2 STUDY SYNOPSIS

Name of Sponsor/Company: Creabilis Sàrl	**Individual Study Table Referring to Part of the Dossier Volume:**	*For National Authority Use Only*
Name of Finished Product: CT327		
Name of Active Ingredient: Pegylated K-252a	**Page:**	

TITLE OF STUDY: A Randomised, Double-Blind, Placebo Controlled Phase II, Multi-Centre, Study of the Efficacy and Safety of CT327, a Topical Cream Formulation of Pegylated K-252a, when Administered Twice Daily for Eight Weeks to Patients with Mild to Moderate Psoriasis Vulgaris

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STUDY CENTRES: Six centres in Switzerland (two centres did not recruit), three centres in the United Kingdom (UK), and five centres in the United States of America (USA).

PUBLICATIONS: None

STUDY PERIOD:	**DEVELOPMENT PHASE:** II
First subject recruited 23 March 2010 Last subject completed 11 January 2011	

OBJECTIVES:
Primary:

To assess the efficacy of CT327 versus placebo in terms of improvements from baseline on:

- Proportion of lesions with a reduction in the modified Psoriasis Area Scoring Index (m-PASI) score of ≥50% at Week 8. Treatment groups were compared by continuity corrected two-sided McNemar test.

Secondary:

The secondary endpoints were to assess the following efficacy and tolerability parameters:

- Proportion of lesions with a reduction in m-PASI-score of ≥75% at Week 8 compared to baseline values. Treatment groups were compared by continuity corrected two-sided McNemar test.
- Time to onset of effect: At each visit and for each subject, reduction in m-PASI-score compared to baseline values were determined. Time to onset of effect was determined for each subject as the time period needed to obtain at least 50% reduction in m-PASI-score compared to baseline values (= response). Therefore, for each treatment, the time to onset of effect was estimated as the median time to response estimated by Kaplan-Meier survival analysis. Treatments were compared by log-rank test. □
- Investigator Global Assessment (IGA) was assessed at Week 8.
- Local tolerability (investigator assessment and adverse events [AEs]) were analysed by descriptive analysis only.
- Plasma levels of CT327 and K-252a, and skin biopsy data, were compared between the treatments, as appropriate.

METHODS: Original study design: Forty-eight subjects with mild to moderate psoriasis vulgaris (PV) aged >18 and <71 years were planned to be assigned to one of the two treatment groups. Twenty-four subjects were to receive 1.0 g CT327 (0.1%) twice daily on one target lesion (>10 cm2) on one side of the body. The same subjects were to receive 1.0 g placebo twice daily on a target lesion on the opposite side of the body. The treatment period was 8 weeks. The other twenty-four subjects would receive 1.0 g placebo twice daily on both target lesions. The assignment to treatment group (active plus placebo or placebo only)

was determined by a randomisation schedule. Within the active treatment group, assignment of active versus placebo treatment to body side was also determined by at randomisation schedule.

Modified Study Design – Submitted under UK CTA and US IND: The study was designed in a way to assure both intra- and inter-subject comparison of efficacy and safety of a novel kinase inhibitor CT327 compared to placebo in subjects with mild to moderate PV. Forty-eight subjects were to be randomised in two arms, twenty-four receiving placebo on one side and active substance on the opposite side of the body and twenty-four receiving placebo on both sides.

The study design was modified, changing from a parallel group of N=36 subjects with symmetrical skin lesions. The active treatment was administered to lesions on one body side, placebo was concomitantly administered to lesions on the opposite side of the body (randomised intra-subject comparison study). Thus, each subject served as his own control, reducing variability by avoiding inter-subject comparison.

The data from subjects enrolled before this amendment to the placebo-only arm were also analysed for efficacy and safety parameters at the end of the study.

NUMBER OF SUBJECTS:
Planned: 48 subjects (36 post amendment)
Screened: 81 subjects
Randomised: 58 subjects
Completed: 52 subjects

INDICATION AND MAIN CRITERIA FOR INCLUSION: Aged between >18 and <71 years of age with a diagnosis of mild (affecting <3% body surface area [BSA]) to moderate (affecting <10% BSA) PV, including, at baseline visit, two symmetrical, similar sized, target plaques, comparable in severity, on either side, of at least 10 cm^2 each. Target lesions must not have been treated with topical corticosteroids or other topical treatments for PV within the last 2 weeks prior to study entry, or herbal preparation to the area selected for treatment within 4 weeks prior to study entry, or had received systemic treatment for psoriasis (including systemic corticosteroids, nonsteroidals, immune-suppressants, or immune-modulating drugs, or treatment with light). Subject must not have been clinically diagnosed with a bacterial infection of the skin including impetigo and abscesses, or suffered from erythrodermic psoriasis, psoriasis punctata and pustular psoriasis or extended chronic stationary forms of psoriasis.

TEST PRODUCT: CT327, batch number: 09164

COMPARATOR PRODUCT: Placebo, batch number: 09163

DURATION/FOLLOW-UP: 8 weeks

CRITERIA FOR EVALUATION: Efficacy: Clinical scoring of lesions was performed using the m-PASI target lesion assessment scale at screening, Visit 2 (Day 0) (pre-first dose), Visit 3 (Day 14), Visit 4 (Day 28), and Visit 5 (Day 56).

For those subjects who consented to undergo biopsy procedures, punch skin biopsies were taken on Visit 2 (Day 0) and Visit 5 (Day 56). One biopsy specimen from lesional skin before therapy. Two biopsy specimens from lesional skin (e.g. one on right hand side of body and one on left hand side of body) showing >50% improvement, if reached, in m-PASI between baseline and end of treatment. Appropriate histological, immunohistochemical and double immunofluorescence analysis were performed.

Patient Reported Symptoms and the Investigator Global Assessment (IGA) were performed at screening, Visit 2 (Day 0) (pre-first dose), Visit 3 (Day 14), Visit 4 (Day 28), and Visit 5 (Day 56). Photographs of target lesions were also taken at these time points and assessed by the investigator only (they were not included in the report).

Safety: AEs and vital signs were collected throughout the study. Electrocardiogram (ECG), height and body weight, and clinical laboratory tests (haemogram, differential blood count, coagulation, electrolytes, substrates, enzymes and urinalysis) were collected at screening and follow-up.

Pharmacokinetic: Blood samples were collected at Visit 5 (Day 56) for the measurement of plasma concentrations of CT327 and K-252a.

STATISTICAL METHODS: The safety analysis set included all subjects with informed consent, who were randomised to one of the treatment groups and applied at least one dose of the study medication, and

was used for all safety analyses.

The intent-to-treat (ITT) analysis set included all subjects with informed consent, who applied at least one dose of the study medication and had at least one valid post-baseline measure of efficacy. The ITT analysis set was the primary analysis set for efficacy endpoints.

Efficacy Analysis: The primary endpoint, the proportion of subjects achieving ≥50% reduction in m-PASI-score for each of their lesions at Visit 5 (Day 56), was tested using McNemar's test. The proportion of subjects for each lesion with ≥50% reduction was summarised by absolute counts and percentages. Subjects enrolled under Group 2 are summarised but were not included in any of the formal statistical testing. All data were listed.

A similar analysis to the primary endpoint was conducted for the proportion of subjects achieving ≥75% reduction in m-PASI-score for each of their lesions at Visit 5 (Day 56).

The number and percentage of subjects who had a response (i.e. a reduction ≥50%) was summarised. The median time to response and 95% confidence interval (CI) was presented for each of the treatment groups, along with the first and third quartiles.

For the Kaplan-Meier analysis, information on both Group 1 and Group 2 was used. For subjects enrolled under Group 1, information was split by CT327 and contralateral placebo. For subjects enrolled under Group 2, the time to first reduction for lesions on the right and left hand sides of their bodies was calculated and both summaries used.

The number and percent of subjects in each category of the IGA score was presented for each relevant time point. A Wilcoxon matched-pairs signed rank test was used to test the difference between treatments (for Group 1 subjects only). The p-value from the Wilcoxon matched-pairs signed rank test was presented for the Visit 4 (Day 28) and Visit 5 (Day 56) comparison, with Visit 5 (Day 56) being considered the primary time point of interest.

Safety Analysis: AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA; Version 13). Concomitant medications were coded using the World Health Organisation (WHO; 01 June 2010) drug dictionary.

RESULTS:

Subject Disposition: Fifty-eight subjects were randomised to the study. One subject withdrew prior to first dose and as a result fifty-seven subjects entered into the study. In Group 1, forty-eight subjects received CT327 and contralateral placebo. In Group 2, nine subjects received pure placebo to two contralateral lesions and as a result are counted as a total of eighteen subjects in the efficacy analysis. Fifty-two (89.7%) subjects completed the study; four subjects did not complete from Group 1 (three lost to follow-up and one withdrew their consent) and two subjects did not complete from Group 2 (one study medication ran out and one withdrew).

Data Sets: The safety analysis set consisted of all fifty-eight subjects. The ITT analysis set consisted of fifty-seven subjects.

Demographic and Other Baseline Characteristics: Of the fifty-eight (100%) Caucasian subjects enrolled, twenty-two (38%) were female and thirty-six (62%) were male, with a mean age of 49.0 years (standard deviation [SD] = 12.56; range 19 to 71 years). Mean time from initial diagnosis was 21.0 years (SD = 14.80; range = 0.7 to 61.3 years).

Efficacy: The primary endpoint was the proportion of subjects achieving ≥50% reduction in m-PASI-score at Visit 5 (Day 56). In Group 1, seventeen (38%) subjects achieved ≥50% reduction on the side treated with CT327 compared to twenty-one (47%) on the side treated with contralateral placebo and four (29%) in Group 2 (subjects treated with placebo only). A McNemar's test of within-subject comparison, using subjects randomised to Group 1 only, was not statistically significant at the 5% level at Visit 5 (Day 56) for CT327 versus contralateral placebo. However, more subjects were seen to respond on CT327 when compared to Group 2 placebo. The proportion of subjects achieving ≥50% reduction in m-PASI-score at Visit 4 (Day 28) was twenty-two (48%) in Group 1 for the side treated with CT327 compared to nineteen (41%) for the side treated with contralateral placebo and three (19%) for placebo in Group 2.

Again, more subjects were seen to respond on CT327 when compared to Group 2 placebo.

A secondary endpoint was the proportion of subjects achieving ≥75% reduction in m-PASI-score at Visit 5 (Day 56). In Group 1, five (11%) subjects achieved ≥75% reduction on the side treated with CT327 compared to six (13%) subjects on the side treated with contralateral placebo. No subjects in Group 2 achieved a response of ≥75%. A McNemar's test of within-subject comparison, using subjects randomised to Group 1 only, was not statistically significant at the 5% level at Visit 5 (Day 56) for CT327 versus contralateral placebo.

The proportion of subjects achieving ≥75% reduction in m-PASI-score at Visit 4 (Day 28) was five (11%) in Group 1 for the side treated with CT327 compared to six (13%) for the side treated with contralateral placebo and two (13%) in Group 2.

A qualitative improvement on active CT327 in Group 1 over pure placebo in Group 2 was observed.

A Kaplan-Meier analysis was conducted on the time to first reduction in m-PASI-score ≥50%. The median value for both body sides in Group 2 (placebo only) was not estimated due to few subjects achieving ≥50% reduction. For subjects treated under Group 1, the median (95% CI) time to event for the body side treated with CT327 was 41 (27, upper limit not reached) days compared to 56 (28, upper limit not reached) days for contralateral placebo.

At Visit 5 (Day 56), fifteen (33%) subjects had their degree of disease severity rated on the IGA scale as 'Mild' on the IGA scale, twenty-two (49%) subjects rated as 'Moderate' and eight (18%) rated as 'Severe' for sides treated with CT327 compared to nineteen (42%) subjects rated as 'Mild', seventeen (38%) subjects rated as 'Moderate' and nine (20%) rated as 'Severe' for sides treated with placebo. For Group 2, one (7%) subject had his degree of disease severity rated as 'Mild' on the IGA scale, nine (64%) subjects rated as 'Moderate' and four (29%) rated as 'Severe'.

A Wilcoxon Signed Rank test of within-subject comparison, using subjects randomised to Group 1 only, was not statistically significant (p-value = 0.375) at Visit 5 (Day 56) for CT327 versus contralateral placebo.

In Group 1, CT327 and contralateral placebo showed similar baseline IGA scores and change through Day 56. However, there was a marked difference in response between CT327 treated subjects in Group 1 and the pure placebo subjects treated in Group 2, particularly those moving into a categorisation of 'Mild' by Day 56.

Safety: There were no deaths or serious adverse events reported during the study. Overall, thirty-one (53%) subjects experienced treatment emergent AEs, twenty-eight (57%) subjects in Group 1 who received CT327 and contralateral placebo and three (33%) subjects who were in Group 2 and received placebo only. Although there is a difference in the proportions of subjects experiencing AEs between the two groups, the number of subjects randomised to the pure placebo group is relatively low.

The most frequently occurring AEs were rhinitis (five [9%] subjects) and diarrhoea (four [7%] subjects). The majority of AEs were reported as mild to moderate and not related or unlikely to be related to study drug. Two subjects, both of whom were in Group 1, experienced severe AEs.

There were no clinically significant clinical laboratory test changes identified, although increased alanine aminotransferase and aspartate aminotransferase, glycosuria, increased blood creatinine phosphokinase and raised cholesterol and were all recorded as AEs.

There were no clinically significant findings in systolic, diastolic blood pressure or pulse rate during the study including changes from predose on the day of first cream administration at Visit 2.

One subject had a clinically significant ECG finding at follow-up: complete right bundle branch block..

Pharmacokinetic: There were no detectable levels of CT327 or K-252a.

CONCLUSIONS:

- In Group 1, CT327 and contralateral placebo performed similarly with an effect of treatment observed on clinical endpoints which failed to reach significance.

- When comparing CT327 from Group 1 and pure placebo subjects in Group 2:
  - A greater proportion of subjects treated with CT327 had at least a 50% reduction in m-PASI-score from baseline compared to those on placebo at both 4 and 8 weeks.
  - A greater proportion of subjects treated with CT327 had an improvement in their IGA score from baseline compared to those on placebo at both 4 and 8 weeks.
- Topical administration of CT327 (0.1% w/w twice daily) for 56 days was safe and well tolerated. There were no significant application site reactions.
- No systemic levels of CT327 or K-252a were detected.

DATE OF FINAL REPORT: 15 September 2011