**Study title:**
A long-term safety and efficacy study of CD5789 50µg/g cream in subjects with acne vulgaris

**Short Title:**
CD5789 Long Term Study (LTS) on acne vulgaris

**Study Phase:**
Phase 3

**Eudract Number:**
2014-001755-23

**IND Number:**
111091

**Treatment Indication:**
Topical treatment of moderate (IGA/PGA score 3) acne vulgaris

**Study Population**
Subjects age 9+ years old, male and female

**Background and Rationale:**
*Acne vulgaris* is the most common skin disease, affecting almost 80 percent of the population at some time between the ages of 11 and 30 years. It can persist for years and result in disfigurement and permanent scarring, and may have serious adverse effects on psychosocial development, resulting in emotional problems, withdrawal from society, and depression.

Truncal (back and chest) acne has been estimated to occur in over half the number of acne patients even if facial acne is the most common and often the most visible form of acne. In one study of patients referred to a dermatology clinic revealed that more than 60 percent of individuals had back acne. In another cohort of 696 patients from five cities, half of patients with facial acne were found to have coexistent truncal involvement.

Acne is a multifactorial inflammatory disease affecting pilosebaceous follicles.

Both clinically and pathophysiologically, truncal acne and facial acne are similar in terms of specific lesions (eg closed comedones, open comedones, papules and pustules etc.). Further, the management of truncal acne vulgaris warrants an approach similar to what is used for the treatment of facial acne.

Several Proof of Concept studies have shown that CD5789 formulated in gel and creams at various concentrations (25, 50 and 100 µg/g) was effective in reducing inflammatory, non-inflammatory and thus total lesion counts within 4 to 8 weeks of topical treatment in subjects

with moderate acne vulgaris of the face in comparison to its placebo. This was confirmed by investigators' and subjects' assessments.

A recent Phase 2 study evaluated three doses of CD5789 cream (25 µg/g, 50 µg/g, and 100 µg/g) in subjects with moderate and severe acne. The study concluded that CD5789 at 25 µg/g represents the minimally effective dose. CD5789 50 µg/g, and 100 µg/g were both determined to be efficacious with only a modest efficacy advantage in favor of the higher dose.

For safety, a dose response trend was observed in the overall summary of adverse events (AEs), with CD5789 100µg/g reporting the highest event rate of any adverse event, related adverse events, related adverse events leading to study withdrawal. Overall and for all categories of AEs, CD5789 50 µg/g had an AE profile that was comparable to vehicle control and notably better than CD5789 100 µg/g. The superior safety and local tolerability profile of CD5789 50 µg/g cream led to the choice of this dose for carrying forward to Phase 3 in this indication.

The local tolerability profile of CD5789 was also dose dependent and followed the usual pattern whereby mean scores peaked at week 1 and gradually decreased over the succeeding weeks. In comparative terms, CD5789 50 µg/g was generally better tolerated than tazarotene 1% gel for most of the parameters assessed, whereas CD5789 100 µg/g was either comparable or less well tolerated than tazarotene 1% gel.

Although both doses of 50 µg/g and 100 µg/g of CD5789 provide a positive benefit risk ratio in the treatment of acne vulgaris, the superior safety and local tolerability profile of CD5789 50 µg/g cream argues in favour of carrying forwards this dose in Phase 3.

**Study Objectives**

This study objectives are to determine the safety and efficacy of CD5789 50µg/g cream in the long-term treatment (up to 52 Weeks) of subjects with acne vulgaris. Efficacy will be evaluated as a secondary objective.

**Study Design**

Multi-center, open-label, non-comparative safety and efficacy study with up to 52 Weeks of treatment on the face and trunk for acne vulgaris.

From Baseline to Week 12 visits, subjects will apply the study drugs once daily in the evening to the Face and to the Trunk (except for children between 9 and 11 years old who do not have moderate acne on the trunk at Baseline, it is up to the investigators to decide if these 9 to 11 years old subjects should be treated or not for truncal acne).

From Week 12 to Week 52/ET visits, subject will apply the study drug according to the IGA and PGA assessment as follow:

| IGA Facial acne | PGA Truncal acne | Study Treatment regimen |
|---|---|---|
| 0 | 0 | Stop on the Face<br>Stop on the Trunk |
| At least 1 | 0 | Stop on the Trunk<br>Continue on the Face |
| 0 | At least 1 | Stop on the Face<br>Continue on the Trunk |
| At least 1 | At least 1 | Continue on the Face<br>Continue on the Trunk |

Specific requirements for children between 9 and 11 years old who do not have moderate acne on the trunk at Baseline (i.e. who do not have PGA of 3, at least 20 inflammatory lesions on the trunk and at least 20 non-inflammatory lesions on the trunk):

In this case, it is up to the investigators to decide if these 9 to 11 years old subjects should be treated or not for truncal acne. In these subjects, treatment can be started (based on investigator's decision) even if e.g. PGA=1, or the subject has less than 20 inflammatory lesions on the trunk and/or less than 20 non-inflammatory lesions on the trunk). These subjects will not be assessed for efficacy, but they will be assessed for safety and local tolerability.

In any case the subject should continue in the study until the Week 52 visit.
Unscheduled visit maybe carried-out if the subject experiences an acne flare or a local tolerability issue that may need to reintroduce or to adapt the study treatment regimen.

**Total Number of Sites**
The total number of sites is expected to be 33 to 47 approximately.

**Region / Countries**
The study will be conducted in Europe, Japan and USA.

**Study Duration**
The planned clinical trial duration, from First Subject In (FSI) to Last Subject Out (LSO) is approximately 24 months.
The planned duration of recruitment, from FSI to Last Subject In (LSI), is approximately to 6 to 12 months.

**Duration of Subject Participation**
Clinical trial participation for each subject is approximately 12 months (up to 54 weeks +/- 3 days including a screening period of up to 2 weeks).

**Total Number of Subjects**

Approximately 665 subjects will be screened to enrol 500 subjects worldwide (Europe, USA and Japan), including approximately 50 Japanese subjects.

**Treatment Duration**
Each subject will be treated for up to 52 weeks.

**Inclusion Criteria**
In order to be eligible for the study, subjects must fulfill all of the following criteria:

1. Male or female, 9 years of age and older at Screening visit.
2. The subject has a facial acne severity grade of IGA 3 (moderate) at Screening and Baseline visits.
3. The subject has a minimum of 20 inflammatory lesions and 25 non-inflammatory lesions on the face at Screening and Baseline visits.
4. The subject has truncal acne severity grade of PGA 3 (moderate) at Screening and Baseline visits on the shoulders, anterior chest and upper back reachable to self-application of study drug by the subject (this inclusion criterion is optional for children between 9 and 11 years old).
5. The subject has a minimum of 20 inflammatory lesions and 20 non-inflammatory lesions at Screening and Baseline visits on the shoulders, upper back and anterior chest (this inclusion criterion is optional for children between 9 and 11 years old).
6. Female of non-childbearing potential pre-menarcheal or postmenopausal (absence of menstrual bleeding for 1 year prior to Screening, without any other medical reason), hysterectomy or bilateral oophorectomy.
7. Female of childbearing potential:
    a. With a negative urine pregnancy test (UPT) at Screening and Baseline visits,
    b. Who has been strictly abstinent for 1 month prior to Baseline and agrees to continue for the duration of the clinical trial and at least 1 month after the last study drug application,

    OR

    c. Who agrees to use an effective and approved contraceptive method(s) for the duration of the study and at least 1 month after the last study drug application. An effective method of contraception is defined as:
        i. bilateral tubal ligation;

ii. combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives or hormonal contraceptive vaginal rings with a stable dose for at least 1 month prior to the Baseline visit;
iii. hormonal intra-uterine device (IUD) inserted at least 1 month prior to the Baseline visit;
iv. vasectomized partner for at least 3 months prior to the Baseline visit.

8. Female of childbearing potential uses combined oral contraceptives approved as acne treatment (e.g., Ortho Tri-Cyclen®, Yaz®, Diane-35®), the dose should be stable for at least 6 months prior to the Baseline visit.
9. For pre-menstrual female who begin menses during the study:
   a. Who agrees to be strictly abstinent for the duration of the clinical trial and at least 1 month after the last study drug application,

   OR

   b. Who agrees to use an effective and approved contraceptive method(s) for the duration of the study and at least 1 month after the last study drug application and agrees to undergo pregnancy tests. An effective method of contraception is defined as combined oral contraceptives (oestrogens and progesterone) or implanted or injectable contraceptives, or hormonal intra-uterine device (IUD) or hormonal contraceptive vaginal rings.
10. The Subject is willing and is able to comply with all of the time commitments and procedural requirements of the protocol (for subjects who are minors, the parent(s)/legal representative must be also willing and able to comply with study requirements).
11. The subject agrees to participate in the study, verified by dating and signing an approved written Informed Consent Form (ICF) or, for subjects under age of majority, an assent form signed by the subject in conjunction with an ICF signed by the parent(s)/legal representative at the Screening visit before any study procedures.

    In selected sites (outside Japan): Child between 9 and 11 years old and the parent(s)/legal representative agrees to participate in PK assessment, will accept the PK procedure in the Consent / Assent form. Participation to PK sampling is not mandatory to participate in the Study.

    In selected sites: The subject agrees to participate to the study photographs, verified by dating and signing a separate approved written Informed Consent Form for photos and for subjects under age of majority, an assent form signed by the subject in conjunction with an photo ICF signed by the parent(s)/legal representative at the Screening visit. Participation to photo procedures is not mandatory to participate in the Study.
12. In USA centers only: Apprised of the Health Insurance Portability and Accountability Act (HIPAA) and is willing to share personal information and data, as verified by signing a written authorization at the Screening visit.

**Exclusion Criteria**

Any subjects who meet one or more of the following exclusion criteria will not be eligible for this study.

1. The Subjects with severe forms of acne (acne conglobata, acne fulminans) or secondary acne form (chloracne, drug-induced acne, etc.).
2. The Subject has more than 1 nodule on the face at Screening or Baseline.
3. The subject has more than 1 nodule on the trunk at Screening or Baseline.
4. The Subject has any acne cyst on the face at Screening and at Baseline visits.
5. The Subject has any acne cyst on the trunk at Screening and at Baseline visits.
6. The Subject has a beard or facial/body hair that may interfere with the study assessments.
7. The Subject with tattoos on the face, the shoulders, upper back and anterior chest on evaluable area that may interfere with the study assessments or subject who intend to have tattoos on these areas during the course of the study.
8. The Subjects has any uncontrolled or serious disease or any medical or surgical condition that may either interfere with the interpretation of the trial results and/or put the subject at significant risk (according to the Investigator's judgment) if the subject takes part in the trial.
9. The Subject has clinically significant abnormal laboratory values at Screening visit (results to be checked at Baseline visit) that may either interfere with the interpretation of the trial results and/or put the subject at significant risk (according to the Investigator's judgment) if the subject takes part in the trial.
10. The Subject has known or suspected allergies or sensitivities to any components of any of the study drugs (see Investigator's Brochure).
11. The Subject is a Female who is lactating.
12. The Subject is a Female who intends to conceive a child during the trial or for at least 1 month after the last study drug application.
13. The Subject is currently participating in any other clinical trial of a drug or medical device OR participated in any other clinical trial within the 30 days prior to the Baseline visit
14. The Subject has received, applied, or ingested the following treatments within the specified time frame prior to the Baseline visit

| | |
|---|---|
| **Topical treatment on the face and trunk:** | |
| Antibiotics,<br>Benzoyl peroxide,<br>Azelaic acid,<br>Zinc<br>Corticosteroids<br>Other topical treatments (including laser) | 2 weeks |
| Retinoids | 4 weeks |
| **Topical procedures on the face and trunk:** | |
| Phototherapy devices for acne (e.g., ClearLight™)<br>Adhesive cleansing strips (e.g., Pond®, Biore®)<br>Cosmetic procedures (i.e., facials, peeling, comedone extraction) | 1 week |
| **Systemic treatment:** | |

| | |
|---|---|
| Non- steroidal anti-inflammatory drugs | 2 weeks |
| Corticosteroids (except inhaled corticosteroids or intrathecal corticosteroids ) | 4 weeks |
| Antibiotics (except plain penicillin) | 4 weeks |
| Oral retinoids | 6 months |
| Immunomodulators, including biologics | 6 months |

Note: No time frame period is specified for Alpha-hydroxy acid products, medicated shaving creams, after-shaves, colognes, astringents, or preparations with alcohol, but their application is prohibited during the study.

15. The Subject has been exposed to excessive ultraviolet (UV) radiation on the face and/or on the trunk treated area within one month prior to the Baseline visit or the subject is planning intense UV exposure during the study (i.e. occupational exposure to the sun, subject used to sunbathing, tanning salon use, phototherapy, etc.)
16. The Subject is unwilling to refrain from use of prohibited medication during the clinical trial
17. The Subject is vulnerable (e.g., deprived of freedom) as defined in Section 1.61 of International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

**Efficacy Assessments**

Efficacy will be evaluated as a secondary objective. IGA and PGA assessments are to be performed by a qualified investigator. Training is required for all evaluators who perform IGA/PGA.

***IGA (Investigator's Global Assessment) of facial acne***

The areas defined for IGA assessment are forehead, each cheek, chin and nose. Investigators will evaluate the facial acne at predetermined visits (see table 1) according to the following scale.

| **Investigator's Global Assessment Scale (IGA)** | | |
|---|---|---|
| 0 | Clear | Clear skin with no inflammatory or non inflammatory lesions. |
| 1 | Almost Clear | A few scattered comedones and a few small papules. |
| 2 | Mild | Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules. |
| 3 | Moderate | More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present. |
| 4 | Severe | Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present. |
| Note: At Screening and Baseline visits IGA assessment is to be done prior to lesion counts. Time of IGA assessment should be recorded in the source data and the eCRF (before assessing lesions counts on the face). | | |

***PGA (Physician's Global Assessment) of truncal acne***

The areas defined PGA assessment are shoulders, upper back and anterior chest which are accessible to self-application by the subject, i.e. the regions that the subject can easily reach and apply the study drug by himself or herself without assistance.
Investigators will evaluate the truncal acne at predetermined visits (see table 1) according to the following scale.

Specific requirements for children between 9 and 11 years old who do not have moderate acne on the trunk at Baseline (i.e. who do not have PGA of 3, at least 20 inflammatory lesions on the trunk and at least 20 non-inflammatory lesions on the trunk):

The PGA scale will be completed at all visits (including Week 1, 2, 4 and 8 visits), and used by the investigators to decide if they want to start the treatment for truncal acne.

| **Physician Global Assessment Scale (PGA)** | | |
|---|---|---|
| 0 | Clear | Clear skin with no inflammatory or non -inflammatory lesions. |
| 1 | Almost Clear | A few scattered comedones and a few small papules. |
| 2 | Mild | Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules. |
| 3 | Moderate | More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present. |
| 4 | Severe | Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present. |
| Note: At Screening and Baseline visits PGA assessment is to be done prior to lesion counts. Time of PGA assessment should be recorded in the source data and the eCRF (before assessing lesions counts on the trunk). | | |

**Efficacy Assessments**

- Success rate of IGA (defined as 0=clear or 1=almost clear) at each time point
- Success rate of PGA (defined as 0=clear or 1=almost clear) at each time point
- Grade change from baseline of IGA at each time point
- Grade change from baseline of PGA at each time point
- Subject's assessment of facial acne improvement at each time point.

**Safety Assessments**

- Local tolerability (erythema, scaling, dryness, and stinging/burning) on the face and trunk,
- Adverse event,
- Laboratory parameters,

- Vital signs and physical examination

**Other Assessments**

- Lesion counts on the face and on the trunk at Screening and Baseline visit
- DLQI and C-DLQI at each time point,
- PK data

In selected sites only, a PK assessment will be performed only in 9 to 11 year old subjects who have agreed in the parents/guardian ICF and Assent form to have a PK sample taken. At week 4, the application will be done **on site** at this specific day at any time. One single blood sample will be collected 4 hours (± 10 min) after on-site study drug application.

**Principal Statistical Methods**

A Statistical Analysis Plan (SAP) will be developed as a separate document. The SAP will contain a more detailed and technical description of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in the sections of the clinical trial protocol below.
The SAP will be finalized prior to Database Lock.
Any changes to the statistical analyses decided after the Database Lock should be justified and documented in the clinical trial report.

**Sample Size**

This study was designed to ensure that at least 300 subjects will be exposed to CD5789 50µg/g cream for 6 months, and 100 subjects exposed for 1 year.

**Table 1 – Schedule of Assessments**

| | Scheduled Visits [i] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedures** | **Screening** [a] (up to 14 days prior to Baseline) | **Baseline** [a] | **Wk 1** (±3 day) | **Wk 2** (±3 day) | **Wk 4** (± 3days) | **Wk 8** (±3 days) | **Wk 12** (±5days) | **Wk 20** (±5days) | **Wk 26** (±5 days) | **Wk 38** (±5 days) | **Wk 52/ ET** (±5 days) | **Unscheduled**[k] |
| Informed Consent/ HIPAA (US only)/ Assent Form/ Photo Consent | X | | | | | | | | | | | |
| Demographics | X | X [d] | | | | | | | | | | |
| Medical History | X | X [d] | | | | | | | | | | |
| Previous Therapies/Procedures | X | | | | | | | | | | | |
| Vital Signs/Physical Examination | X | X [d] | | | | | X | | X | | X | X |
| Laboratory Safety Test | X | | | | | | | | X | | X | |
| Urine Pregnancy Testing [c] | X | X | | | X | X | X | X | X | X | X | X |
| Subject's Assessment of Acne improvement (face) | | | | | | | X | | X | | X | |
| Face and trunk Photographs (only in selected centers) | | X | | | | | X | | X | | X | |
| IGA | X | X [d] | | | | | X | X | X | X | X | X |
| PGA [l] | X | X [d] | X[m] | X[m] | X[m] | X[m] | X | X | X | X | X | X |
| Acne Lesion Counting (face) | X | X [d] | | | | | | | | | | |
| Acne Lesion Counting (trunk) [e] | X | X [d] | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X [d] | | | | | | | | | | |
| Local Tolerability (face) [f] | | X | X | X | X | X | X | X | X | X | X | X |
| Local Tolerability (trunk) [f] | | X | X | X | X | X | X | X | X | X | X | X |

| Scheduled Visits [i] | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedures** | **Screening** [a] (up to 14 days prior to Baseline) | **Baseline** [a] | **Wk 1** (±3 day) | **Wk 2** (±3 day) | **Wk 4** (± 3days) | **Wk 8** (±3 days) | **Wk 12** (±5days) | **Wk 20** (±5days) | **Wk 26** (±5 days) | **Wk 38** (±5 days) | **Wk 52/ ET** (±5 days) | **Unscheduled**[k] |
| Adverse Event recording [g] | X | X | X | X | X | X | X | X | X | X | X | X |
| Pharmacokinetic assessment (only in selected sites and to eligible subjects [9 to 11 years old]) | | | | | X | | | | | | | |
| DLQI or C-DLQI | | X | | | | | X | | X | | X | |
| Study drug dispensing (D) and Accountability (A) | | D | | | D/A | | D/A [j] | D/A [j] | D/A [j] | D/A [j] | A [j] | D |
| Moisturizer/cleanser Dispensing (D) | | D | | | D | | D | D | D | D | | D |
| Dosing calendar given (G) returned and reviewed (RR) | | G | RR | RR | RR | RR | RR | RR | RR | RR | RR | RR |
| Concomitant therapies/procedures [h] | X | X | X | X | X | X | X | X | X | X | X | X |
| Exit Form | | | | | | | | | | | X [b] | |

a) Baseline visit must be performed maximum 14 days after Screening. For women of childbearing potential, there must be 14 days between Screening and Baseline Visit (for UPT reason). No re-screen will be allowed

b) Should be conducted earlier if subject discontinues prior to Week 52.

c) For Subject of childbearing potential only: The determination of Urine Pregnancy Tests is mandatory at Screening, Baseline, Week 4, Week 8, Week 12, Week 20, Week 26 ,Week 38 and Week 52 before if there is early termination and in case of an Unscheduled Visit.

d) Confirm information at Baseline.

e) Lesion counts on the trunk : except for Children between 9 and 11 years old with no moderate acne on the trunk at Baseline

f) The Baseline local tolerability assessment will occur prior the first study drug application on the given area.
Subjects between 9 and 11 years old with no moderate acne on the trunk at Baseline (i.e. who do not have PGA of 3): the local tolerability assessment will only be performed if study drug treatment has been started on the trunk (based on investigator decision)

g) Adverse events occurring from the time the informed consent is signed should be recorded in the eCRF.

h) Medication that continues after Screening visit should be recorded on the Concomitant Medication page of the eCRF. Medical or surgical procedures occurring after Screening visit should be recorded on the Procedures page of the eCRF.

i) To enhance subject compliance, a study window of plus or minus 3 days will be allowed for Week 1, Week 2; Week 4 and Week 8. A study window of plus or minus 5 days will be allowed for Weeks 12, 20, 26, 38, 52. All study visits should be scheduled based on the actual date of Baseline visit date.

j) From Week 12 to Week 52 the dispensation will be done only if the skin assessment is not clear (IGA or PGA >=1); Accountability should occur only when a prescription has been done at the previous corresponding visit and the Subject returns the study drugs.

k) An unscheduled visit can take place in case of need for any dose regimen adaptation or study drug restart necessary for managing local skin tolerability or acne flare.

l) Mandatory PGA assessment for all the study population, at Screening, Baseline and all visits from Week 12.

m) PGA assessment ONLY for Subjects between 9 and 11 years old with no moderate acne on the trunk at Baseline.

**Table 2 – Description and usage of Study Drugs**

| | **Investigational Product** |
|---|---|
| Trade Name or Equivalent | N/A |
| Internal Code | CD5789 |
| Pharmaceutical Form | Cream |
| Strength/ Concentration | 50µg/g |
| Formula number | 0219.0102 |
| Packaging (type and size) | 50mL bottle with pump and overcap |
| Storage conditions | Store below 25°C / 77°F, do not freeze, do not refrigerate |
| Dosage (total daily dose) | Apply a thin film on the face on affected and not affected areas. A pea-size amount for each area of the face (forehead, chin, nose and each cheek), should be used; avoiding the nostrils, mouth, lips, eyelids and periorbital areas.<br><br>Apply a thin film on the trunk on the upper back, shoulders and anterior chest on the affected and not affected areas. At least a pea-size amount for each area of the trunk (right & left upper back, right & left shoulders and right & left anterior chest) should be used. |
| Route | Topical |
| Dose Regimen | Once daily in the evening after washing the treated areas with preferred or the provided cleanser , the study drug will be applied.<br><br>Subjects are also encouraged to use their preferred moisturizer or provided moisturizer as desired but respecting an interval of approximately 1 hour (before and after) the study drug application. |
| Duration of administration | Up to 52 Weeks (+/- 5 days) |
| Location of Treated Area | Face (forehead, chin, nose and each cheek) and trunk (upper back, shoulders and anterior chest) |

N/A = Not Applicable