A Multi-Center, Randomized, Double-Blind, Parallel-Group Vehicle Controlled Study To Compare The Efficacy And Safety Of CD5789 50µg/g Cream Versus Vehicle Cream In Subjects With Acne Vulgaris

RD.06.SPR.18252

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1/ CLINICAL TRIAL OBJECTIVES

The clinical trial objectives are to assess the efficacy and safety of CD5789 50 µg/g cream applied once daily for 12 weeks in subjects with moderate facial and truncal acne vulgaris.

2/ STUDY DESIGN

Phase 3, multi-center, randomized, double blind, vehicle controlled study comparing CD5789 cream applied once daily in the evening for 12 weeks versus its vehicle.

Group 1: CD5789 50µg/g cream

Group 2: Vehicle cream

Subjects treated once daily for 12 weeks and evaluated at Baseline, Weeks 1, 2, 4, 8 and 12/Early Termination.

3/ CLINICAL STUDY DURATION

The planned clinical trial duration (from FSI to LSO) is approximately 26 months.

The planned duration of recruitment (i.e. From FSI to LSI) is approximately 23 months.

4/ DURATION OF SUBJECT PARTICIPATION & SUBJECTS' VISITS

Clinical trial participation for each subject is approximately 14 weeks (screening period of 14 days with a time window of + 3 days followed by 12 weeks of study treatment ±5 days).

5/ TOTAL NUMBER OF SUBJECTS (PLANNED):

Approximately 1430 subjects will be screened in order to obtain 1200 randomized subjects (600 per treatment arm).

6/NUMBER OF CLINICAL TRIAL CENTERS (PLANNED):

Approximately 85 sites

7/ REGION(S) / COUNTRY(IES) INVOLVED (PLANNED):

United States, Europe, and Russia

8/ INCLUSION/EXCLUSION CRITERIA

8.1/ Inclusion criteria:

1. The subject is a male or female, 9 years of age and older at the Screening visit.

   For Russia : The subject is a male or female, 9-17 years of age OR 18 years and older, at Screening visit

2. The subject has a facial acne severity grade of 3 (moderate) on the Investigator Global Assessment (IGA) scale at Screening and Baseline.
3. The subject has a minimum of 20 inflammatory lesions and 25 non-inflammatory lesions on the face at Screening and Baseline.
4. The subject has a truncal acne severity grade of 3 (moderate) on the Physician Global assessment (PGA) scale at Screening and Baseline visits on trunk (shoulders, upper back and upper anterior chest) reachable for self-application of study drug by the subject (optional criterion for subject between 9 and 11 years of age).
5. The subject has a minimum of 20 inflammatory lesions and 20 non-inflammatory lesions but no more than 100 non-inflammatory lesion counts on the trunk (shoulders, upper back and upper anterior chest) reachable to self-application of study drug by the subject at Screening and Baseline (optional criterion for subject between 9 and 11 years of age).
6. The subject is a 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. The subject is a female of childbearing potential:

   7.1. With a negative urine pregnancy test (UPT) at Screening and Baseline visits,

   7.2. 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

   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:

   7.2.a. bilateral tubal ligation;

   7.2.b. approved combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives, or hormonal contraceptive vaginal rings with a stable dose for at least 1 month prior to the Baseline visit;

   7.2.c. hormonal intra uterine device (IUD) inserted at least 1 month prior to the Baseline visit;

   7.2.d. vasectomized partner for at least 3 months prior to the Baseline visit.

8. If a female of childbearing potential uses combined oral contraceptives approved as acne treatments (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 a pre-menstrual female who begins menses during the study:

   9.1. Agrees to be strictly abstinent for the duration of the clinical trial and at least 1 month after the last study drug application,

   OR

   9.2. 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 approved combined oral contraceptives (oestrogens and progesterone), 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 (if required) in conjunction with an ICF signed by the parent(s)/legal representative at the Screening visit before any study procedures.

    At selected sites: If the subject agrees to participate to study photographs, verified by dating and signing a separate approved Informed Consent Form for photos and for subjects under the age of majority, an assent form signed by the subject in conjunction with a 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. The subject is apprised of the Health Insurance Portability and Accountability Act (HIPAA), if in the US, Personal Information Protection and Electronic Documents Act (PIPEDA), if in Canada or local privacy act if in other countries, and is willing to share personal information and data, as verified by signing a written authorization at the Screening visit.

8.2/ Exclusion criteria:

1. The subject has severe forms of acne (e.g., acne conglobata, acne fulminans) or secondary acne form (e.g., chloracne, drug-induced acne, etc.).
2. The subject has more than 1 nodule on the face at Screening and Baseline.
3. The subject has more than 1 nodule on the trunk at Screening and Baseline.
4. The subject has any acne cyst on the face at Screening and Baseline.
5. The subject has any acne cysts on the trunk at Screening and Baseline.
6. The subject has a beard or facial hair that may interfere with the study assessments.
7. The subject has tattoos on the shoulders, upper back or upper anterior chest reachable to self-application of study drug by the subject (evaluable area) that may interfere with the study assessments.
8. The subject 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 to the trial.
9. The subject has clinically significant abnormal laboratory values according to the Investigator at Screening (to be checked prior to Baseline).
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 within 1 month after the last study drug application.
13. The subject is currently participating in any other clinical trial of a drug or device OR past participation in any other clinical trial within the 30 days prior to the Baseline visit.
14. The subject was previously or is currently enrolled in the long term safety study RD.03.SPR.18250 conducted by Galderma.
15. The subject has received, applied, or ingested the following treatments within the specified time frame prior to the Baseline visit as defined in below:

Treatment restrictions

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

1) During the study, the use of Non-steroidal Anti-Inflammatory Drugs (NSAIDs) is acceptable for up to 21 days (cumulative) of treatment; however, it should be avoided during the 1 week period prior to the final study assessment.

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.

16. The subject has been exposed to excessive ultraviolet (UV) radiation 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, sunbathing, tanning salon use, phototherapy, etc.)

17. The subject is unwilling to refrain from use of prohibited medication during the clinical trial (see Section **Error! Reference source not found.** of the protocol v06 March 2017).

18. The subject is vulnerable (such as deprived from freedom) as defined in Section 1.61 of the ICH GCP.

9/ EFFICACY ASSESSMENT

9.1 Efficacy Measurements

9.1.1 Investigator's Global Assessment (IGA)/ Physician Global Assessment (PGA):

The IGA/PGA assessments will be performed before the lesion counting.

The areas defined for IGA assessment are forehead, each cheek, chin and nose.

The areas defined for 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 without assistance.

Qualified Investigators who successfully complete IGA/PGA training will evaluate the facial and truncal acne at Screening, Baseline, Week 1, Week 2, Week 4, Week 8 and Week 12/Early Termination visit, according to the following scale:

Global Assessment Scale (IGA/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.

For PGA assessments there are specific requirements for subjects 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 and at least 20 non-inflammatory lesions on the trunk): The PGA scale will be used by the investigators to decide if they want to start the treatment for truncal acne. If the subjects are treated, the PGA data from these subjects will not be analyzed.

9.1.2 Lesion counts on the face and on the trunk

Lesions Count will be performed by Investigators or qualified Study personnel

Lesion counting will be performed using both visual observations and palpation strictly, after assessing the IGA and the PGA at all visits.

Specific requirements for subjects 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 truncal lesion counts will not be performed.

It will be performed separately on the face and on the trunk at Screening, Baseline, Week 1, Week 2, Week 4, Week 8 and Week 12/Early Termination visit.

9.1.3 Subject self-assessment of facial acne improvement

Subject self-assessment should occur prior to any Investigator assessment in order to not influence the subject.

Subjects will evaluate their facial acne improvement at the Week 12/ET visit compared to the start of the study.

9.2 Primary Efficacy Endpoint

The primary efficacy endpoint consists of the following 3 co-primary endpoints:

1. Success Rate, defined as the percentage of subjects who achieve an IGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12.
2. Absolute Change in facial non-inflammatory lesion count from Baseline to Week 12.

3. Absolute Change in facial inflammatory lesion count from Baseline to Week 12.

10/ SAFETY ASSESSMENTS

The safety parameters are Adverse Events, local tolerability assessments, laboratory safety tests, physical exams and vital signs.

11/ OTHER ASSESSMENTS

11.1 Photographs (at selected sites)

Facial and truncal photographs will be taken according to a standardized procedure guideline at the Baseline, Week 2, 4, 8, and Week 12/Early Termination Visits at selected sites to illustrate the effect observed.

11.2 Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (C-DLQI)

Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (C-DLQI) will be completed by the subject at the Baseline and Week 12/ET visits prior to any Investigator assessments to not impact the subject's answers to the quality of life questionnaire.

11.3 Skin Oiliness Scale Questionnaire (SOS)

A facial skin oiliness questionnaire will be completed by the subject 18 years of age and older with moderate facial acne vulgaris and returned at the Baseline and Week 12/ET visits.

As the questionnaire is only validated in English, only subjects who are native English speakers will complete it.

11.4 Nodules and cysts count

Nodules and cysts, if present, will be recorded at each visit.

12/ STUDY DRUG DESCRIPTION

	Investigational Product	Comparator Product
Trade Name or Equivalent	N/A	N/A
Name of Drug Substance	N/A	Vehicle
Internal Code	CD5789	N/A
Pharmaceutical Form	Cream	Cream
Strength/ Concentration	50µg/g	N/A
Formula number	0219.0102	0219.0082P
▪ Packaging (type and size)	50 mL bottle with pump and overcap	50 mL bottle with pump and overcap
▪ Storage conditions	Store below 25°C (77°F), do not freeze or refrigerate	
▪ Location of Treated Area	Face: forehead, nose, chin and right and left cheeks	Face: forehead, nose, chin and right and left cheeks

	Investigational Product	Comparator Product
	Truncal region: right and left shoulders, right and left upper anterior chest, and right and left upper back; reachable to self-application by the subject.	Truncal region: right and left shoulders, right and left upper anterior chest, and right and left upper back; reachable to self-application by the subject.
▪ Route	Topical	Topical
▪ Dose Regimen	Once daily in the evening after washing the treated areas	Once daily in the evening after washing the treated areas
▪ Duration of administration	12 Weeks	12 Weeks

▪ N/A = Not Applicable

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Schedule of assessments

	Screening Visit [1] (maximum 14 days+3 days prior to Baseline)	Baseline Visit	Week 1 Visit (±3 days)	Week 2 Visit (±3 days)	Week 4 Visit (±3 days)	Week 8 Visit (±3 days)	Week 12 Final/ET Visit[2] (±5 days)
Informed Consent/ HIPAA (US only)/ PIPEDA (Canada only) and Assent Form/ Photo Consent (selected sites)	X						
Demographics	X	X[3]					
Medical History	X	X[3]					
Previous Therapies/Procedures	X						
Vital Signs/Physical Examination	X	X					X
Laboratory Safety Test (hematology, chemistry, Urine Analysis)	X						X
Urine Pregnancy Test[4]	X	X[3]			X	X	X
IGA (face)	X	X[3]	X	X	X	X	X
PGA (trunk)[5]	X	X[3]	X[5]	X[5]	X[5]	X[5]	X
Acne Lesion Counting on the Face	X	X[3]	X	X	X	X	X
Acne Lesion Counting on the Trunk[5]	X	X[3]	X[5]	X[5]	X[5]	X[5]	X
Local tolerability on treated areas		X	X	X	X	X	X
Photographs (Face and Trunk at selected centers)[6]		X		X	X	X	X
Inclusion/Exclusion Criteria[3]	X	X[3]					
Randomization		X					
Adverse Event recording[7]	X	X	X	X	X	X	X
Concomitant Therapies/Procedures[8]		X	X	X	X	X	X
DLQI or CDLQI[9]		X					X

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	Screening Visit [1] (maximum 14 days+3 days prior to Baseline)	Baseline Visit	Week 1 Visit (±3 days)	Week 2 Visit (±3 days)	Week 4 Visit (±3 days)	Week 8 Visit (±3 days)	Week 12 Final/ET Visit[2] (±5 days)
Skin Oiliness Scale (SOS) Questionnaire[11]		X					X
Self-assessment of facial acne improvement							X
Study drug(s) Dispensing (D) and Accountability (A)		D			D/A	D/A	A
Moisturizer/cleanser Dispensing (D)		D[10]					
Dosing calendar Dispensed (D) returned and reviewed (RR)		D	RR	RR	RR	RR	RR
Exit Form[11]							X

(1) Baseline visit must be performed maximum 14 days after Screening with a time window of +3 days. For women of childbearing potential, there must be at least 14 days between Screening and Baseline visits (for UPT reason). No re-screening will be allowed.

(2) Week 12 procedures will be performed earlier in case of study discontinuation.

(3) Confirm information at Baseline

(4) For subject of childbearing potential only: Urine Pregnancy Tests will be performed at Screening, Baseline, Week 4, Week 8, Week 12. For pre-menstrual subjects re-confirm pre-menses status at every visit and in case of status change collect information on contraceptive method and perform a UPT. For the ones who begin menses after the Screening visit, urine pregnancy tests will be performed at the visit where there was a change in status and according to the schedule for females of childbearing potential (Baseline, Week 4, 8, 12/ET). Additional UPTs may be performed at the Investigator's discretion.

(5) Subjects 9 to 11 years of age who did not meet the criteria for moderate truncal acne at Baseline: PGA will be evaluated after baseline to allow the investigators to decide to start the treatment on the trunk if the subject develops truncal acne during the study whatever the PGA grade. Local tolerability will be assessed. The Lesion counts will not be evaluated.

(6) Photos are not mandatory; subjects will be able to participate in the study even if they refuse to participate in photo procedures.

(7) Collection of Adverse Events will begin after signing of the informed consent/assent form.

(8) 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

(9) Dermatology Life Quality Index (DLQI) (age 17 and older)/Children's Dermatology Life Quality Index (C-DLQI) (for 16 years and younger). If the subject completed a CDLQI at the Baseline visit, a C-DLQI should be completed at the Week 12/ET Visit, regardless of the subject's age at the Week 12/ET visit.

(10) Subjects will be encouraged to use a provided or personally preferred non-comedogenic and hypoallergenic moisturizer liberally from the Baseline visit throughout the end of the study.

(11) The Skin Oiliness Scale (SOS) Questionnaire is only to be completed by subjects who are native English speakers. The subject should be provided with the SOS questionnaire at Screening and Week 8, with instructions to complete and return it at the Baseline visit and Week 12 visit respectively.

(12) Exit form should be completed after subject data collection including evaluation of the laboratory test results has been completed.

HIPAA=Health Insurance Portability and Accountability Act of 1996; PIPEDA=Personal Information Protection and Electronic Documents Act