunosuppressant (e.g. methotrexate or purine metabolites), antibiotics or anti-inflammatory treatment (e.g. 5-ASA) will after signing the informed consent enter a screening period of a minimum of 7 days and a maximum of 28 days. Subjects considered eligible after screening will return for a baseline visit (Visit 2, Day 1). Baseline visit may be conducted over more than one day depending on each study site's logistical arrangements but no more than 3 days. In this case, the visit will still be considered as one visit. At baseline visit, if the eligibility of the subject is confirmed, the subject will be randomized (2:1 ratio) to receive either AIN457 given in a dose of 10mg/kg, or placebo administered as a 2 hours intravenous (i.v.) infusion.

Subjects will be participating on an outpatient basis and will be in-house only on infusion days (Days 1 and 22) for 4 hours post-infusion (after the start of the infusion). If any infusion-related or other adverse events occur, the subject will remain under observation until cleared by the investigator.

Following the first infusion, the subjects will be visiting the site on Day 2 for a 24 hour post-infusion (after the start of the infusion) pharmacokinetic (PK) sampling and sampling for biomarker analysis.

Subjects will return for weekly visits thereafter (Days 8 and 15) to assess the response to treatment and safety evaluation.

On Day 22 after the conduct of all efficacy and safety assessments (laboratory and CDAI), the subject will receive the second i.v. infusion of AIN457 or placebo and will remain at the site until 4 hour post-infusion blood samples are obtained and will return on Day 23 for the 24 hour post-infusion pharmacokinetic (PK) sampling and sampling for biomarker analysis.

Subjects will be observed for up to 15 weeks following the second infusion. Weekly study visits will continue until Day 43. From Day 43 onwards, until end of study (Day 127), the study visits will be performed every 4 weeks.

Subjects must attend all study visits as per study schedule until the end of the study. The study visits between two infusions should be performed on the specified days as per protocol. A visit window of ± 1 day is allowed in exceptional cases. For the study visits after Day 29, a visit window of ± 3 days is acceptable.

Every effort should be made to administer the second infusion on Day 22. However, exceptionally the second infusion may be administered on Day 22 + 3 days.

During the study period subjects will continue being evaluated for safety, disease recurrence and for the use of any subsequent treatment for Crohn's disease. If, in the investigator's opinion, the subject requires additional medical therapy for their Crohn's disease due to persistently high disease activity or worsening based on CDAI score (>400, or an increase by 100 points), the study treatment may be stopped and subjects may receive conventional treatment for active disease with corticosteroids, 5-aminosalicylates, immunosuppressive agents or antibiotics as per investigator's judgment. All subjects should remain in the study for safety assessment until study completion. All medications must be recorded on the Concomitant medications/Significant non-drug therapies CRF after the start of study drug.

Subjects will be allowed to take loperamide or diphenoxlate+atropine for the control of diarrhea at any time during the study. Use of loperamide must be recorded on the Concomitant medications/Significant non-drug therapies CRF after the start of study drug.

All subjects will undergo study completion evaluations and will be discharged from the study. Study completion evaluations will also be performed for subjects who discontinued the study earlier than planned end of study.

Subjects will be assessed for safety and tolerability of AIN457 throughout the study until the last study visit (Day 127). The follow-up period of 15 weeks after the second infusion is based on the maximum possible expected lag time between administration of AIN457 and possible appearance of late-developing adverse events (AEs).

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis), adverse event and serious adverse event monitoring.

The pharmacokinetics of AIN457 and changes of IL-17 in serum will be investigated at several visits throughout the study (see PK and IL-17 assessment section below).

The exploratory goals of this study are to define the biomarker profile in subjects with moderate to severe active Crohn's disease and to characterize whether AIN457 treatment will affect the disease specific biomarkers.

Serum protein markers will be measured to identify potential blood markers associated with active Crohn's and treatment response to AIN457. The following markers will be determined: CRP (C-reactive protein) and soluble serum protein markers related to the targeted pathway including TNFα, IFNγ, IL-1β, IL-6, IL-8, IL12p40, and IL-23. The assessments will be completed at baseline, at visits throughout the study and at study completion.

Fecal calprotectin, a Ca^{2+} binding protein from neutrophils, will be analyzed as a specific marker for gut inflammation to explore its relationship to clinical efficacy.

Gene expression (mRNA) patterns of blood cells will be determined at several visits throughout the study if agreed by the subject, to possibly monitor disease activity and identify potential response markers.

Exploratory pharmacogenetic assessments will be performed if agreed by the subject, to examine whether individual genetic variation in genes related to Crohn's disease and drug target pathway confer differential response to AIN457.

For a detailed outline of safety assessments, please refer to the assessment table.

Further details on study design are presented in Section 4.

Subject replacement: Subjects who discontinued from the study prematurely will not be replaced. In the case of study discontinuation, subjects will be required to undergo all assessments at the study completion visit.

Interim Analysis: The first interim analysis was performed on 17 patients. An additional interim analysis will be conducted when at least 30 patients have completed their visit at 6 weeks.

The primary CDAI analysis and key safety analysis will be performed to obtain preliminary safety and efficacy data in this disease population. The aim of the interim analysis is to be able to evaluate and stop the study early for success or futility.

The final analysis will be performed in 2 steps. The primary CDAI analysis and key safety analysis will be performed after the complete population of 60 patients has reached 6 weeks. The full analysis will be performed after all patients remaining in the study reached the LPLV after 15 weeks of follow-up phase.

All patients who complete the study up to and including visit 8 (6 weeks) will be offered to enter an extension study, which is run to provide long term safety and efficacy data, as well as extended follow-up and access to AIN457 to these patients. Details are defined in a separate study protocol. The last visit in the core trial will be the EOS visit of this patient (all assessments of EOS performed) and at the same time also serve as the baseline visit of the extension trial.

Planned number of subjects:

Seventy-two (72) subjects (48 on AIN457 and 24 on placebo) will be enrolled, for a total of at least 60 evaluable subjects (40 on AIN457 and 20 on placebo), to account for anticipated dropouts.

Patient population:

The study population will comprise subjects who have passed screening assessments, comply with inclusion / exclusion criteria and have provided written consent:

Inclusion criteria:

1. Male or female; 18-75 years old
2. All female subjects must have negative pregnancy test results at screening and baseline.

   Women of childbearing potential (WoCBP) must be using simultaneously double-barrier or two acceptable methods of contraception, (e.g., intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc., hormone replacement as either oral or implantable is acceptable as one form), from the time of screening and for the duration of the study, through study completion and for 4 months following study completion.

   Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

   Postmenopausal females must have had no regular menstrual bleeding for at least two (2) years prior to initial dosing. If menopause is confirmed by a serum FSH level of >40 IU/L at screening, pregnancy test will be required only at screening.

   Female subjects who report surgical sterilization must have had the procedure at least six (6) months prior to initial dosing. Surgical sterilization procedures should be supported with clinical documentation made available to the sponsor and/or Principle Investigator and noted in the Relevant Medical History / Current Medical Conditions section of the CRF.

   If female subjects have male partners who have undergone vasectomy, the vasectomy must have occurred more than six (6) months prior to first dosing.
3. Male subjects willing to use simultaneously two acceptable methods of contraception (e.g. spermicidal gel plus condom) for entire duration of the study, up to the study completion visit and at least for 6 months following the completion of the study.

   Periodic abstinence and withdrawal are not acceptable methods of contraception.
4. Diagnosis of Crohn's disease for at least 3 months prior to screening
5. Confirmation of Crohn's disease by endoscopic or imaging examination
6. Moderate to severe active Crohn's disease at baseline, defined as:

- CDAI ≥220 and ≤450

Note: Baseline CRP values may be either within normal limits or elevated. However, not more than 50% of all patients included in the trial should belong to the subgroup of patients with normal CRP values. The upper limit of normal (ULN) for serum CRP is defined as ≤10mg/L (≤1mg/dL).

7. Patients with active disease despite prior treatment with corticosteroids for at least 2 weeks, or immunosuppressants for at least 3 months.

   Patients who are being treated with azathioprine, 6-MP or MTX are eligible but must have been on a stable dose for at least 10 weeks prior to baseline.

   Patients treated with corticosteroids are eligible but must have been on a stable doses of prednisone not exceeding 40 mg for two weeks prior to baseline.

   Patients who are being treated with immunosuppressants other than those listed above, such as cyclosporine, tacrolimus and mycophenolate, are not eligible. These subjects will be required to stop immunosuppressants prior to baseline. These patients are eligible after observing a wash out period as specified in Exclusion criterion #7.
8. Absence of clinically relevant abnormalities for screening laboratory test results
9. Able to communicate well with the investigator, and to understand and comply with the requirements of the study.
10. Understand and sign the written informed consent.

Exclusion criteria

1. Body Mass Index >34
2. Positive Purified Protein Derivative (PPD) tuberculin skin test of ≥ 5 mm at screening or 6 months prior to screening A positive PPD test will be defined using the [MMWR 2000 guidance], summarized as criteria for tuberculin positivity by risk group.

   A PPD test should not be done in subjects who had a tuberculosis vaccination in the past. These subjects will be eligible to participate if – according to local guidelines – latent tuberculosis can be excluded.

   For those study sites using QuantiFeron test a positive test at screening will exclude the subject from the participation in the study.

   If the result for either PPD or QuantiFeron test is indeterminate, the subject will be excluded.
3. Subjects with symptoms associated with active bowel structuring disease and pre-stenotic dilation on radiography.
4. Fistulizing disease if complicated by sepsis and/or untreated abscess.
5. Subjects with multiple bowel surgeries and clinically important short bowel syndrome defined as an inability to maintain caloric intake.
6. a. Concomitant treatment with anti-TNF-α therapy (or other biological therapy) and systemic immunosuppressive agents such as ***c***yclosporine, mycophenolate, pimecrolimus, or tacrolimus**,** except azathioprine, its metabolite 6-MP and MTX.

   The following washout period will be required for subjects to be eligible to participate in the trial.

   - Three (3) months washout prior to baseline for certolizumab
   - Two (2) months washout prior to baseline for adalimumab, etanercept and infliximab
   - One (1) month washout prior to baseline for cyclosporine, mycophenolate, pimecrolimus, tacrolimus, and any other systemic immunosuppressants not listed under exclusion criterion # 7b

   b. Patients who are being treated with azathioprine, 6-MP and MTX are eligible but must have been on a stable dose for at least 10 weeks prior to baselina and throughout the whole study period.
7. Prior therapy with rituximab.

8. Receiving corticosteroids dose equivalent to a >40mg dose of prednisone per day.
9. Subjects demonstrating clinical improvement due to other Crohn's therapy.
10. Current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, psychiatric, or other disease which would make the subject unsuitable for the trial.
11. Subjects with active or history of clinically significant cardiac abnormalities, for example:
    - Requiring drugs with QT-prolonging properties (e.g. antiarrhythmic drugs, such as amiodarone, solalol, dofetilide, quinidine, procainamide, disopyramide).
    - QTc >450msec, long QT-syndrome (own or with a family history) or with a family history of sudden unexplained death.
    - Left branch bundle block (LBBB), or subjects who have been hospitalized for heart failure of cardiac etiology in the previous 6 months, and subjects who have significant and persistent left-ventricular dysfunction (LVEF < 40%).
    - History of, in the preceding 3 months, significant and persistent arrhythmias such as ventricular fibrillation or tachycardia, or atrial fibrillation or flutter.
    - Symptomatic coronary artery disease.
    - Presence of severe cardiac disease (New York Heart Association Classification ≥ III) and/or an abnormal ECG and considered by the investigator unsafe for the study.
12. Liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), γ-GGT, alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
    - Any ***single parameter*** may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error.
    - If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L).

    Re-check results must be within normal limits (or returning to within normal limits) in order for subject to qualify.
13. Total WBC count which falls outside the range of 4500–13,000/µl, or platelets <100,000/µl at screening.
14. History of severe hypersensitivity to any biological agents (antibody or soluble receptor), including serious allergic reaction (hypotension, wheezing, urticaria), lupus-like syndrome, or demyelinating disease.
15. Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing or longer if required by local regulation.
16. Administration of live vaccines within 6 months prior to dosing.
17. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
18. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
19. Significant illness within the two weeks prior to dosing or any active systemic infection or medical condition that may require treatment or therapeutic intervention during the study.
20. Subject with:
    - History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine >1.3 mg/dL or blood urea nitrogen (BUN) >30 mg/dL, or the presence of greater than +1 albumin on the urinary dipstick.
    - Presence of proteinuria, active sediments, casts or WBCs in urine.
    - Evidence of urinary obstruction or difficulty in voiding at screening.

- History of renal trauma, glomerulonephritis, or subject with one kidney.

21. History of malignancy (other than basal cell carcinoma or adequately treated carcinoma-in-situ of the cervix).
22. Unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins
23. Conditions associated with an immune-compromised condition such as recent surgical procedure; or history of drug or alcohol abuse within the 12 months prior to dosing. Subjects, who are unable to discontinue analgesic medications containing opiates and opioids, as well as cannabinoids for medical use.
24. Participation in any clinical investigation within four (4) weeks prior to initial dosing or five half-lives of the investigational agent, whichever is longer, and for any other limitation of participation based on local regulations.

Full inclusion / exclusion criteria are presented in Section 5.1.1 and Section 5.1.2 respectively.

Investigational drug:

AIN457 50 mg vials

AIN457 is a fully human monoclonal antibody against human IL-17A.

AIN457 is supplied as 50 mg lyophilized cake (Powder for Solution for Infusion): Reconstitution with 1.2 mL sterile water for infusion (SWFI) will produce a 47 mg/mL concentrate solution for infusion. The AIN457 concentrate will be diluted in 250 mL 5% glucose bags for infusion through a 0.2 micron in-line filter.

The concentrated solution for infusion contains AIN457 in an isotonic solution of histidine, sucrose and Polysorbate 80. The formulation does not contain a preservative and is to be used for single-dose administration only. After reconstitution, the solution in the vial must be stored at room temperature no longer than 4 hours or refrigerated at 2-8 °C no longer than 18 hours.

AIN457 Placebo vials must be handled the same way as AIN457 50 mg vials.

Comparator drug:

No active comparator is used in this study.

Duration of study and treatment:

Two i.v. infusions given over 2 hours each (Day 1 and Day 22) with primary endpoint at 6 weeks following first infusion and follow-up to 15 weeks after the second (last) infusion. Total duration of the study for each subject will be a minimum of 19 weeks or a maximum of 22 weeks.

Assessments and evaluations:

The following assessments will be performed during the study. Specific timings are presented in the assessment schedule.

Details on measurement / recording of the assessments and collection of samples are presented in the main text of the protocol.

All references to “pre-dose” refer to prior to the infusion and “post-dose” refer to after the start of the infusion.

All samples (blood and feces) will be sent to a central laboratory who will be either perform analysis or distribute the samples to various reference laboratories for analysis.

Background, demographic and administrative assessments

- Inclusion/exclusion criteria; relevant medical history/current medical conditions

- Demography
- Physical examination

  A complete physical exam must be done at screening, baseline, prior to second infusion and study completion. At the remaining time points, the physical exam should focus on major body systems, including heart, lungs, abdomen, extremities, skin (including oral mucosa) and lymph nodes.
- Hepatitis screen, HIV screen
- Pregnancy test: serum and urine

  Pregnancy test at all visits except screening may be omitted in post-menopausal women for whom menopause is confirmed and documented by elevated serum FSH at screening.
- FSH in post-menopausal women to confirm/document menopause by elevated serum FSH (>40 IU/L).

  PPD skin test or QuantiFeron test
- Drug administration
- Study completion information
- Comments

Efficacy assessments

- Crohn's Disease Activity Index (CDAI)
- Components for CDAI:
  - Patient diary
  - Symptoms or findings related to Crohn's disease
  - Diarrhea medication (Lomotil®/diphenoxylate+atropine or opiates)
  - Presence of an abdominal mass
  - Hematocrit; by local lab to allow timely assessment of CDAI
  - Body weight
- Patient-reported outcomes as an exploratory objective; IBDQ (Inflammatory Bowel Disease Questionnaire). The questionnaire will be completed by the subject prior to any study assessment.
- Subsequent treatments for Crohn's

Safety and tolerability assessments

- Vital signs and body measurements
  - Body height
  - Body weight
  - Body temperature
  - Blood pressure, pulse rate

    Note: measurements are supine. At screening and baseline measurements are supine and after 3 min standing if deemed necessary by the investigator.

    Body temperature, blood pressure and pulse rate will be measured on the infusion days during the infusion and after the infusion. Measurements will be pre-infusion and then every 15 minutes during the infusion (2 hours) and every 30 minutes during two hours after the end of the infusion.

    Body temperature, blood pressure and pulse rate will be measured also at 24 hours post infusion.
- ECG evaluation
- Hematology; Blood chemistry; Urinalysis

At baseline (Day 1) both by central lab and local lab. The randomization of the subject will be based on the local lab assessment for hematology, blood chemistry and CRP, provided that all screening lab results from central lab are within acceptable ranges as judged by the investigator and the subject meets all other entry criteria. This is to avoid any delay in the randomization.

- **Adverse events:** from time of first administration of study drug until study completion. Adverse events occurring before starting study treatment but after signing the informed consent are recorded on the Medical History/Current Medical Conditions CRF.
- **Serious adverse events**: from time of consent until 4 weeks after Study Completion
- **Concomitant medications/Significant non-drug therapies:** Refer to entry criteria (Section 5.1) and Concomitant medication (Section 6.6.5) for details of recording requirements for allowed and restricted medications during the study.
- Medication taken prior to first dosing: all prescription medications taken within one month, and over-the-counter drugs (including vitamins, herbals and alternative therapies) taken within 14 days prior to baseline and throughout the study must be recorded on the Concomitant Medications/ Non-Drug Therapies CRF.
- Immunogenicity (anti-AIN457 antibody in serum): one (1) mL blood per sample in plain barrier tubes to obtain 0.5 mL serum.

  Any subject testing positive for antibodies will be retested every 3 months until antibody levels return to baseline when no longer detected or stable for 1.5 years.

Pharmacokinetic assessments

- Blood collection:

  Three (3) mL blood per sample in plain barrier tubes (serum) to obtain 1.5 mL of serum.

  On dosing days (Day 1 and Day 22) samples will be taken at pre-dose (0 h), 1 h, 2 h, 4 h and 24 h post-dose (from the start of the infusion). At other study visits, one sample will be taken at any time during the study visit.
- Analytes:

  Media and methods: determination of AIN457 concentration in serum by a competitive ELISA assay.
- PK parameters: AUC_{0-t}, AUC_{inf}, AUC_{τ}, C_{max}, t_{max}, $t_{½}$, λ_z, CL, V_z and V_{ss} from serum concentration-time data

Pharmacodynamic assessments

Quantification of serum IL-17: all sampling to coincide with the sampling for PK. Four (4) mL blood per sample in plain barrier tubes to obtain 2 mL of serum. On dosing days (Day 1 and Day 22) samples will be taken at pre-dose (0 h), 1 h, 2 h, 4 h and 24 h post-dose (from the start of the infusion). At other study visits, one sample will be taken at any time during the study visit.

Biomarkers

C-reactive protein (CRP): study sites will be blinded to the CRP results after randomization in order to eliminate the risk for unblinding of treatment.

Calprotectin /Lactoferrin in faeces: analysis of fecal calprotectin and lactoferrin as non-invasive, inflammatory disease marker by ELISA to explore its relationship to clinical efficacy. Approx. 2 x 5g feces are collected into 30mL stool collection tubes.

Soluble protein panel in serum: serum levels of proteins (TNFα, IFNγ, IL-1β, IL-6, IL-8, IL12p40, and IL-23) will be explored as a measure of inflammation induced changes in CD patients. Two (2) mL whole blood are collected into EDTA tubes to obtain approx. 1 mL of serum.

Exploratory Biomarkers assessments:

Pharmacogenomics

A single 5 mL blood sample will be collected in two PAXgene tubes at 5 different time points from each subject who agrees, in writing, to participate in the biomarker assessments (optional). The blood draw at baseline pre-dose is necessary in order to perform relevant analysis between pre- and post-dose treatment.

Pharmacogenetics

A single 10 mL blood sample will be collected in an EDTA tube at baseline from each subject who agrees, in writing, to participate in the biomarker assessments (optional). If the baseline time point is missed for any reason, the blood sample should be drawn at the next scheduled blood draw.

Estimated total blood volume taken per subject: 367 mL.

Statistical methods

Primary target variable and analysis: A Bayesian approach will be adopted to assess the efficacy of AIN457 in Crohn's disease as measured by the change from baseline in the Crohn's Disease Activity Index (CDAI) 6 weeks after infusion 1, that is, at visit 8 (primary endpoint and analysis). For subjects dropping out because of persistently high disease activity or worsening, the last available observation will be carried forward. A Bayesian posterior distribution will be calculated for the difference, AIN457 minus placebo, of the CDAI changes from baseline. Posterior probabilities that (a) AIN457 reduces the CDAI more than placebo, and that (b) AIN457 reduces the CDAI by at least 50 points more than placebo, will be derived from this distribution. If, at the interim (see below) or final analysis, probability (a) is at least 95% and probability (b) is at least 50% ("50% level of proof at 50 points"), then this will be considered a positive proof-of-concept.

Interim Analysis: The first interim analysis was performed on 17 patients. An additional interim analysis will be conducted when at least 30 patients have completed their visit at 6 weeks.

The primary CDAI analysis and key safety analysis will be performed to obtain preliminary safety and efficacy data in this disease population. The aim of the interim analysis is to be able to evaluate and stop the study early for success or futility, if needed. The study will be stopped for success if the criterion for positive PoC (see section 10.7) is already met. The study will be stopped for futility if at this interim analysis, the posterior probability that AIN457 reduces the CDAI by less than 40 points more than placebo is at least 90%.

The final analysis will be performed in 2 steps. The primary CDAI analysis and key safety analysis will be performed after the complete population of 60 patients has reached 6 weeks. The full analysis will be performed after all patients remaining in the study reached the LPLV after 15 weeks of follow-up phase.

Secondary analyses: Analogous secondary analyses will be performed (separately) for the data from week 2 (visit 4), week 4 (visit 6) and week 10 (visit 9). The time course of the CDAI over all available time points will additionally be evaluated descriptively by treatment group. This will also be done separately for the sum scores of the "subjective" (items 2 and 3) and the "objective" (all other items) parts of the CDAI.

The area under the CDAI score curve from week 4 to week 10 will be analyzed by means of an analysis of covariance model, incorporating the baseline CDAI score as continuous covariate, and testing the null hypothesis of no treatment difference between AIN457 and placebo.

Three dichotomized endpoints are defined based on the CDAI:

1. remission: CDAI < 150 points
2. response: CDAI reduction from baseline of at least 70 points
3. remission or response: CDAI <150 points or CDAI reduction from baseline of at least 70 points.

For each of the three binary target variables based on a dichotomization of the CDAI, frequency tables will be produced by treatment group and time point. That is, frequency tables will display the number of subjects achieving remission (response; either of the two), and p-values will be displayed based on a

chi-square test of the null hypothesis of no treatment difference between AIN457 and placebo. Analogous evaluations may also be considered, where “response” is defined as a CDAI reduction from baseline of at least 70 points.

Maintenance of remission and/or response will be analyzed based on the subjects that have achieved remission (CDAI < 150 points) 6 weeks after infusion 1 (visit 8) only. These subjects will be classified with respect to whether or not they are still in remission at week 10, and similarly (separately) for all subsequent time points. Frequency tables will be produced by treatment group and time point, and p-values will be displayed based on a chi-square test of the null hypothesis of no treatment difference between AIN457 and placebo.

Safety and tolerability variables including vital signs, AEs, ECG and laboratory variables, as well as demographic information, will be analyzed in a descriptive manner by treatment group and time point. Descriptive statistics for background and demographic variables such as age, weight, height, and gender will be provided by treatment group. Descriptive statistics will also be used for the evaluation of the pharmacokinetic variables and to correlate clinical outcome with biomarker data.

Prior distributions: The prior probability distribution for placebo will draw information worth 20 patients from six previous studies with comparable patient population (Hanauer et al., 2006; Sandborn et al., 2001a; Sandborn et al., 2001b; Sandborn et al., 2007a; Sandborn et al., 2007b; Winter et al., 2004). Based on the same references, 88 points is used for the standard deviation of the CDAI changes from baseline. For AIN457, a "flat" non-informative prior probability distribution will be assumed.

Sample size determination

A sample size of 60 evaluable subjects (40 on AIN457, 20 on placebo) was determined based on historic data to allow for a robust comparison between the treatment arms. Together with the incorporated historical information (worth 20 subjects on placebo, see above), the information is balanced over the treatment arms. Assuming a CDAI reduction of 50 points under placebo, the probability of concluding positive PoC is about 1% if AIN457 is equal to placebo, and it is above 90% if AIN457 reduces the CDAI by 70 points more than placebo. To account for anticipated dropouts, 72 subjects will be included in this study (48 on AIN457, 24 on placebo).

Assessment schedule

Study phase	Screening	Baseline Randomization		Treatment				Follow-Up					Study Completion
[1] Visit Numbers	1	2[3]		3	4	5[3]		6	7	8	9	10	11 (777)
[2]Time (Day)	D -28 to 0	1	2 24h post-infusion	8	15	22[2]	23 24h post-infusion	29	36	43	71	99	127
Inclusion /Exclusion criteria	X	X[4]											
Relevant medical History / Current medical conditions	X	X[4]											
Demography	X												
Physical examination[5]	X	X		X	X	X		X	X	X	X	X	X
Hepatitis and HIV screen	X												
Serum pregnancy test[6]	X												X
Urine pregnancy test[6]		X		X	X	X				X	X	X	
FSH to confirm menopause[7]	X												
PPD tuberculin skin test or QuantiFeron test	X[8]												
Vital signs and body measurements													
Body height	X												
Body weight	X	X		X	X	X		X	X	X	X	X	X
Body temperature	X	X[10]	X	X	X	X[10]	X	X	X	X	X	X	X
Blood pressure / Pulse rate[9]	X[9]	X[9,10]	X	X	X	X[10]	X	X	X	X	X	X	X
ECG evaluation	X	X		X	X	X		X	X	X	X	X	X
Hematology, Blood chemistry, Urinalysis	X	X[11]		X	X	X		X	X	X	X	X	X
Hematology, Blood chemistry and CRP at local lab		X[11]											
Adverse Events[12]		As required											
Concomitant meds/Therapies	As required												
Blood collection[13]													

Study phase	Screening	Baseline Randomization		Treatment				Follow-Up					Study Completion
[1] Visit Numbers	1	2[3]		3	4	5[3]		6	7	8	9	10	11 (777)
[2]Time (Day)	D -28 to 0	1	2 24h post-infusion	8	15	22[2]	23 24h post-infusion	29	36	43	71	99	127
PK		X[14]	X	X	X	X[14]	X	X	X	X	X	X	X
Immunogenicity[15]		X				X					X		X
IL-17		X[14]	X	X	X	X[14]	X	X	X	X	X	X	X
CRP[16]	X	X	X	X	X	X	X	X	X	X	X	X	X
Soluble proteins		X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenomics (mRNA)		X	X			X	X						X
Pharmacogenetics		X[17]											
Stool sampling (fecal calprotectin)[13]		X		X		X		X		X			X
Crohn's disease activity index (CDAI)		X		X	X	X		X	X	X	X	X	X
Patient diary (frequency of stools; abdominal pain; general wellbeing)		X		X	X	X		X	X	X	X	X	X
Symptoms or findings related to Crohn's disease		X		X	X	X		X	X	X	X	X	X
Diarrhea medication (loperamide, diphenoxylate+atropine or +opiates)		X		X	X	X		X	X	X	X	X	X
Presence of an abdominal mass		X		X	X	X		X	X	X	X	X	X
Hematocrit by local lab for CDAI assessment		X		X	X	X		X	X	X	X	X	X

Study phase	**Screening**	**Baseline Randomization**		**Treatment**				**Follow-Up**					**Study Completion**
[1] Visit Numbers	1	2[3]		3	4	5[3]		6	7	8	9	10	11 (777)
[2]Time (Day)	D -28 to 0	1	2 24h post-infusion	8	15	22[2]	23 24h post-infusion	29	36	43	71	99	127
Inflammatory Bowel Disease Questionnaire (IBDQ)[18]		X								X			X
Call to IVRS for randomization		X											
Drug administration record		X				X							
Subsequent treatments for Crohn's				X	X	X	X	X	X	X	X	X	X
Comments	As required												
Study completion information													X

[1] Visit structure given for internal programming purpose only.

[2] Baseline visit may be conducted over more than one day (but no more than three days) depending on each site's logistical arrangements. A visit window of ± 1 day is allowed between Day 1 and Day 22 and for Day 29. Second infusion must be administered on Day 22 + 3 day. For visits after Day 29, a visit window of ± 3 days is acceptable. Screening and early morning assessment will be performed after an overnight fast.

[3] All assessments and samples at baseline and Day 22 should be performed pre-infusion.

[4] Review of inclusion and exclusion criteria and current medical conditions is required at baseline evaluation.

[5] A complete physical exam is required at screening, baseline and study completion. At the remaining timepoints, the physical exam should focus on major body systems, including heart, lungs, abdomen, extremities, skin and lymph nodes.

[6] Pregnancy test at all visits except screening may be omitted in post-menopausal women, for whom menopause is confirmed and documented by elevated serum FSH at screening.

[7] Only in post-menopausal women.

[8] At screening or within 6 months prior to screening. The results must be available prior to baseline/randomization. The test is not required for subjects who had tuberculosis vaccination in the past.

[9]Measurements are supine. At screening and baseline the measurements are supine and after 3 minutes standing if deemed necessary by the investigator.

[10] Baseline, pre-infusion, every 15 minutes during the infusion (2 hours) and every 30 minutes during 2 hours after the end of infusion.

[11]Provided that all screening lab results from central lab are within acceptable ranges as judged by the investigator and the subject meets all other entry criteria, the site may use the local lab results at baseline to randomize the subject.

[12]Serious adverse events will be collected from the time the subject signs the informed consent

[13] Sample collection on dosing days will be pre-infusion.

[14]Samples will be taken pre-infusion, 1 hour, 2 hours (or at the end of infusion) and 4 hours after the start of infusion.

[15]Any subject testing positive for antibodies will be retested every 3 months until antibody levels return to baseline when no longer detected or stable or at 1.5 years.

[16]The sites will be blinded to the CRP results after the randomization.

[17]If sampling missed for any reason, the blood sample should be drawn at the next scheduled blood draw.

[18] The questionnaire will be completed by the subject prior to any other study assessment.

Supplementary File 2 - Secondary Endpoints

	Secukinumab N=39	Placebo N=20	∆Secukinumab - Placebo	p-value
LS Mean (SE)	280 (14)	231 (19)	49 (23)	0·043*
95% CI	(252, 309)	(194, 269)	(2, 96)	

2a: Average scores (week4-10) based on area under the CDAI curve week 4- week 10) analysis

Week	Secukinumab N=39 n (%)	Placebo N=20 n (%)	∆Secukinumab - Placebo (95% CI)	p-value
2	1 (3)	4 (20)	-0·17 (-0·36, 0·01)	0·075
4	3 (8)	3 (15)	-7 (-25, 10)	0·671
6	4 (10)	3 (15)	-5 (-23, 14)	0·914
10	5 (13)	4 (20)	-7 (-28, 13)	0·731
14	4 (10)	2 (10)	0 (-16, 16)	1
18	5 (13)	2 (10)	3 (-14, 20)	1

2b: Patients with remission (CDAI<150 points)

Week	Secukinumab N=39 n (%)	Placebo N=20 n (%)	∆Secukinumab - Placebo (95% CI)	p-value
2	4 (10)	3 (15)	-0·05 (-0·23, 0·14)	0·914
4	5 (13)	4 (20)	- 7 (-28, 13)	0·731
6	7 (18)	6 (30)	-12 (-35, 11)	0·468
10	7 (18)	6 (30)	-12 (-35, 11)	0·468
14	8 (21)	3 (15)	6 (-35, 11)	0·872
18	6 (15)	3 (15)	0 (-19, 20)	1

2c: Patients with CDAI reduction of ≥100 points

	Secukinumab N=22	Placebo N=11	∆Secukinumab-Placebo	p-value
LS Mean (SE)	283 (18)	221 (26)	62 (31)	0·054
95% CI	(247, 320)	(170, 273)	(-1, 125)	

2d: Post hoc subgroup analysis· Average scores (week 4-10) based on area under the CDAI curve : Inflammatory subgroup (N =33)

	Secukinumab N=17	Placebo N=9	∆Secukinumab - Placebo	p-value
LS Mean (SE)	253 (21)	245 (29)	8 (35)	0·826
95% CI	(211, 294)	(187, 302)	(-63, 78)	

2e: Post hoc subgroup analysis· Average scores (week 4-10) based on area under the CDAI curve: Non-inflammatory subgroup (N = 26)

Legend Table a,d,e: LS mean = least square mean; * = p value considered significant if <0·05

Supplementary File 3: Candidate SNPs tested in pharmacogenetic analysis

dbSNP ID	chromosome	position	gene(s) of interest	nucleotide substitution	location in gene	amino acid change
rs7517847	1	67454256	IL23R	G/T	intron	
rs2476601	1	114179090	PTPN22	A/G	exon	TRP/ARG
rs2274910	1	159118669	ITLN1	C/T	intron	
rs9286879	1	171128856		A/G		
rs11584383	1	199202488		C/T		
rs2241880	2	233848106	ATG16L1	C/T	exon	THR/ALA
rs3197999	3	49696535	MST1	C/T	exon	ARG/CYS
rs4613763	5	40428484	PTGER4	C/T		
rs2188962	5	131798703	C5ORF56	C/T	intron	
rs11747270	5	150239059	IRGM	A/G		
rs10045431	5	158747110	IL12B	A/C		
rs6908425	6	20836709	CDKAL1	C/T	intron	
rs3763313	6	32484448	BTNL2, SLC26A3, HLA-DRB1, HLA-DQA1	A/C		
rs7747909	6	52162207	IL17A	A/G	3' UTR	
rs1974226	6	52163293	IL17A	A/G	3' UTR	
rs7746082	6	106541961		C/T		
rs2301436	6	167357977	FGFR1OP	A/G	intron	
HLA-DRB1*04	6		HLA-DRB1			
rs1456893	7	50240217		A/G		
rs1551398	8	126609232		C/T		
rs10758669	9	4971601	JAK2	A/C		
rs4263839	9	116606260	TNFSF15	A/G	intron	
rs17582416	10	35327655		G/T		
rs10995271	10	64108491	ZNF365	C/G		
rs11190140	10	101281582	NKX2-3	C/T	5' upstream	
rs7927894	11	75978963	C11ORF30	C/T		
rs11175593	12	38888206	LRRK2, MUC19	C/T		
rs3764147	13	43355924	C13ORF31	A/G	exon	ILE/VAL
rs2076756	16	49314381	NOD2	A/G	intron	
rs2872507	17	35294288	ORMDL3	A/G		
rs744166	17	37767726	STAT3	C/T	intron	
rs2542151	18	12769946	PTPN2	G/T		
rs4807569	19	1074377	SBNO2	A/C	intron	
rs1736135	21	15727090		C/T		
rs762421	21	44439988	ICOSLG	A/G		