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CJM112

Clinical Trial Protocol CCJM112X2203

# A randomized, subject and investigator blinded, placebo-controlled, multi-center study in parallel groups to assess the efficacy and safety of CJM112 in patients with moderate to severe inflammatory acne

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## Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not be part of the Clinical Study Report.

## Notification of serious adverse events

**Dear Investigator,**

You must report a Serious Adverse Event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the SOM for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Drug Safety and Epidemiology (DS&E) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the SOM.

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## List of abbreviations

| | |
|---|---|
| γ-GT | Gamma-Glutamyl transferase |
| ACR | Albumin-Creatinine Ratio |
| ADA | Anti-Drug Antibody |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| BD-2 | β-Defensin-2 |
| BM | Biomarker |
| BMI | Body Mass Index |
| CAH | Congenital adrenal hyperplasia |
| CASS | Comprehensive Acne Severity Scale |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulation |
| COA | Clinical Outcome Assessments |
| COAR | Clinical Operations, Analytics & Regions |
| CPK | Creatinine Phosphokinase |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| CRP | C-reactive protein |
| CV | Coefficient of Variation |
| DAR | Dose Administration Record |
| DLQI | Dermatology Life Quality Index |
| DNA | Deoxyribonucleic acid |
| DS&E | Drug Safety and Epidemiology |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| ELISA | Enzyme-linked immunosorbent assay |
| EOS | End of Study |
| FDA | Food and Drug Administration |

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|---|---|
| FIH | First in Human |
| GCP | Good Clinical Practice |
| GEE | Generalized Estimating Equations |
| GLMM | Generalized Linear Mixed Model |
| h | hour |
| hCG | Human Chorionic Gonadotropin |
| H&E | Hemotoxyllin-Eosin |
| HIV | Human Immunodeficiency Virus |
| HS | Hidradenitis Suppurativa |
| IA | Interim Analysis |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IGA | Investigator Global Assessment |
| IgG | Immunoglobulin G |
| IHC | Immunohistochemistry |
| IL | Interleukin |
| IN | Investigator Notification |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IUD | Intrauterine device |
| IUS | Intrauterine system |
| i.v. | intravenous |
| LLOQ | Lower Limit of Quantification |
| LOCF | Last Observation Carried Forward |
| LTB4 | Leukotriene B4 |
| mAb | Mouse Antibody |
| MAR | Missing at Random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram(s) |

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|---|---|
| mL | milliliter(s) |
| MMRM | Mixed effect Model for Repeated Measures |
| MPO | Myeloperoxidase |
| MRI | Magnetic Resonance Imaging |
| ng | nanogram |
| NIBR | Novartis Institute of Biomedical Research |
| NOAEL | no observed adverse effect level |
| NRS | Numerical rating scale |
| OTC | Over the counter |
| PAPA | Pyogenic arthritis pyoderma gangrenosum and acne |
| PASH | Pyoderma gangrenosum, acne, and suppurative hidradenitis |
| PASI | Psoriasis Area Severity Index |
| PCR | Protein-Creatinine Ratio |
| PD | Pharmacodynamic(s) |
| PDT | Photodynamic Therapy |
| PK | pharmacokinetic(s) |
| POC | Proof of Concept |
| PRIDE | Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to Epidermal growth factor receptor inhibitors |
| PRO | Patient reported outcomes |
| PSTPIP1 | Proline-Serine-Threonine Phosphatase Interacting Protein 1 |
| PT/INR | Prothrombin Tine/ International Normalized Ratio |
| q4w | Every four weeks |
| SAD | Single Ascending Dose |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAPHO | Synovitis Acne Pustulosis Hyperostosis Osteitis |
| s.c. | Subcutaneous |
| sCR | serum Creatinine |
| SD | standard deviation |
| SER | Sebum Excretion Rate |
| SOC | Standard of Care |

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|---|---|
| SOM | Site Operations Manual |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TBL | Total Bilirubin |
| ULN | Upper limit of normal |
| WHO | World Health Organization |
| WOCBP | Woman of Child Bearing Potential |

## Pharmacokinetic definitions and symbols

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| Cmin,ss | The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume] |
| Cmax,ss | The observed maximum serum concentration following drug administration at steady state [mass / volume] |
| Cav,ss | The average steady state serum concentration during multiple dosing |
| λz | The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume] |
| T1/2 | The terminal elimination half-life [time] |
| AUCtau,ss | The area under the serum concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume] |

## Glossary of terms

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| Assessment | A procedure used to generate data required by the study |
| Cohort | A specific group of subjects fulfilling certain criteria |
| Control drug | Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial |
| Dosage | Dose of the study treatment given to the subject in a time unit |
| Enrollment | Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) |
| Healthy volunteer | A person with no known significant health problems who volunteers to be a study participant |
| Investigational drug | The study drug whose properties are being tested in the study; this definition is consistent with USA CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance" |
| Investigational treatment | All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage. |
| Medication number | A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system. |
| Medication pack number | A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system |
| Patient | An individual with the condition of interest |
| Period | A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc. |
| Premature subject withdrawal | Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned. |
| Randomization number | A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment |

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| Screen Failure | A subject who is screened but is not treated or randomized |
| Stage | A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc. |
| Study completion | Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later. |
| Study drug discontinuation | Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal. |
| Study treatment | Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s) |
| Study treatment discontinuation | When the subject permanently stops taking study treatment prior to the defined study treatment completion date |
| Subject | A trial participant (can be a healthy volunteer or a patient) |
| Subject number | A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc. |
| Treatment number | A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm |
| Variable | A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study |
| Withdrawal of consent (WoC) | Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material |

## Protocol synopsis

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| **Protocol number** | CCJM112X2203 |
| **Title** | A randomized, subject and investigator blinded, placebo-controlled, multi-center study in parallel groups to assess the efficacy and safety of CJM112 in patients with moderate to severe inflammatory acne |
| **Brief title** | Study of efficacy and safety of CJM112 in patients with moderate to severe inflammatory acne |
| **Sponsor and Clinical Trial Phase** | Novartis<br>Phase II |
| **Intervention type** | Biologic |
| **Study type** | Interventional |
| **Purpose and rationale** | The study is designed primarily to assess preliminary efficacy and safety of CJM112 in patients with moderate to severe inflammatory acne and to determine if CJM112 has an adequate clinical profile for further clinical development. In addition, sustainability of response and dose relationship will be explored. |
| **Primary Objective** | To assess the efficacy of CJM112 versus placebo on facial inflammatory lesion counts in patients with moderate to severe inflammatory acne. |
| **Secondary Objectives** | To assess the safety and tolerability of CJM112 in patients with moderate to severe inflammatory acne.<br>To assess the pharmacokinetics of CJM112 in patients with moderate to severe acne. |
| **Study design** | This is a randomized, placebo controlled, subject and investigator blinded, multicenter, non-confirmatory, parallel group, proof of concept study in patients with moderate to severe inflammatory acne. After an initial screening period (up to 4 weeks), the study is conducted in 2 consecutive treatment periods, each of 12 weeks, to show clinical efficacy in treatment period 1, and potential sustainability of response in extension period 2. At the beginning of treatment period 1, patients are randomized to one of 3 treatment groups for the first 12 weeks only:<br>1 CJM112 s.c. at monthly intervals<br>2 CJM112 s.c.at monthly intervals<br>3 Placebo s.c. at monthly intervals<br>At the end of treatment period 1, all patients will be offered the opportunity to remain in the study for extension period 2. Patients who enter extension period 2 will receive the following treatments:<br>• Treatment Period 1, Extension Period 2,<br>• Treatment Period 1, Extension Period 2,<br>• Treatment Period 1, Placebo. Extension Period 2, via re-randomization.<br>Therefore, exposure to placebo will be limited to a maximum of 12 weeks (treatment period 1). |

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| **Population** | The patients included in the study are patients with moderate to severe inflammatory acne who have previously failed other systemic therapies, and do not have more than 5 nodules to exclude severe cases of nodulocystic acne, often associated with a high potential for scarring. A minimal count of 25 facial inflammatory lesions (papules, pustules, nodules) is needed for inclusion. |
| **Key Inclusion criteria** | • Written informed consent must be obtained before any assessment is performed.<br>• Male and female subjects aged 18 to 45 years of age included and otherwise in good health as determined by medical history, physical examination, vital signs, ECGs and laboratory tests at screening.<br>• Body weight between 50 and 120 kg, inclusive at screening.<br>• Patients with papulo-pustular acne vulgaris having between 25 and 100 facial inflammatory lesions (papules, pustules and nodules), and presence of non-inflammatory lesions (open and closed comedones) on the face at screening and baseline, who have failed systemic therapy for inflammatory acne.<br>• No more than 5 facial inflammatory nodules at screening and baseline.<br>• Investigator's Global assessment (IGA) score of at least moderate (3) acne severity at screening and baseline.<br>• Able to communicate well with the investigator, to understand and comply with the requirements of the study. |
| **Key Exclusion criteria** | • Use of investigational drugs at the time of screening, or within 4 weeks or 5 half-lives of screening, whichever is longer; or longer if required by local regulations.<br>• Use of any topical anti-acne prescription treatment within 2 weeks and any OTC anti-acne treatment within 1 week of baseline (use of medicated (anti-acne) creams, medicated cleansers or medicated soaps is prohibited for treatment period 1).<br>• Use of any oral/systemic treatment for acne, including oral antibiotics, dapsone, within 4 weeks prior to baseline.<br>• Use of systemic or lesional injected (for acne) corticosteroids or systemic immunomodulators (such as cyclosporine, methotrexate, azathioprine, etc.) within 4 weeks before baseline (see Section 5.2).<br>• Use of any systemic hormonal treatment (in particular anti-androgens, such as spironolactone, finasteride and cyproterone acetate) within 1 month before baseline.<br>  ○ Oral contraceptives can be continued if stable for the last 3 months before baseline if stable in dose and dosing regimen and type (brand) and if the patient plans to continue throughout the study period.<br>• Previous treatment with biologics (such as anti-TNFα agents or anti-IL-1) within 3 months prior to baseline; Anti-IL-12/23 blocking agents (such as briakinumab and ustekinumab or p19 antibodies) within 6 months prior to baseline.<br>• Any previous treatment with IL-17 or IL17R blocking agents, including, but not limited to secukinumab, ixekizumab or brodalumab.<br>• Use of oral retinoids (in particular isotretinoin) within the last 6 months prior to baseline.<br>• Previous surgical, physical (such as ThermaClear™), light (including blue or UV light, photodynamic therapy [PDT]) or laser therapy within 4 weeks prior to baseline. After baseline, use of any tanning device, or excessive exposure to sun [with intention to tan], any handheld light device to treat skin or procedures for hair removal in the evaluated areas (face, neck and trunk) are not |

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| | permitted.<br>• Use of facial medium depth chemical peels (excluding home regimens) within 3 months prior to baseline.<br>• Any live vaccines (this includes nasal-spray flu vaccine) starting from 6 weeks before baseline<br>• Any other forms of acne, such as:<br>o Presence of cysts and severe nodulocystic acne, and any acne type with a high risk of severe scarring.<br>o Secondary acne, including drug induced acne.<br>o Acne associated with known hormonal imbalances such as polycystic ovaries, Cushing syndrome, congenital adrenal hyperplasia (CAH), etc.<br>o Acne as part of a known genetic syndrome.<br>o Extensive (acne) keloids and hypertrophic scarring making clinical evaluation difficult.<br>o Hidradenitis suppurativa, also called acne inversa.<br>o Other forms of acne rosacea, peri-oral dermatitis and gram-negative folliculitis.<br>• History of severe systemic Candida infections or evidence of Candidiasis in the 2 weeks prior to baseline.<br>• At screening, history or symptoms of malignancy of any organ system Evidence of active tuberculosis at screening.<br>• Patients with known active Crohn's disease<br>• History of immunodeficiency diseases (positive Hepatitis B surface antigen or Hepatitis C test result at screening)<br>• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.<br>• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 13 weeks after stopping medication. |
| **Study treatment** | Treatment group 1:<br>Treatment period 1 (12 weeks): CJM112 high dose monthly<br>Extension period 2 (12 weeks): CJM112 high dose monthly<br>Treatment group 2:<br>Treatment period 1 (12 weeks): CJM112 low dose monthly<br>Extension period 2 (12 weeks): CJM112 low dose monthly<br>Treatment group 3:<br>Treatment period 1 (12 weeks): Placebo monthly<br>Extension period 2 (12 weeks): CJM112 low dose monthly or CJM112 |
| **Efficacy/PD assessments** | Corporate Confidential Information |

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| **Key safety assessments** | • AE monitoring<br>• Physical examinations<br>• Monitoring of laboratory markers in blood and urine<br>• ECG<br>• Vital signs |
| **Other assessments** | Corporate Confidential Information |
| **Data analysis** | The log transformed inflammatory facial lesion count will be analyzed using a Bayesian mixed effect model for repeated measures (MMRM), with log transformed baseline inflammatory facial lesion count as a covariate; treatment group, visit, treatment group by visit interaction and log transformed baseline inflammatory facial lesion count by visit interaction as fixed effects and an unstructured covariance structure will be used.<br>Efficacy criteria (only for primary objective) Corporate Confidential Information<br>• If there is at least 90% probability that the treatment effect of CJM112 at Week 12 is better than placebo and<br>• If there is at least 50% probability that the treatment effect at Week 12 is at least 30% (0.357 in the log scale) in favor of CJM112.<br>Futility criterion<br>• If there is at least 60% probability that the treatment effect of CJM112 at Week 12 is worse than placebo.<br>The posterior estimates of the treatment effect and the treatment difference (along with its 90% credibility interval) at each visit (with Week 12 being of primary interest) will be provided. The results will be reported in terms of ratio of geometric means. Corporate Confidential Information |
| **Key words** | Acne, efficacy, safety, PK |

# 1 Introduction

## 1.1 Background

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure (IB).

Moderate to severe inflammatory acne is a debilitating disease, with visible inflammatory lesions on the face and subsequent risk of permanent scars. The current treatment is often a combination or association of several topical treatments (such as topical retinoids and antibacterials such as benzoylperoxide and antibiotics) with oral antibiotics, and/or hormonal treatment or retinoids, such as isotretinoin. However, oral antibiotic and hormonal treatments are often only moderately effective, and isotretinoin, while effective in many cases, is associated with severe side effects, including teratogenicity, but also suicidal ideation, bone development issues, or increase of blood lipids. These are all sensitive side effects for a young adult. The side effects and the associated administrative hurdles due to pregnancy prevention programs in many countries preclude many patients to receive adequate effective treatment.

### Relevant data summary

It is more and more recognized that inflammatory acne is not an infectious disease, but rather an inflammatory skin disease, in which Propionibacterium acnes (*P. acnes*) and innate immunity play critical roles (Das and Reynolds 2014). Recently the role of IL-17A in early acne lesions has been demonstrated by upregulated IL-17A in lesional versus non-lesional acne skin, both at RNA as well as at protein level (Kelhälä et al 2014). *In vitro* data point to increased IL-17A production by T-cells that are stimulated by *P acnes*. This *P acnes* induced increase of IL-17A was decreased by retinoids, a classical anti-acne treatment (Agak et al 2014). Serum IL17A is increased in acne patients and reduced by effective treatment after 12 weeks (Karadag et al 2012). In addition, beta-defensin-2, a main downstream marker for the IL-17A pathway, was shown to be increased in serum of patients and decreased after successful treatment (Borovaya et al 2014). Together these data frame evidence that an anti-IL-17A therapeutic strategy may be useful in patients with moderate to severe inflammatory acne.

CJM112 is an affinity matured fully human monoclonal antibody (mAb) that demonstrates high affinity to IL-17A and IL-17AF. Its potency is higher as compared to a recently approved anti-IL-17A blocker, secukinumab. Corporate Confidential Information

The preliminary clinical safety and efficacy of CJM112 was investigated in a First in Human (FIH) study in psoriasis patients, which showed a positive outcome, as patients receiving the high doses achieved responder rates (75% in improvement of the Psoriasis Area and Severity Index; PASI75) with single doses

The clinical efficacy was sustained over several months. The multiple dose therapeutic regimens over 12 weeks achieved similar PASI reductions as seen with secukinumab, but with roughly 4 to 7-fold lower doses (see Section 1.3.1 for further details).

While overall CJM112 was well tolerated in the FIH study, the only relevant safety finding from this study is an expected slight increase of general infections during treatment with CJM112. This effect may be dose-dependent with increasing multiple doses of CJM112. There was no pattern of any special kind of infections, and most infections were upper respiratory tract infections. No opportunistic infections and no fungal infections occurred.

This proposed proof of concept (PoC) clinical study in moderate to severe inflammatory acne patients is a placebo-controlled, randomized, subject and investigator blinded, multi-center study with three parallel groups receiving monthly administrations of CJM112 in two dosage regimens or its placebo over a 24 week treatment period. While this is the first time testing an anti-IL-17A in this disease, it is anticipated that all doses tested would have at least a minimal beneficial effect, based on effects at similar dose levels seen in another skin disease, psoriasis. It is anticipated that the clinical safety at these doses is similar to that observed with other anti-IL-17A compounds, which seems appropriate for young adults and thus is anticipated to be superior to the one of oral isotretinoin, often used in this indication.

## 1.3 Clinical data

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the IB.

### 1.3.1 Human safety and tolerability data

#### First in Human study in patients with moderate to severe plaque type psoriasis

Clinical development of CJM112 was initiated in a FIH study in patients with chronic plaque type psoriasis (CCJM112X2101). The initial single ascending dose (SAD) study (Part 1) was conducted in 5 cohorts with single doses between 5 mg and 450 mg s.c. with each 4 treated with active and 2 with placebo. An additional single dose extension cohort was planned for 50 mg (n=8 active and n=4 placebo). A subsequent multi-dose part in parallel arms with active (secukinumab) and placebo controls and 4 different treatment regimens for CJM112 (Part 2) has been completed.



An additional clinical trial in patients with moderate to severe hidradenitis suppurativa is ongoing and has completed recruitment.

## 1.4 Study purpose

The study is designed primarily to assess preliminary efficacy and safety of CJM112 in patients with moderate to severe inflammatory acne, and to determine if CJM112 has an adequate clinical profile for further clinical development. In addition, sustainability of response and dose relationship will be explored.

# 2 Study objectives and endpoints

## 2.1 Primary objective

| *Primary objective* | *Endpoints related to primary objective* |
|---|---|
| • To assess the efficacy of CJM112 versus placebo on facial inflammatory lesion counts in patients with moderate to severe inflammatory acne | • Total inflammatory facial lesion count at week 12 |

## 2.2 Secondary objective(s)

| *Secondary objective(s)* | *Endpoints related to secondary objective(s)* |
|---|---|
| • To assess the safety and tolerability of CJM112 in patients with moderate to severe inflammatory acne | • Number and severity of AEs<br>• Safety and tolerability assessments including general safety parameters (laboratory parameters, physical examination, vital signs, ECG assessed at baseline and repeatedly until study completion visit. |
| • To assess the PK of CJM112 in patients with moderate to severe acne | • Cmin,ss (multiple doses) from serum concentration data (non-compartmental analysis) |

# 3 Investigational plan

## 3.1 Study design

This is a randomized, placebo-controlled, subject and investigator blinded, multi-center, non-confirmatory, parallel-group, proof of concept study in patients with moderate to severe inflammatory acne. After an initial screening period (up to 4 weeks), the study will be conducted in 2 consecutive treatment periods, each of 12 weeks, to show clinical efficacy in treatment period 1, and potential sustainability of response in extension period 2. At the beginning of treatment period 1, patients will be randomized to one of the 3 treatment groups for the first 12 weeks only:

1. CJM112 s.c. at monthly intervals.
2. CJM112 s.c.at monthly intervals.
3. Placebo s.c. at monthly intervals.

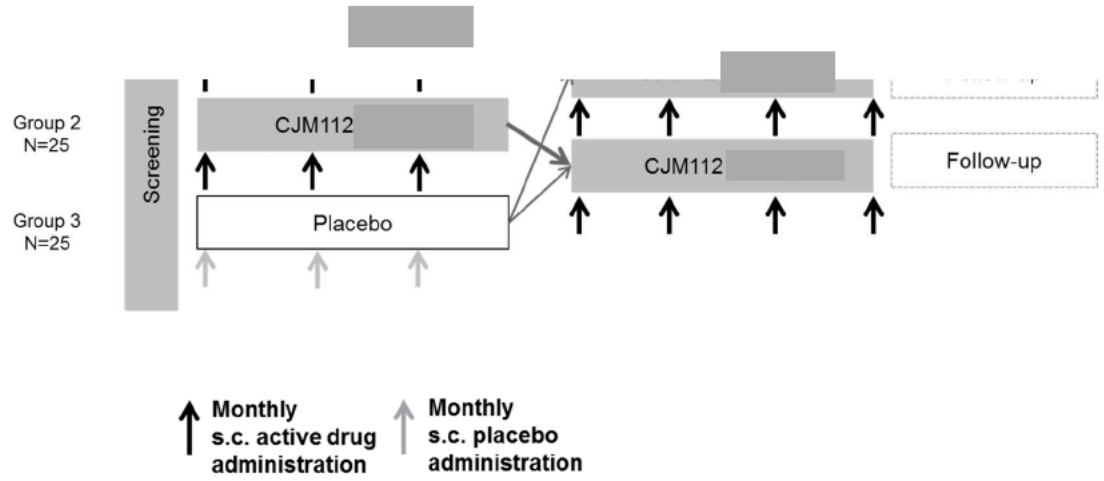
At the end of treatment period 1, all patients will be offered the opportunity to remain in the study for the extension period 2. Patients who enter extension period 2 will receive the following treatments:

- Treatment Period 1, Extension Period 2,
- Treatmend Period 1, Extension Period 2,
- Treatment Period 1, Placebo. Extension Period 2, via re-randomization

Therefore, exposure to placebo will be limited to a maximum of 12 weeks (treatment period 1). To keep the blinding at each time point, 3 injections will be given.

Whether patients continue or do not continue into extension period 2, all patients will be followed up for safety and potential sustainability of efficacy, for an additional 13 weeks without any study treatment. This corresponds to about 5 times the half-life of CJM112 (overall, in CCJM112X2101-SAD, the mean elimination half-life for CJM112 was 17 to 19 days). However, if medically justified other anti-acne treatment may be used during this period.

**Figure 3-1 Study design**




## 3.2 Rationale of study design

Moderate to severe inflammatory acne is a debilitating disease, with visible inflammatory lesions on the face and subsequent risk of permanent scars. Available treatments are either associated with serious side effects (such as isotretinoin) or are only modestly effective. It is more and more recognized that acne is not an infectious disease, but rather an inflammatory skin disease, in which Propionibacterium acnes (*P. acnes*) and innate immunity play critical roles (Das and Reynolds 2014). Recently the role of IL-17A in clinical acne lesions has been hypothesized by (Kelhälä et al 2014), which led to the proposal of testing a human monoclonal high affinity specific anti-IL-17A inhibitor, CJM112, in moderate to severe inflammatory acne.

### Study population

The patients included in the study are patients with moderate to severe inflammatory acne who have previously failed other systemic therapies. There is no universally accepted classification of moderate to severe inflammatory acne. A minimal count of 25 facial inflammatory lesions (papules, pustules, nodules) is needed for inclusion, which is similar to other studies in this indication (Fleischer et al 2006). For this study, no more than 5 facial nodules are accepted to exclude severe cases of nodulo-cystic acne, often associated with a high potential for scarring. Included patients should be otherwise in good health as determined by medical history and respect specified washout periods for anti-acne treatments (see Section 4.2 and Section 5.2). The chosen wash-out periods for anti-acne treatments are similar to what was done in other phase 3 programs in moderate to severe acne (Fleischer et al 2006; see as well sarecycline trials such as ClinicalTrial.gov, NCT02322866 2014).

To target a typical moderate to severe inflammatory acne population in adults, patients 18 - 45 years of age will be included. The upper age group is consistent with diagnosis of inflammatory acne.

To limit variability in exposure to +/- 40% (based on AUCtau,ss; from preliminary/draft modeling exercise with reference body weight of 70 kg) a body weight range of 50 to 120 kg was selected for inclusion.

### Clinical and other endpoints

It is assumed that the anti-inflammatory effect with an anti-IL-17A compound is the clinically most pronounced effect. Consequently, inflammatory lesion count is the primary endpoint, as outlined by CDER 2005. Inflammatory lesions are defined as papules, pustules and nodules. As counts on the face are best validated, the count will focus on the face, but other areas, such as truncal (upper chest and upper back and neck), will be assessed as well, when feasible.

In addition to lesion counting, the investigator's global assessment (IGA) for the face will be used as exploratory assessment of efficacy, in order to determine the clinical responder rate (achievement of clear or almost clear; or 2 grade improvement from baseline; CDER 2005. Other endpoints include global assessments on non-facial areas, such as the comprehensive acne severity scale (CASS), as described by (Tan et al 2007), as well as nodule counts.

The clinical counts will be complemented in selected sites by standardized serial photographic imaging (such as Visia CR™), which provides the possibility of a central expert read and / or semi-automatic lesion counting. Imaging may be performed in different modalities and in particular the surface area of redness or area of inflammation may be explored as reflecting clinical inflammation. In selected sites, fluorescence imaging may explore a potential effect on P. acnes colonization on the skin (such as Visia CR™ imaging).

As this is the first time that an anti-IL-17A inhibitor is tested in this population,
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## Treatment arms and study methodology

The primary endpoint is a comparison of facial inflammatory lesion counts at week 12, an established duration period for anti-acne treatments, but other time points will be explored. Many acne treatments, including isotretinoin, need longer treatment duration for full efficacy. However, in this moderate to severe acne population, the increased acne scarring risk in the face makes it difficult to include patients in a placebo controlled study with more than 12 weeks duration, hence, it is planned to offer placebo-treated patients to be re-randomized after 12 weeks to either the Corporate Confidential Information treatment group in extension period 2. As the placebo effect can be quite high (up to 30-40% reduction in inflammatory lesion count at week 12) and the endpoints dependent on the investigator assessment, a blinded study is deemed optimal to generate reliable data for treatment period 1, which are not influenced by investigator's perception. Extension period 2 data may be influenced by a lower severity due to a long run-in and drop-outs, but may show a similar trend. Given the high placebo effect, a parallel comparison is preferred over a cross over design.

The randomization scheme overall is planned to be 1:1:1. This ensures that groups are balanced and the interpretation of results is possibly more robust. However, unbalanced randomization will be used at the start of trial to enhance early comparison of vs placebo and interim efficacy/futility assessment. A 3:1:3 randomization Corporate Confidential Information will be used for the first 35 patients and thereafter 1:2:1 Corporate Confidential Information for the remaining 40 patients. In case more than 75 patients are randomized to the study, the randomization ratio will be 1:1:1 after the first 75 patients. Patients who have been randomized to placebo group in treatment period 1 and agree to continue into extension period 2 will be re-randomized into the two active dosing groups for another 12 weeks treatment, again with randomization ratio 1:1.

## 3.3 Rationale for dose/regimen, route of administration and duration of treatment

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In the present study, the dose Corporate Confidential Information is proposed to explore efficacy in the moderate to severe acne population, which corresponds to one dose Corporate Confidential Information administration monthly, considered as practical and feasible for this population. It is anticipated that the onset of action in acne is seen within months and well within treatment period 1 and extension period 2, thus, no loading dose during the first month was selected. In adult psoriasis patients, a cumulative dose over 12 weeks (with a loading dose over the first month) was safe and effective. This dose achieved a clear clinical reduction of the PASI75 responders (achieving a reduction of 75% over baseline in PASI score) of over 80% of the included patients in the dose group. Corporate Confidential Information

As outlined in Section 1.3.1, the safety signals in the HS population versus placebo are consistent with the safety data known from other anti-Il-17A blockers and previous results in psoriasis patients. While reducing the frequency to monthly doses, Corporate Confidential Information has a reasonable chance to distribute even in typical acne lesions, such as papules, which are more superficial and smaller than nodules, where tissue distribution is assumed difficult.

To explore a preliminary dose-efficacy relationship, a lower dose regimen in this study Corporate Confidential Information in moderate to severe acne patients is proposed. Indeed, in a previous study in psoriasis patients, Corporate Confidential Information weekly for the 1st month and then monthly for a total of 3 months, showed clear efficacy versus placebo. The dose is, thus anticipated to demonstrate potential efficacy in acne,

as the exposure should be close to the one tested in psoriasis patients. Indeed, the clinical potency difference between CJM112 Corporate Confidential Information and secukinumab in psoriasis is about 7-fold based on exposure, or about 4-fold based on dose, as demonstrated (preliminary modeling) in the psoriasis study. Thus, CJM112 roughly corresponds in terms of clinical potency to secukinumab, another anti-IL-17A antibody, approved in psoriasis, psoriatic arthritis and ankylosing spondylitis.

So far, in psoriasis patients, CJM112 has demonstrated typical IgG1 antibody disposition characteristics with dose-independent systemic clearance, and predictable PK. Body weight appeared to explain most of the inter-individual variability (in psoriasis), and bioavailability of the s.c. route was approximately 50% (based on preliminary/draft population modeling using SAD data from CCJM112X2101 study and historical secukinumab data).

Treatment duration is referenced by the CDER 2005 to be at least 12 weeks despite the fact that maximum effects may not yet be achieved. Currently ongoing or completed studies with biologics have used a similar or slightly longer duration (such as ClinicalTrials.gov, NCT01498874 2011, with gevokizumab, an interleukin-1β antibody; ClinicalTrials.gov, NCT01474798 2011 with Xilonix or RA-18C3, a monoclonal anti-IL-1α antibody and phase III studies using sarecycline, ClinicalTrials.gov, NCT02320149 2014 and ClinicalTrials.gov, NCT02322866 2014). Several studies in moderate to severe inflammatory acne show strong clinical effects at 6 months (in particular with isotretinoin, see Lee et al 2011, or hormonal treatment, see Lucky et al 1997). Although the primary endpoint is evaluated at week 12, patients who have been randomized to active treatment in treatment period 1 and decide to continue into extension period 2 will have receive another 12-week treatment, which may provide evidence of sustainability or even further improvement of clinical efficacy from week 12 up to week 24.

In order to reduce in this sensitive population the risk of persistent scarring on the face, placebo will not be used longer than 12 weeks. Thus, all patients randomized to placebo and who accept to continue will be re-randomized into an active treatment arm for extension period 2.

A safety follow-up period of 13 weeks is proposed for all patients since this corresponds to approximatively 5 half-lives, based on SAD data from psoriasis patients (CCJM112X2101). Patients who complete but decide not to continue after treatment period 1 would also be followed for another 13 weeks, just as those who complete extension period 2.

## 3.4 Rationale for choice of comparator

Often, acne patients are recruited for study entry at their worst severity and usually improve during the course of therapy, whether the therapy is active or placebo. Thus, to explore efficacy of a new anti-acne drug, generally a demonstration of superiority to placebo using a double blind methodology is needed. In this trial, a matching placebo will be used. No injectable approved anti-acne drugs exist.

Using a controlled and double blind design, a potential assessment bias will be reduced, the more as outcomes rely on subjective evaluation.

## 3.5 Rationale for choice of background therapy

Acne is a disease where inflammatory lesions, such as papules and pustules appear and disappear in irregular intervals and numbers. Similarly, treatment adherence for anti-acne treatment is considered poor (Thiboutot et al 2009). In order to avoid as much as possible potential confounders due to intermittent treatment in treatment period 1, all medication to treat acne or acne inflammation is to be washed out and thus no background therapy is needed (see relevant exclusion criteria, (Section 4.2) and prohibited treatment, (Section 5.2)). In extension period 2, topical anti-acne treatments are permitted (see Section 5.2).

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## 3.7 Risks and benefits

CJM1112 has been well tolerated in the FIH study in patients with plaque psoriasis including 28 patients exposed to a single dose Corporate Confidential Information and 42 patients exposed to multiple doses of CJM112 Corporate Confidential Information over 12 weeks in comparison to secukinumab and placebo (n=6 each). In addition, 33 patients with moderate to severe HS have been exposed to CJM112 weekly for one month and bi-weekly for 4 months. As described in Section 1.3.1, the safety signal even at these high doses did not reveal new concerns. As expected, the safety profile of CJM112 appears comparable to that of secukinumab, another anti-IL-17A monoclonal antibody, which has data from an extensive number of patients with longer exposure durations and is now approved in three indications (see Section 1.3). Primarily non-serious upper respiratory tract infections have been observed (in particular pharyngitis and nasopharyngitis) more frequently with CJM112 than placebo, and a potential dose-dependent increase in rates of infection was observed in the multi-dose study part over 12 weeks. Small, incremental risks in Candida infections are reported for IL-17 blocking agents but have not been observed so far for CJM112.

Hypersensitivity reactions have not been observed so far for CJM112 but their future occurrence cannot be excluded.

There were no SAEs that are considered expected for CJM112. In clinical studies, urticaria and one case of anaphylactic reaction to secukinumab were observed. However, none of these cases were observed with CJM112.

In study CCJM112X2101, in Part I (SAD), four patients (14.3%) treated with CJM112 were ADA-positive (patients with at least one treatment induced ADA-positive sample at any time during the treatment or follow-up observation period). ADAs may have affected the PK profile of one patient Corporate Confidential Information and an effect on the PASI profile cannot be excluded. For two ADA-positive patients Corporate Confidential Information and for the one ADAs did not appear to have affected their PASI profiles when compared to other patients in the same cohort. In Part 2 (multiple dose), six patients (14.3%) treated with CJM112 were ADA-positive and the frequency of ADA-positive subjects appeared to have an inverse correlation with the dose and was 5/11 subjects (45.5%), 0/10 subjects, 1/10 subjects (10%) and 0/11 subjects, Corporate Confidential Information For 3 patients Corporate Confidential Information while the positive ADA response was generally characterized with low titers, it cannot be excluded that the ADA response has had a consequence on the target capture profile or on the PASI reduction time course. For the ADA-positive patient Corporate Confidential Information the presence of ADAs is unlikely to have affected the PASI reduction time course.

Due to the same mechanism of action and similar class of drugs (fully human monoclonal antibodies of IgG1 type) potential risks identified in the large clinical experience for secukinumab are of relevance for CJM112, as the safety profile of CJM112 still remains preliminary in early stages of development. The most frequently reported adverse drug reactions (ADRs) were upper respiratory tract infections (most frequently nasopharyngitis, rhinitis). Most of the events were, however, mild or moderate in severity.

In addition to the above mentioned events, injection site reactions, elevations in liver enzymes, drops in neutrophil counts and ECG abnormalities have been observed sporadically and very rarely in secukinumab trials. These cases have not yet been observed with CJM112. Nevertheless, these constitute events that may be observed and should be monitored routinely, as with any investigational biologic treatment.

As secukinumab was ineffective in a phase II trial in patients with moderate to severe Crohn's disease, patients with active Crohn's disease will be excluded from this study (see Hueber et al 2012).

Women of child bearing potential (WOCBD) and sexually active males should be informed that taking the investigational drug may involve unknown risks to the fetus if a subject or their partner were to become pregnant during the study. He/she must agree that in order to participate in the study they will adhere to the highly effective contraception requirement for the duration of the study and for 13 weeks after the last dose. If there is any question that the subject will not strictly comply, he/she should not be entered in the study.

Of note, for the present study population, moderate to severe acne, co-morbidities may be observed more frequently than in the overall population, such as depression and suicidal ideation (Purvis et al 2006, Halvorsen et al 2011). However, frequency of suicidal ideation,

even if difficult to be compared, seems to be in a similar range as for other chronic skin diseases, such as psoriasis (Picardi et al 2013, Kurd et al 2010). Thus, no specific suicidality assessment is being performed.

Treatment for AEs should follow general guidelines for standard-of-care, and is at the discretion of the investigator or treating physician. There are no specific treatment recommendations for AEs that may possibly occur in in this trial.

The expected benefit is that CJM112 shows some level of clinical efficacy in reducing inflammatory acne lesions. This is based on the assumption that multiple and even single doses of CJM112 Corporate Confidential Information had sustained clinical efficacy in psoriasis patients for over 3-4 months (see Section 1.3.). As no previous studies using an IL-17A inhibitor have been conducted, this benefit is difficult to quantify. Patients randomized to placebo are unlikely to benefit from the trial in treatment period 1, even if generally the placebo effect accounts for 20-30% of lesion reduction. All patients will be exposed in extension period 2 to CJM112 and may have a potential benefit from the proposed therapy. Furthermore, subjects with clinical worsening of their acne and/or any active ongoing scarring are to be discontinued from study treatment (see Section 7.2) to benefit from approved anti acne treatments, if needed.

The risks to subjects in this trial will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring, and adequate safety follow-up, which has been determined based on the expected half-life of CJM112 in acne patients (i.e. similarity with psoriasis patients), to capture late occurring AEs. Based on available clinical knowledge about effects of IL-17A targeting therapies, it is anticipated that the risks to experience AEs is comparable to the experience with secukinumab.

Due to the early stage of development, there may be unknown risks of CJM112 which may be serious and/or unforeseen.

Additional risks are related to the procedures of the trial, such as blood sampling and skin biopsy sampling. During the collection of blood samples, patients may experience pain and/or bruising at the injection site. In addition, although rare, localized clot formation, infections and nerve injuries may occur. Lightheadedness or fainting may also occur during or after the blood draw. The skin biopsy will be in general a punch biopsy, commonly performed in dermatological practice, and performed under local anesthesia. On rare occasions, local bruising, bleeding, pain, discomfort and a low risk of infection, wound healing difficulties or a scar are possible. Biopsies will be performed on non-facial areas, generally on upper back or neck.

### 3.7.1 Blood sample volumes

A maximum of approximately 350mL of blood is planned to be collected over a period of 36 weeks, from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

All blood samples will be taken by direct venipuncture in a forearm vein contra-lateral to the site of subcutaneous injection. All sampling should have a unique sample numbering. The actual sample collection date and time will be recorded on the immunogenicity blood

collection page of the CRF. Sampling problems will be noted on the comments field of the CRF.

Timings of blood sample collection are outlined in the Assessment Schedule.

A summary blood log is provided in the SOM, together with instructions for all sample collection, processing and storage and shipment information.

See Section 8.8 regarding the potential use of residual samples.

# 4 Population

The study population will be comprised of male and female subjects, aged 18-45 years of age, with moderate to severe inflammatory acne. A total of approximately 75 patients will be randomized.



The investigators must ensure that all patients being considered for the study meet the eligibility criteria. No additional criterion should be applied by the investigators, in order that the study population will be representative of all eligible patients.

## 4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any study procedures are performed.
2. Male and female subjects aged 18 to 45 years of age included, and otherwise in good health as determined by medical history, physical examination, vital signs, ECGs and laboratory tests at screening.
3. Body weight between 50 and 120 kg, inclusive at screening.
4. Patients with papulo-pustular acne vulgaris with between 25 and 100 facial inflammatory lesions (papules, pustules and nodules), and presence of non-inflammatory lesions (open and closed comedones) in the face at screening and baseline, who have failed systemic therapy for inflammatory acne.
5. No more than 5 facial inflammatory nodules at screening and baseline.
6. Investigator's Global assessment (IGA) score of at least moderate (3) acne severity on the face at screening and baseline.
7. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

## 4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Use of investigational drugs at the time of screening, or within 4 weeks or 5 half-lives of baseline, whichever is longer; or longer if required by local regulations.
2. Use of any topical anti-acne prescription treatment within 2 weeks and any over the counter (OTC) anti-acne treatment within 1 week of baseline (use of medicated (anti-acne) creams, medicated cleansers or medicated soaps is prohibited for treatment period 1).
3. Use of any oral/systemic treatment for acne, including oral antibiotics, dapsone, oral zinc within 4 weeks prior to baseline.
4. Use of systemic or lesional injected (for acne) corticosteroids or systemic immunomodulators (such as cyclosporine, methotrexate, azathioprine, etc.) within 4 weeks before baseline (see Section 5.2).

5. Use of any systemic hormonal treatment (in particular anti-androgens, such as spironolactone, finasteride and cyproterone acetate) within 1 month before baseline. Oral contraceptives can be continued if stable for the last 3 months before baseline and if stable in dose and dosing regimen and type (brand) and if the patient plans to continue throughout the study period.
6. Previous treatment with biologics (such as anti-TNFα agents or anti-IL-1) within 3 months prior to baseline; Anti-IL-12/23 blocking agents (such as briakinumab and ustekinumab or p19 antibodies) within 6 months prior to baseline.
7. Any previous treatment with IL-17 or IL17R blocking agents, including, but not limited to secukinumab, ixekizumab, bimekizumab or brodalumab.
8. Use of oral retinoids (in particular isotretinoin) within the last 6 months prior to baseline.
9. Previous surgical, physical (such as ThermaClear™), light (including blue or UV light, photodynamic therapy [PDT]) or laser therapy within 4 weeks prior to baseline. After baseline, use of any tanning device, or excessive exposure to sun [with intention to tan], any handheld light device to treat skin or procedures for hair removal in the evaluated areas (face, neck and trunk) are not permitted.
10. Use of facial medium depth chemical peels (excluding home regimens) within 3 months prior to baseline.
11. Any live vaccines (this includes nasal-spray flu vaccine) starting from 6 weeks before baseline.
12. Any other forms of acne, such as:
    - Presence of cysts and severe nodulocystic acne, and any acne type with a high risk of severe scarring.
    - Secondary acne, including drug induced acne (steroids, cloracne, lithium, EGFR-inhibitors [cetuximab, erlotinib, panitumumab und gefitinib, etc.], associated with acneiform eruptions, including PRIDE syndrome).
    - Acne associated with known hormonal imbalances such as polycystic ovaries, Cushing syndrome, congenital adrenal hyperplasia (CAH), androgen-secreting tumors, and acromegaly. Patients with signs/symptoms of hyperandrogenism such as hirsutism should undergo hormonal status assessment at the discretion of the investigator.
    - Acne as part of a known genetic syndrome, such as SAPHO, PAPA, PASH or other variants possibly associated with PSTPIP1 gene.
    - Extensive (acne) keloids and hypertrophic scarring making clinical evaluation difficult.
    - Hidradenitis suppurativa also called Acne inversa.
    - Other forms of acne rosacea, peri-oral dermatitis and gram-negative folliculitis.
13. Any severe, progressive or uncontrolled medical or psychiatric condition or other factors at randomization that in the judgment of the investigator prevents the patient from participating in the study.
14. History of hypersensitivity or allergy to the investigational compound/compound class being used in this study.
15. Active systemic infections (other than common cold) during the 2 weeks prior to baseline.

16. History of severe systemic Candida infections or evidence of Candidiasis in the 2 weeks prior to baseline.
17. At screening, history or symptoms of malignancy of any organ system (except for a history of basal cell carcinomas and/or up to 3 squamous cell carcinomas of the skin, if successful treatment has been performed, with no signs of recurrence; actinic keratoses, if present at screening, should be treated according to standard therapy before randomization), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
18. Evidence of active tuberculosis at screening. All patients will be tested for tuberculosis status using a blood test (QuantiFERON®-TB Gold In-Tube). Patients with evidence of tuberculosis may enter the trial after adequate treatment has been started according to local regulations.
19. Patients with known active Crohn's disease.
20. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result at screening.
21. A positive Hepatitis B surface antigen or Hepatitis C test result at screening
22. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
23. WOCBP, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 13 weeks after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (i.e., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

    In case of use of oral contraception women should have been treated with the same pill and dose for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

24. History of drug or alcohol abuse within the 12 months prior to dosing.
25. Donation or loss of 400 ml or more of blood within 8 weeks prior to baseline, or longer if required by local regulation.
26. Inability or unwillingness to undergo repeated venipunctures (e.g., due to poor tolerability or lack of access to veins).
27. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

# 5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the restrictions outlined in this section.

## 5.1 Contraception requirements

As the reproductive toxicity studies are not yet final, highly effective contraception is proposed for all trials with CJM112 that include WOCBP, until further information is available. WOCBP, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 13 weeks (= 5 times the mean terminal half-life in psoriasis patients) after stopping CJM112.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (i.e., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
- Use of oral, injected or implanted hormonal methods of contraception or placement of an IUD or IUS or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

## 5.2 Prohibited treatment

**Table 5-1 Prohibited treatment**

| Medication/treatment | Action to be taken | Required wash-out (prior to randomization/first treatment) |
|---|---|---|
| Exposure to any IL-17 or IL-17R blocking agents | Do not include in the study/discontinue study treatment | Exclusion criterion |
| TNFα blockers such as adalimumab and infliximab | Discontinue study treatment | Wash-out: 3 months |
| IL-12 or IL-23 blocking agents such as briakinumab and ustekinumab, including investigational p19 antibodies | Discontinue study treatment | Wash-out: 6 months |
| Any biologics, other than above | Discontinue study treatment | Wash-out: 3 months or at least 5 times the half life |
| Any systemic immunosuppressant or immunomodulator, such as cyclosporine, methotrexate, cyclophosphamide, azathioprine, corticosteroids (includes local injections), etc. | Discontinue study treatment (unless local injections: to be discussed with sponsor on case by case basis) | Wash-out: 4 weeks |
| Any systemic treatment with antibiotics (longer than 2 weeks), in particular tetracyclines and/or macrolides, but as well other oral anti-acne treatment such as dapsone and zinc. These treatments are accepted for periods shorter than 2 weeks, if medically indicated. | Discontinue study treatment if antibiotic treatment (not for acne) is longer than 2 weeks<br>All other cases to be discussed with Sponsor on case by case basis | Wash-out: 4 weeks |
| Use of any systemic hormonal treatment (with the exception of hormonal contraceptive) (including anti-androgens, such as spironolactone, finasteride and cyproterone acetate) within 1 month before baseline. | To be discussed with sponsor on case by case basis | Wash-out of 1 month |
| Oral contraceptives can be continued if stable for the last 3 months before baseline if stable in dose and dosing regimen and type and if the patient plans to continue throughout the study. | To be discussed with sponsor on case by case basis | Wash out for change in dose, regimen or type: 3 months |
| Systemic retinoids, in particular isotretinoin | Discontinue study treatment | Wash-out: 6 months |
| Comedo extraction, electrocautery, and medical chemical peels using glycolic acid, salicylic acid, and trichloroacetic acid (for acne or acne lesions and /or done on areas of evaluation (face, back, chest, shoulder, etc.)) | Discontinue study treatment for medium depth facial peels<br>Sporadic local treatment to be discussed with sponsor on case by case basis | No wash-out<br>Medium depth peels 3 months wash out |

| Medication/treatment | Action to be taken | Required wash-out (prior to randomization/first treatment) |
|---|---|---|
| Surgical or physical (such as ThermaClear™ ) light and laser therapy (including blue light, use of handheld devices, tanning devices or photodynamic therapy [PDT]) on area of evaluation.<br>After baseline, use of any tanning device, or excessive exposure to sun [with intention to tan], any handheld light device to treat skin or procedures for hair removal in the evaluation areas are not permitted. | To be discussed with sponsor on case by case basis. | Wash-out: 4 weeks |
| Any live vaccines (this incl. nasal-spray flu vaccine) | Discontinue study treatment | 6 weeks |
| Any topical for acne on area for evaluation (face, back, chest, shoulder, neck), including retinoids (such as adapalene, tazarotene, isotretinoin or tretinoin), antibacterial and antibiotics (such as benzoyl peroxide, clindamycin or erythromycin) and any other topical keratolytic or peeling agents (such as salicylic acid, or lactic acid) or any other anti-acne drug (such as dapsone, azelaic acid). These topicals include over the counter (OTC) products for acne, such as medicated emollients, medicated cleansers or medicated soaps. | To be discussed with sponsor on case by case basis for treatment period 1.<br>In the extension period 2, topical anti-acne treatment is allowed, if needed (to be recorded as concomitant medication). | Wash out for 1 week (for OTC products) and for 2 weeks (for prescription drugs (RX)). |

## 5.3 Dietary restrictions and smoking

In this study, no particular dietary restrictions are required. However, acne patients are recommended to follow a healthy diet, but will not receive specific dietary restrictions

## 5.4 Other restrictions

During the trial, all patients should avoid excessive sun bathing, including for the purpose of tanning. To avoid sunburn, appropriate sun avoidance and protection should be exercised. In particular, patients with outdoor activity should be counseled regarding appropriate sun avoidance and protection.

No procedures to reduce acne lesions are allowed, including chemical peels, laser or light procedures and surgery (see Section 5.2).

Topical products used on the area of evaluation, such as emollients, cleansers, day creams etc. used by the patient should be checked by the investigator to see if she/he can continue using it, to avoid use of any medicated anti-acne products in treatment period 1 (see Section 4.2. or Section 5.2). Use of facial medium depth chemical peels (excluding home regimens) within 3 months prior to baseline are prohibited.

Planned vaccination is allowed, unless live vaccines are needed. Any live vaccines (this includes nasal-spray flu vaccine) should be initiated at least 6 weeks before baseline.

# 6 Treatment

## 6.1 Study treatment

Details on the requirements for storage and management of IMP, and instructions to be followed for subject numbering, prescribing/dispensing and taking IMP are outlined in the SOM.

### 6.1.1 Investigational treatment and placebo

**Table 6-1 Overview of Investigational treatment**

| Study drug name | Formulation | Appearance | Unit dose | Packaging | Provided by |
|---|---|---|---|---|---|
| CJM112 | Liquid in Vial | clear liquid | Corporate Confidential Information | Individual Patient Packs | Novartis |
| Placebo to CJM112 | Liquid in Vial | clear liquid | | Individual Patient Packs | Novartis |

### 6.1.2 Additional study treatment

No additional treatment beyond investigational treatment and placebo are included in this trial.

## 6.2 Treatment arms

Overall subjects will be assigned to one of the following 3 treatment arms in a ratio of 1:1:1.

Study treatments are defined as:

- CJM112 once monthly for a total of up to 7 doses
- CJM112 once monthly for a total of up to 7 doses
- Placebo for a total of up to 3 doses, followed by re-randomization into either active treatment group for extension period 2 for a total of up to 4 active doses

Both CJM112 and placebo will be provided as liquid in vial according to the dose that is required. Placebo will be matched by volume and number of syringes/injections to maintain double-blind. Details on the study medication preparation will be provided in the Pharmacy Manual provided separately. Dosing is by s.c. administration at time points specified in the Assessment Schedule.

Unbalanced randomization will be used at the start of trial to enhance early comparison of CJM112 vs placebo and interim efficacy/futility assessment. A 3:1:3 randomization

will be used for the first 35 patients and thereafter 1:2:1 for the remaining 40 patients. In case more than 75 patients are randomized to the study, the randomization ratio will be 1:1:1 after the first 75 patients.

## 6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual patients by way of a randomization number at the beginning of treatment period 1. At week 12 visit, patients who have been randomized to placebo group in treatment period 1 and also agree to continue in extension period 2 will again be assigned randomly to one of the two active treatment groups via a new randomization number.

The randomization number is only used to identify which treatment the patients have been randomized to receive. The Subject number assigned to a patient at screening remains the unique identifier for the patient throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

Replacement randomization numbers will be in the same range of the initial randomization list. If a subject requires a replacement, the replacement subject will be assigned a randomization number corresponding to the original patient (e.g. Subject 6103 would replace Subject 5103). Any additional patients enrolled will use sequential subject numbering.

Patients who discontinued from study treatment before completion of Visit 201 assessments for reasons other than safety may be replaced by an equal number of newly enrolled patients, until sufficient number of completers per arm at week 12 is achieved (Section 11.7). Patients who discontinue from study treatment after week 12 will not be replaced. The observed dropout rate from the first 35 patients will be used to evaluate the final total recruitment needed.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A subject randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of patients.

## 6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling and schedule of administration, appearance, and odor.

**Site staff**

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

**Sponsor staff**

The following unblinded sponsor roles are required for this study:

- Unblinded BM bio-analyst (BM samples)
- Unblinded PK bio-analyst (PK samples)

Both will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. They will provide the sample data to the study team under blinded conditions unless otherwise allowed.



All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

**Table 6-2 Blinding levels**

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| Role | Time or Event | | |
|---|---|---|---|
| | **Randomization list generated** | **Treatment allocation & dosing** | **Safety event (single subject unblinded)** |
| Subjects/Patients | B | B | UI |
| Site staff | B | B | UI |
| Data Manager | B | B | UI |
| Monitor | B | B | UI |
| Drug Supply and Randomization Office | UI | UI | UI |
| Unblinded sponsor staff (see text for details) | UI | UI | UI |
| Statistician/statistical programmer/data analysts | B | B | UI |
| CTT and decision boards | B | B | UI |

B Remains blinded

UI Allowed to be unblinded on individual patient level

## 6.5 Treating the subject

CJM112 will be administered to the subject via s.c. dosing. See the SOM for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

## 6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted. Occasional interruptions in study treatment must be recorded as protocol deviations.

These changes must be recorded on the Dosage Administration Record Case Report Form (CRF).

## 6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system

will automatically inform the study monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The inves tigator will need to provide:

- protocol number
- study drug name (if available)
- subject number

In addition, the investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject..

## 6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with CJM112, as detailed in Section 8.6.

## 6.9 Recommended treatment of adverse events

There are no known expected AE associated with CJM112 that would warrant specific treatment. Necessary medication as well as surgical or physical treatment used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

## 6.10 Rescue medication

No specific rescue treatments are planned for this study. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

## 6.11 Concomitant treatment

All prescription medications, OTC drugs and significant non-drug therapies (including laser or light / photodynamic therapy, physical therapy, chemical peel, medicated cleansers or surgery and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

# 7 Study completion and discontinuation

## 7.1 Study completion and post-study treatment

Each patient will be required to complete the study and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last patient completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All patients should have safety follow-up for 12 weeks after the last treatment received, whenever possible. The information collected is kept as source documentation. All SAEs reported must be reported as described in Section 9.2 and the SOM. Documentation of attempts to contact the patient should be recorded in the source documentation.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

## 7.2 Discontinuation of study treatment

**Individual Treatment Discontinuation Rules**

Patients may voluntarily discontinue the study for any reason at any time. The investigator must discontinue study treatment for a given subjects, if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment **must** be discontinued under the following circumstances:

- Patient withdraws consent
- Pregnancy
- Emergence of the following AEs (CTCAE grading v4.03):
  - Grade 3 or higher allergic or hypersensitivity reaction
  - Acute, grade 3 or higher infection as judged by the investigator
  - Neutropenia grade 3 or higher
- Clinical worsening of acne (worsening of at least one grade in the IGA, e.g. from severe to very severe) and/or any active ongoing scarring as per investigator judgement
- Any other protocol deviation that results in a significant risk to the patient's safety

Use of prohibited treatment as per Section 5.2 might result in treatment discontinuation (decision will be taken on case by case basis after consultation with Sponsor).

The appropriate personnel from the site and Novartis will assess whether treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Subjects who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Where possible, they should return for the assessments as defined in the Assessment table for the post-treatment follow-up visits.

If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in Section 7.1.

## 7.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore and
- Does not want any further visits or assessments and
- Does not want any further study related contacts and
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

## 7.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

## 7.5 Study stopping rules

The study must be put on hold pending full safety data review if one or more of the following criteria are met:

- Two or more investigational drug (CJM112)-related SAEs are reported
- Other clinically significant events that in the opinion of the investigator or sponsor preclude to continue dosing (especially events that are suspected to be drug related, such as severe skin infections)

In these cases, ad hoc internal experts will carefully evaluate the safety data of the entire study. The experts will recommend whether the study can be continued, should be stopped or if other safety measures need to be taken. The findings and recommendations of the internal experts will be documented and will be made available to the respective Institutional Review Board/Independent Ethics Committee (IRB/IEC).

## 7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

# 8 Procedures and assessments

**Table 8-1 Assessment Schedule**

| Study Epoch | Screening | Treatment Period 1 | | | Extension Period 2 | | | | Post-treatment Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Numbers[1] | V1 | V101 | V102 | V103[2] | V201 | V202 | V203 | V204[2] | V301[16] | V302[2,16] |
| Study Day(s) | -28 to -2 | 1<br>+2 | 29<br>-5 +5 | 57<br>-5 +5 | 85<br>-5 +5 | 113<br>-5 +5 | 141<br>-5 +5 | 169<br>-3 +3 | 218<br>-10 +10 | 260<br>-15 +15 |
| Time (post-dose) | - | - | - | - | - | - | - | - | - | - |
| Informed consent | X | | | | | | | | | |
| Corporate Confidential Information | X | | | | | | | | | |
| Inclusion / Exclusion criteria | X | X | | | | | | | | |
| Physical examination[3] | X | X | X | X | X | | | X | | X |
| Medical history/current medical conditions | X | | | | | | | | | |
| Concomitant medications | As required | | | | | | | | | |
| Demography | X | | | | | | | | | |
| Body height | X | | | | | | | | | |
| Body weight | X | X | | | | | | X | | |
| Body temperature | X | X | X | X | X | X | X | X | X | X |
| Pulse rate | X | X | X | X | X | X | X | X | X | X |
| Blood pressure | X | X | X | X | X | X | X | X | X | X |
| ECG evaluation[3] | X | X | X | | X | | | X | | X |
| Blood chemistry | X | X | X | X | X | X | X | X | X | X |
| Hematology | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test[4] | X | X | X | X | X | X | X | X | X | X |
| Hepatitis and HIV Screen | X | | | | | | | | | |
| Tuberculosis test[3] | X | | | | | | | | | |

| Study Epoch | Screening | Treatment Period 1 | | | Extension Period 2 | | | | Post-treatment Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Numbers[1] | V1 | V101 | V102 | V103[2] | V201 | V202 | V203 | V204[2] | V301[16] | V302[2,16] |
| Study Day(s) | -28 to -2 | 1<br>+2 | 29<br>-5 +5 | 57<br>-5 +5 | 85<br>-5 +5 | 113<br>-5 +5 | 141<br>-5 +5 | 169<br>-3 +3 | 218<br>-10 +10 | 260<br>-15 +15 |
| Time (post-dose) | - | - | - | - | - | - | - | - | - | - |
| Serious adverse events (SAEs)[5] | As required | | | | | | | | | |
| Adverse events (AEs) | As required | | | | | | | | | |
| Drug administration record | | X | X | X | X | X | X | X | | |
| PK blood collection[6] | | X | X | X | X | X | X | X | X | X |
| Corporate Confidential Information | | X | | | X | | | X | | X |
| Facial inflammatory lesion counts[7] | X | X | X | X | X[17] | X | X | X | X | X |
| Facial non-inflammatory lesion count[8] | | X | X | | X | | | X | | X |
| Corporate Confidential Information | X | X | X | X | X | X | X | X | X | X |
| | | X | X | | X | | | X | | X |
| Facial and non-facial nodule count | | X | X | | X | | | X | | X |
| Corporate Confidential Information | | X | X | | X | | | X | | X |
| | | X | | | X | | | X | | X |
| | | X | | | X | | | X | X | X |
| | X | X | X | | X | | | X | | X |
| | | X | | | | | | | | |
| | X | X | | | X | | | X | | |
| | X | X | | | X | | | X | | |
| | | X | X | | X | | | | | |
| Study completion information | | | | | | | | | | X |

[1] Visit structure given for internal programming purpose only
[2] The end of each Epoch is marked by the completion of the disposition CRF (x99) in the summary CRF section...
[3] Collected in source documentation only.
[4] Blood test at screening and EOS or last visit; additional urine tests are done throughout the study if pregnancy is suspected (e.g. if subject experience irregular menstrual period).
[5] SAEs collected up to 30 days following the EOS Visit
[6] Pre-dose sample on dosing days.
[7] Papules, pustules and nodules
[8] Open and closed comedones



[16] Visits to be completed by patients who discontinue from a treatment period early, or decide not to proceed to extension period 2 after participation in treatment period 1.
[17] Responder status will be assessed pre-dose.

## 8.1 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the patient agrees to future research. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the patient.

Ensure patients are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.



In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional IRB and/or IEC approval will be obtained.

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

## 8.2 Subject screening

Information on what data should be collected for screening failures is outlined in the SOM.

## 8.3 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the SOM.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

## 8.4 Efficacy / Pharmacodynamics

Pharmacodynamic and efficacy assessments are specified below, with the methods for assessment and recording specified in the SOM. As clinical efficacy measures are rater dependent, each evaluator should be appropriately trained and qualified for these assessments. Every effort should be made that the same evaluator assesses and counts the lesions throughout the study.

Assessments will be performed and pharmacodynamic samples will be collected at the timepoints defined in the Assessment Schedule. Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment.

In order to better define the Pharmacodynamic (PD) profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

PD samples will be obtained and evaluated in all subjects at all dose levels.

#### 8.4.1.4 Patient-Reported Outcomes (PRO)

All PROs should be completed pre-dose on the dosing days.



##### 8.4.1.4.2 Patient global assessment

The patients will be asked at predefined visits, what their perception of efficacy and treatment satisfaction is. The question asked will be “How would you rate your acne today?”

The following rating will be used:

**Table 8-4 Patient Global Assessment**

| Grade | Rating |
|---|---|
| 0 | Clear |
| 1 | Minimal / Almost clear |
| 2 | Mild |
| 3 | Moderate |
| 4 | Severe |
| 5 | Very severe |

##### 8.4.1.4.3 Patient's treatment satisfaction questionnaire

Patient’s treatment satisfaction questionnaire is to inform about the overall satisfaction from the patient's perspective. The following questions will be asked at visits as specified in the Assessment Schedule:

1. How satisfied or dissatisfied are you with this acne treatment?
2 Overall, and taking all things into account, how satisfied or dissatisfied are you with this medication?
3 Would you use this medication again if you were in the same condition as at the start of the trial?

All above questions will be answered by using a 7 point Likert scale approach (question 1-3 with extremes such as ‘Extremely Satisfied' to 'Extremely Dissatisfied').

## 8.5 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment Schedule detailing when each assessment is to be performed.

### 8.5.1 Physical examination

Physical examination will be done at timepoints specified in the Assessment Schedule.

### 8.5.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

### 8.5.3 Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]$^2$)

### 8.5.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

#### Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured. Both absolute and differential cell counts will be recorded.

#### Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, calcium, cholesterol, chloride, creatinine, CK, CRP, γ-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, BUN and uric acid.

For postmenopausal women, FSH is measured at screening to assist in confirming menopausal status.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

#### Urinalysis

A midstream urine sample (approx. 30 ml) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative “dipstick” evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for protein, leucocytes and/or blood the sample will be sent for microscopic analysis of WBC, RBC and casts.

### 8.5.5 Electrocardiogram (ECG)

Standard 12-lead ECGs will be used to be performed at the visits specified in the Assessment Schedule. The preferred sequence of data collection during study visits is ECG collection first (10 min rest, ECG recording over next 5 min suggested), followed by vital signs (heart rate and BP), and PK sampling.

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

### 8.5.6 Pregnancy and assessments of fertility

All females (irrespectively of reproductive status) will need to have serum pregnancy test at screening and EOS.

All women who are not surgically sterile will have regular urine pregnancy tests during the study as outlined in the Assessment Schedule. Additional urine pregnancy tests may be required, if a reason occurs such as patient reports delay in menstruation. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

### 8.5.7 Tuberculosis test

Blood tuberculosis testing with the Quantiferon assay (QuantiFERON®-TB Gold In-Tube) will be performed as specified in the Assessment Schedule.



## 8.6 Pharmacokinetics

PK samples (total CJM112) will be collected at the time points defined in the Assessment Schedule. Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment, see Section 8.8.

Samples will be analyzed as per laboratory's standard operating procedures, and total CJM112 in serum will be determined by a validated ELISA method. The anticipated Lower Limit of Quantification (LLOQ) is 240 ng/mL in 100% human serum. All procedures and analytical methods will be detailed in the bioanalytical data report.

Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects at all dose levels. Concentrations will be expressed in microg/mL, the time unit is day. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

## 8.7 Other assessments

No additional tests will be performed on subjects entered into this study.

# 9 Safety monitoring

## 9.1 Adverse events

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying AEs. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

For patients that pass screening and enter in the study, AEs must be recorded on the AEs CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. its relationship to the study treatment (no/yes), or investigational treatment (no/yes), or other study treatment (non-investigational) (no/yes), or both or indistinguishable,
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met

5. Action taken regarding investigational treatment.
   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator must also instruct each subject to report any new AE (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

## 9.2 Serious adverse event reporting

### 9.2.1 Definition of SAE

An SAE is defined as any AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the subject's general condition

- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis DS&E as per Section 9.2.2.

### 9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis **within 24 hours of learning of its occurrence** as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the SOM.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been

reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the SOM regarding the submission process for reporting SAEs to Novartis. Note: **SAEs must be reported to Novartis within 24 hours** of the investigator learning of its occurrence/receiving follow-up information.

## 9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

**Follow-up of liver events**

Every liver event defined in Table 15-1-Appendix 1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and γGT) to confirm elevation within 48-72 hours.

  These liver chemistry repeats should be performed using the central laboratory if possible, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and γGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, Creatinine Phosphokinase (CPK) should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.

- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 15-3.
- Imaging such as abdominal US, CT or Magnetic resonance imaging (MRI), as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

## 9.4 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Section 16 -Appendix 2.

Renal events are defined as one of the following:

- confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- new onset (≥1+) proteinuria, hematuria or glucosuria; or as a
- doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

The following two categories of abnormalities/AEs have to be considered during the course of the study:

- Serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter
- Urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

## 9.5 Reporting Medication errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis DS&E department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the AE CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

**Table 9-1 Summary of reporting requirements for medication errors**

| Treatment error type | Document in Dose Administration (DAR) CRF | Document in AE CRF | Complete SAE form/CRF |
|---|---|---|---|
| Unintentional study treatment error | Yes | Only if associated with an AE | Only if associated with an SAE |
| Misuse/Abuse | Yes | Yes | Yes, even if not associated with a SAE |

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

## 9.6 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

## 9.7 Early phase safety monitoring

The Investigator will monitor AEs in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

# 10 Data review and database management

## 10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

## 10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the SOM and Assessment Schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

## 10.3 Database management and quality control

CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to a designated CRO.

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of any protocol deviations (PD) will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Clinical Operations, Analytics & Regions (COAR) Analytics Novartis Institute of Biomedical Research (NIBR) Franchise Head and the relevant NIBR Therapeutic Area Head.

To maximize confidentiality, all samples will be double-coded to prevent the exposure of the subject's identity. This double-coding process allows Novartis to go back and destroy the sample at the subject's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

## 10.4 Data Monitoring Committee

Not required.

## 10.5 Adjudication Committee

Not required.

# 11 Data analysis

The analyses will be conducted on all subject data at the time when interim analysis occurs and also when the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

## 11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

## 11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group. Subject demographics will include age, sex, race, ethnicity, country, height, weight and BMI. Baseline disease characteristics include but are not limited to: inflammatory facial lesion count and IGA.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

## 11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

## 11.4 Analysis of the primary variable(s)

The primary aim of this study is to assess the efficacy of CJM112 versus placebo on inflammatory facial lesion counts in patients with moderate to severe inflammatory acne. Therefore, a statistical analysis will be performed on the log transformed inflammatory facial lesion count after 12 weeks. Details are provided in Section 11.4.2.

### 11.4.1 Variable(s)

The primary variable is the natural log transformed total inflammatory facial lesion counts at Week 12.

### 11.4.2 Statistical model, hypothesis, and method of analysis

The log transformed inflammatory facial lesion count is expected to be approximately normally distributed. It will be analyzed using a Bayesian mixed effect model for repeated measures (MMRM), with log transformed baseline inflammatory facial lesion count as a covariate; treatment sequence, visit, treatment group by visit interaction and log transformed baseline inflammatory facial lesion count by visit interaction as fixed effects. A non-informative prior will be utilized to obtain the posterior estimates. Unstructured covariance structure will be used. Other factors such as gender and race will also be explored for statistical significance if the distribution per factor is reasonably balanced. The log transformed baseline lesion count will be centered and standardized before used in the model.

Data up to Week 12 will be included in the model, for the comparison of CJM112 versus placebo at Week 12, which is of primary interest. Corporate Confidential Information

Bayesian posterior probabilities will be used to assess the following criteria as a guide to decision making (Fisch et al 2015), though other criteria may be taken into account:

Corporate Confidential Information

The posterior estimates of the treatment effect and the treatment difference (along with its 90% credibility interval) at each visit (with Week 12 being of primary interest) will be provided. The results will be reported in terms of ratio of geometric means by back

transforming the estimates from the log-scale. Data will also be presented in graphics such as spaghetti plot.

### 11.4.3 Handling of missing values/censoring/discontinuations

All patients with available data after baseline and until Week 12 will be included in the primary analysis. The primary analysis model is known to give unbiased results under the assumption that missing data are at random (MAR), i.e. given observed data the missingness does not depend on unobserved data. If a patient drops out the study according to the predefined discontinuation criteria (Section 7.2), this MAR assumption remains valid. Besides, last observation carried forward (LOCF) method will be used in a sensitivity analysis to handle missing data.

### 11.4.4 Sensitivity analyses

A negative binomial or Poisson generalized linear model on facial inflammatory lesion count at Week 12 will be applied as a sensitivity analysis. Baseline lesion count will be used as a covariate and treatment group as a factor.

## 11.5 Analysis of secondary variable(s)

### 11.5.1 Safety

#### Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

#### ECG evaluations

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by period, treatment and visit/time.

#### Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by period, treatment and visit/time.

#### Adverse Events (AEs)

All information obtained on AEs will be displayed by treatment group and subject.

The number and percentage of subjects with AEs will be tabulated by body system and preferred term with a breakdown by period and treatment. A subject with multiple AEs within a body system is only counted once towards the total of this body system.

### Other safety evaluations

Pregnancy test results will be listed by treatment group, subject and visit/time.



### 11.5.2 Pharmacokinetics

Total CJM112 serum concentration data (in microg/mL) will be listed by treatment group, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be calculated as described in Section 8.6 and will be listed by treatment and subject. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. A geometric mean will not be reported if the dataset includes zero values.

### 11.5.3 Pharmacokinetic / pharmacodynamic interactions

Not Applicable.

## 11.7 Sample size calculation

A total number of 75 patients with a 1:1:1 randomization ratio should provide around 21 patients in each treatment group with complete 12-week data, assuming a dropout rate of around 15%.



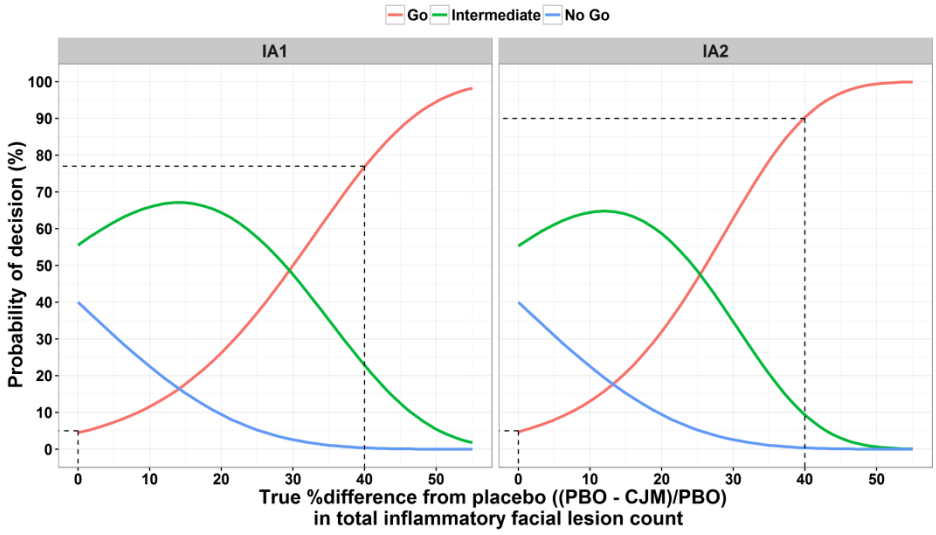
The 30% difference in total inflammatory facial lesion count at Week 12 between a standard care oral antibiotics and placebo, reported by Fleischer et al 2006, served as reference to define a more stringent threshold of at least 40% difference to placebo for the sample size calculation. Assuming a geometric mean of 20 lesions in the placebo group at Week 12, the 30% difference (a delta of 0.357 on the log scale) corresponds to approximately 6 lesions difference in geometric means; a 40% difference (a delta of 0.511 on the log scale) corresponds to approximately 8 lesions difference in geometric means.

**Table 11-1 Operating characteristics of decision rules for n=21 per arm**

| Sample size | True effect = 0% | | True effect = 40% | |
|---|---|---|---|---|
| | Chance of meeting efficacy criteria (Type I error) | Chance of meeting futility criterion | Chance of meeting efficacy criteria (Power) | Chance of meeting futility criterion (Type II error) |
| 10+10 (IA1) | 5% | 40% | 77% | < 1% |
| 21+21 (IA2) | 5% | - | 90% | - |

Note: Calculations assume a SD of 0.47 of log-transformed inflammatory facial lesion count and an effect of 40% over placebo is considered a good effect.

**Figure 11-1 Operating characteristics curve for n=21 per arm**




## 11.8 Power for analysis of key secondary variables

Not applicable.

# 12 Ethical considerations

## 12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

## 12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

## 12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

# 13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

## 13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

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Available upon request

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# 15 Appendix 1: Liver Event Definitions and Follow-up Requirements

**Table 15-1 Liver Event Definitions**

| Definition | Thresholds |
|---|---|
| Potential Hy's law cases | • ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN |
| ALT or AST elevation with coagulopathy | • ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation) |
| ALT or AST elevation accompanied by symptoms | • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia |
| Isolated ALT or AST elevation | • ALT or AST > 8 × ULN<br>• 5 x ULN < ALT/AST £ 8 x ULN<br>• 3 x ULN < ALT/AST £ 5 x ULN |
| Isolated ALP elevation | • ALP > 2 × ULN (in the absence of known bone pathology) |
| Others | • Any clinical event of jaundice (or equivalent term)<br>• Any AE potentially indicative of liver toxicity |

**Table 15-2 Actions required for Liver Events**

| Criteria | Actions required |
|---|---|
| Potential Hy's Law case | • Discontinue the study treatment immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Complete CRFs per liver event guidance |
| ALT or AST elevation accompanied by symptoms<br>Isolated ALT or AST elevation > 8 × ULN<br>Jaundice | ALT or AST elevation with coagulopathy |
| Isolated ALT or AST elevation > 5 to ≤ 8 × ULN | • If confirmed, consider interruption or discontinuation of study drug<br>• If elevation persists for more than 2 weeks, discontinue the study drug<br>• Establish causality<br>• Complete CRFs per liver event guidance |
| Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic) | • Monitor liver chemistry tests two or three times weekly |
| Isolated ALP elevation | • Repeat liver chemistry tests within 48-72 hours<br>• If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality<br>• Complete CRFs per liver event guidance |

| Criteria | Actions required |
|---|---|
| Any AE potentially indicative of liver toxicity | • Consider study treatment interruption or discontinuation<br>• Hospitalize if clinically appropriate<br>• Complete CRFs per liver event guidance |

**Table 15-3 Exclusion of underlying liver disease**

| Disease | Assessment |
|---|---|
| Hepatitis A, B, C, E | • IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA |
| CMV, HSV, EBV infection | • IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV |
| Autoimmune hepatitis | • ANA & ASMA titers, total IgM, IgG, IgE, IgA |
| Alcoholic hepatitis | • Ethanol history, γ GT, MCV, CD-transferrin |
| Nonalcoholic steatohepatitis | • Ultrasound or MRI |
| Hypoxic/ischemic hepatopathy | • Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI. |
| Biliary tract disease | • Ultrasound or MRI, ERCP as appropriate. |
| Wilson disease | • Caeruloplasmin |
| Hemochromatosis | • Ferritin, transferrin |
| Alpha-1-antitrypsin deficiency | • Alpha-1-antitrypsin |

# 16 Appendix 2: Specific Renal Alert Criteria and Actions

**Table 16-1 Specific Renal Alert Criteria and Actions**

| Criteria | Action required |
|---|---|
| Serum creatinine (sCr) increase 25 – 49% compared to baseline | • Consider causes and possible interventions<br>• Follow up within 2-5 days |
| Serum creatinine increase ≥ 50% | • Consider causes and possible interventions<br>• Repeat assessment within 24-48h if possible<br>• Consider drug interruption or discontinuation unless other causes are diagnosed and corrected<br>• Consider hospitalization and specialized treatment |
| Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold<br>or<br>new onset dipstick proteinuria ≥ 1+<br>or<br>Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol;<br>or<br>Protein-creatinine ratio (PCR )≥ 150 mg/g or >15 mg/mmol | • Consider causes and possible interventions<br>• Assess serum albumin & serum protein<br>• Repeat assessment to confirm<br>• Consider drug interruption or discontinuation unless other causes are diagnosed and corrected |
| New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes) | Assess & document:<br>• Blood glucose (fasting)<br>• Serum creatinine<br>• Urine albumin-creatinine ratio |
| New hematuria on dipstick | Assess & document:<br>• Urine sediment microscopy<br>• Assess sCr and urine albumin-creatinine ratio<br>• Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation<br>• Consider bleeding disorder |

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

**Table 16-2 Follow-up of renal events**

| Action | Follow up |
|---|---|
| Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF. | • Urine dipstick and sediment microscopy<br>• Blood pressure and body weight<br>• Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid<br>• Urine output |
| Monitor subject regularly (frequency at investigator's discretion) until: | • Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline)<br>or<br>• Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. |

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.