2 SYNOPSIS OF STUDY REPORT, No. D-10.358 (AC-058A200)

COMPANY:	TABULAR FORMAT REFERRING TO PART Enter Part OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Actelion Pharmaceuticals Ltd	Type … *(ONLY DRA)*	
NAME OF FINISHED PRODUCT:	Volume:	
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NAME OF ACTIVE SUBSTANCE(S):	Page:	
ACT-128800	Type … *(ONLY DRA)*	

TITLE OF THE STUDY	Multicenter, randomized, double-blind, placebo-controlled, Phase IIa study to evaluate the efficacy, safety, and tolerability of ACT-128800, an $S1P_1$ receptor agonist, administered for 6 weeks to subjects with moderate to severe chronic plaque psoriasis.		
INDICATION	Moderate to severe chronic plaque psoriasis		
INVESTIGATORS / CENTERS AND COUNTRIES	Coordinating investigators: Carl Paul, MD, PhD and Ulrike Blume-Peytavi, MD 14 centers in 5 countries: Austria (2), France (3), Germany (4), Hungary (4), and Serbia (1).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	09 October 2008 to 31 July 2009	CLINICAL PHASE	2a
OBJECTIVES	The primary objective was: • To demonstrate the efficacy of ACT-128800 20 mg once daily on Psoriasis Area and Severity Index (PASI) at Week 6 in subjects with moderate to severe chronic plaque psoriasis. The secondary objectives were: • To evaluate the safety and tolerability of ACT-128800 20 mg once daily for 6 weeks in subjects with moderate to severe chronic plaque psoriasis. • To investigate the pharmacokinetics and pharmacodynamics of ACT-128800 in subjects with moderate to severe chronic plaque psoriasis.		

STUDY DESIGN	This was a prospective, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase 2a study. Following a 14- to 28-day screening period, eligible subjects received either ACT-128800 or matching placebo for 6 weeks or until study drug discontinuation. A follow-up safety visit was performed 7 days after the last study drug intake. Serious adverse events (SAEs) were collected by phone, 28 days after the last study drug intake.
NUMBER OF SUBJECTS	60 subjects were planned to be randomized to ACT-128800 or matching placebo with a 2:1 ratio. 66 subjects were recruited and analyzed (45 in the ACT-128800 group, 21 in the placebo group).
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	**Criteria for inclusion:** 1. Males and females aged 18 to 60 years (inclusive). 2. For female subjects, a woman of childbearing potential was to: • have a negative pregnancy test at screening and randomization. • agree to use two methods of contraception. 3. Moderate to severe plaque psoriasis with body surface area (BSA) involvement > 10% and PASI score > 10, which had been stable for at least 3 months, required systemic treatment, and for which treatment in a placebo-controlled study of an investigational drug could be justified. 4. Signed informed consent form. **Criteria for exclusion:** 1. Breast-feeding women. 2. Generalized erythrodermic, generalized pustular psoriasis (von Zumbusch), guttate, and palmo-plantar psoriasis. 3. Treatment with: • Ultraviolet B (UVB) therapy, psoralen-ultraviolet-light (PUVA) therapy and topical treatments for psoriasis other than emollients within 1 month prior to start of study drug.

- Oral retinoids, methotrexate, cyclosporine and systemic corticosteroids within 1 month prior to start of study drug.
- Approved immunosuppressive or immuno-modulatory biologic agents within 3 months prior to start of study drug.
- Investigational non lymphocyte-depleting biologic agents within 6 months prior to start of study drug or lymphocyte-depleting biologic agents at any point in time.
- Other systemic immunosuppressive drugs within 3 months prior to start of study drug.
- Treatment with another investigational drug within 3 months prior to start of study drug.
- Vaccination with live vaccines within 3 months prior to start of study drug.
- Treatment with β-blockers, diltiazem, verapamil, digoxin, amiodarone, and lithium within 1 month prior to start of study drug.

4. Treatment for autoimmune disorders other than psoriasis.
5. Ongoing bacterial, viral or fungal infection, positive hepatitis B surface antigen or hepatitis C antibody tests.
6. Congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection.
7. History or presence of malignancy, lymphoproliferative disease and subjects who received total lymphoid irradiation or bone marrow transplantation.
8. Poorly controlled type I or II diabetes.
9. History or presence of macular edema or diabetic retinopathy.
10. Any of the following cardiovascular conditions:
    - Resting heart rate (HR) < 60 bpm.
    - Electrocardiogram (ECG) PR interval > 180 ms.
    - Symptomatic ischemic heart disease.
    - History of valvular heart disease.

- History of heart failure.
- History or presence of rhythm disorders or subjects who receive anti-arrhythmic therapy.
- History of syncope.
- Arterial hypertension uncontrolled by medications.

11. Any of the following pulmonary conditions:
    - Moderate and severe bronchial asthma or chronic obstructive pulmonary disease (COPD) stage II–IV.
    - History of pulmonary fibrosis, pulmonary Langerhans' cell histiocytosis.
    - History of tuberculosis, or positive chest X-ray at screening or within the previous 3 months, suggestive of active or latent tuberculosis.
12. Abnormal liver function tests as defined by persisting elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or total bilirubin > 2-fold the upper limit of the normal range (ULN).
13. Abnormal laboratory values:
    - Hemoglobin (Hb) < 10 g/dL.
    - White blood cells (WBC) count < 3,500/μL.
    - Lymphocyte count < 1000/μL.
    - Platelets < 100,000/μL.
    - Serum cratinine > 1.7 mg/dL (150 μmol/L).
14. History of clinically significant drug or alcohol abuse.
15. Known allergy to any of the study drug excipients.
16. Any other clinically relevant medical or surgical condition that, in the opinion of the investigator, would have put the subject at risk by participating in the study, and subjects who were confined by order of either judicial or administrative authorities.
17. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits or likelihood of not completing the study including mental condition rendering the subject unable to understand the nature, scope and possible

	consequences of the study, and subjects who are confined by order of either judicial or administrative authorities.
TRIAL DRUG / BATCH No.	ACT-128800 10 mg capsules: Batch No. PD07071 ACT-128800 20 mg capsules: Batch No. PD07072
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	ACT-128800 administered orally once daily at a dose of 10 mg (Days 1–4) and 20 mg (Day 5 to end of treatment period).
REFERENCE DRUG / BATCH No.	Placebo capsules: Batch No. PD07069
REFERENCE DRUG DOSE / ROUTE / REGIMEN / DURATION	Matching placebo capsules
CRITERIA FOR EVALUATION EFFICACY:	**Primary endpoint** • PASI percent change relative to baseline (BL) at Week 6. • The primary endpoint was further explored within the cohort of active-treated subjects in the two subsets of subjects who fulfilled or did not fulfill each of the following criteria: – Peripheral total lymphocyte count $\leq 0.8 \times 10^9$/L at Week 6, pre-dose and 6 h post-dose. – Reduction of peripheral total lymphocyte count by $\geq 80\%$ compared to BL at Week 6, pre-dose and 6 h post-dose. – Peripheral total lymphocyte count $\leq 0.5 \times 10^9$/L at Week 6, pre-dose and 6 h post-dose. **Exploratory endpoints** • PASI30 at Week 6, defined as an improvement (decrease) of at least 30% from BL in PASI. • PASI50 at Week 6, defined as an improvement (decrease) of at least 50% from BL in PASI. • PASI75 at Week 6, defined as an improvement (decrease) of at least 75% from BL in PASI. • "Clear or almost clear" Physician Global Assessment (PGA) at Week 6. • "No signs of psoriasis or almost no signs of psoriasis" (i.e., 0 or 1) Patient's Global Psoriasis

	Assessment(PGPA) at Week 6. • Improvement of at least 2 levels in PGA at Week 6 relative to BL. • PASI percent change relative to BL over time (i.e., at Week 2, 3, 4, 5, and 6). • PASI absolute change relative to BL over time (i.e., at Week 2, 3, 4, 5, 6). • PASI absolute and % change from BL to Week 6 and Week 7. • PASI absolute and % change from BL to each visit (Week 2, 3, 4, 5, and 6), separately. • Trough (pre-dose) total lymphocyte counts at Day 1, 2, 5, 6 and Week 2, 3, 4, 5, 6, and 7. • % change in trough (pre-dose) total lymphocyte counts relative to BL at Day 2, 5, 6 and Week 2, 3, 4, 5, 6, and 7. • Total lymphocyte counts 3 and 6 h post-dose at Day 1, 2, 5, 6 and Week 6. • % change in total lymphocyte counts 3 and 6 h post-dose relative to pre-dose at Day 1, 2, 5, 6 and Week 6. • Change in histological parameters; i.e., acanthosis, papillomatosis index, and cell subpopulations (CD3, CD3d, CD3e, CD1a, CD11c, CD68, CD123) measured on the involved psoriatic skin from BL to end of study.
PHARMACOKINETICS:	• Pre-dose concentrations of ACT-128800 in plasma at Day 1, 2, 5, 6, and Week 2, 3, 4, 5 and 6. • Plasma concentration of ACT-128800 at 3 and 6 h post-dose at Day 1, 2, 5, 6, and Week 6.
SAFETY:	• At each day with multiple assessments, changes in ECG quantitative parameters (HR, PR, QT, QT corrected for heart rate on the basis of Bazzett's formula [QTcB], QT corrected for heart reate on the basis of Fridericia's formula [QTcF] and QRS) from pre-dose to each scheduled assessment during the same day. • At each day with multiple assessments, change in

HR from pre-dose to the nadir (lowest post-dose value) during the same day.

- Nadir HR and change from pre-dose during the same day on Day 1, 2, 5 and 6 for subjects in the 'active' treatment group.
- At each day with multiple assessments, time to reach the nadir (lowest) HR value during the same day.
- Changes in all ECG quantitative parameters from BL to all pre-dose assessments at the different visits during the study.
- Changes in ECG quantitative parameters from BL to end of study.
- Treatment-emergent clinically relevant abnormalities as assessed by 12-lead ECG and Holter monitoring.
- Hourly average HR recorded by Holter monitoring at each hourly interval during each scheduled visit.
- Changes in pulmonary function test parameters (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC (%), and % of the predicted FEV_1 and FVC) from BL to end of study and from BL to Week 6 and to Week 7.
- At each day with multiple assessments, changes in vital signs parameters from pre-dose to each scheduled assessments during the same day.
- Changes in vital signs parameters from BL to all pre-dose assessments at the different visits during the study.
- Changes in vital signs parameters from BL to end of study.
- Change in body weight from BL to end of study.
- Change in laboratory parameters (hematology, blood chemistry and total and differential white blood cell [WBC] counts) from BL to each scheduled pre-dose assessments at the different visits during the study (excluding follow-up).
- Change in total and differential WBC counts from BL to the end of study and from BL to Week 6 (pre-dose).
- Treatment-emergent laboratory abnormalities.

- Treatment-emergent adverse events (AEs), up to 7 days after study drug discontinuation.
- AEs leading to premature discontinuation of study drug.
- Treatment-emergent SAEs up to 7 days after study drug discontinuation.
- AEs with outcome death.
- Occurrence of death.

STATISTICAL METHODS:

- The primary analysis set for this Phase-2 study was the per-protocol set. A supportive analysis was performed on the all-treated set. The per-protocol set was also used for the analysis of exploratory efficacy parameters.
- The null hypothesis was that the active treatment group did not differ from placebo. The alternative hypothesis was that it differed from placebo. The difference to be detected was a placebo-corrected mean decrease of 30 units for the primary parameter: percentage change of PASI. Percentage change of PASI was expected to be normally distributed with a standard deviation (SD) of 29%.
- The experiment-wise type-I error was set to 0.05; the comparisons to placebo were tested by means of the Student's t-test at two-sided 0.05 significance level.
- With 51 evaluable subjects (34 active, 17 placebo), the above-mentioned difference was to be detected with 90% power at the two-sided 0.05 level (nQuery Advisor-MTTOU-1). Based on the assumption that 15% of the randomized subjects would not be eligible for the per-protocol analysis, the total sample size was 60 subjects.
- The exploratory parameters were analyzed descriptively computing appropriate placebo-corrected summary statistics with 95% confidence intervals.
- No interim efficacy analysis was performed.

SUBJECT DISPOSITION:

Fifty-seven subjects (37 in the ACT-128800 group and 20 in the placebo group) completed the study; 9 subjects, 8 on ACT-128800 and 1 on placebo, prematurely discontinued the study. In the ACT-128800 group, 3 subjects discontinued because of an AE, 3 because of lack of efficacy, 1 was lost to follow-up and 1 withdrew consent; in the placebo group, 1 subject discontinued because of an AE. The groups were well matched with regard to demographics and baseline characteristics.

EFFICACY RESULTS:

The primary endpoint was not met; the study did not demonstrate that ACT-128800 decreases the mean PASI of subjects with psoriasis treated for 6 weeks when compared with placebo. At the Week-6 assessment, the PASI (mean ± SD) had decreased from BL by -37.7 ± 25.43% for ACT-128800-treated subjects and by -27.6 ± 26.79% for placebo-treated subjects, resulting in a mean treatment effect of -10.0 ± 25.88%, which was not

statistically significant (p = 0.1738, Student's t-test). These results were confirmed by supportive analyses using the all-treated set and the non-parametric Wilcoxon ranks sum test. Over time, the PASI decreased similarly in both groups up to Week 4, after that the rate of decrease appeared more pronounced in the ACT-128800 group.

At Week 6, no significant differences were reported between the treatment groups for the proportion of subjects with improvement in PASI of at least 30%, 50%, and 75% from BL or for the PGA and PGPA exploratory endpoints.

In the ACT-128800 group, the trough (pre-dose) total lymphocyte counts decreased during the first 2 weeks of treatment before reaching a plateau between 0.68 and 0.76 $\times 10^9$/L. One week after discontinuation of treatment (Week 7), total lymphocyte counts returned to within the range of BL values (1.58 ± 0.486 $\times 10^9$/L). The percentage change reached a plateau between −59.2% and −62.8% compared with BL. One week after discontinuation of treatment (Week 7), the percent change in total lymphocyte reached -13.5% of the BL value. None of the subjects treated with ACT-128800 had a total lymphocyte count below 0.20 $\times 10^9$/L. No obvious relationship could be discerned between the peripheral lymphocyte counts or % change in lymphocyte counts from BL at Week 6 and the PASI percent change from BL to Week 6.

No significant changes in histological findings and cell subpopulations in skin biopsies could be discerned between treatment groups or between BL and study treatment end in either group.

PHARMACOKINETIC RESULTS:

Steady-state plasma concentrations of ACT-128800 were reached at Week 2, with trough concentrations remaining stable until end of treatment. Concentration time profiles suggested that peak concentrations were reached between 3 h and 6 h post-dose.

SAFETY RESULTS:

Administration of ACT-128800 was generally well tolerated. AEs that occurred in a greater proportion of subjects on ACT-128800 than on placebo included headache (20.0% vs 9.5%), bradycardia (8.9% vs 0%), vertigo (8.9% vs 0%), alanine aminotransferase increase (6.7% vs 0%), first degree atrioventricular block (6.7% vs 0%), dizziness (6.7% vs 0%), and nasopharyngitis (6.7% vs 0%).

During the study, 4 subjects, 3 (6.7%) in the ACT-128800 group and 1 (4.8%) in the placebo group were discontinued from study treatment because of an AE. In the ACT-128800 group, 2 subjects were discontinued on Day 1 and 18 because of bradycardia and asthenia, respectively; both events were considered as related to treatment, and resolved without sequelae after treatment discontinuation; 1 subject was discontinued on Day 15 for tuberculosis/left pleural effusion. Although the investigator assessed the event of tuberculosis/left pleural effusion in the subject with a medical history suggestive of pre-existing tuberculosis as unrelated, the potential contribution of study medication to the

event could not be excluded and the case was up-graded to "possibly related" by the sponsor. It was therefore, reported as a suspected unexpected serious adverse reaction (SUSAR). No other SAEs were reported in this study. No subject died during the study.

The effects of ACT-128800 20 mg on clinical chemistry and hematology variables, with the exception of elevation of triglycerides, were in keeping with Phase 1 data. Liver function test abnormalities were observed in 3 subjects (6.7%) in the active group and in 1 subject (2.2%) in the placebo group. Marked elevation of triglycerides was observed at least once during the study in 8 subjects (17.8%) on active treatment compared to 1 subject (4.8%) on placebo.

ACT-128800 showed no effects on mean systolic and diastolic blood pressures (SBP, DBP) in either the supine or standing position. Two AEs of increased blood pressure were reported in two subjects, one in the active arm and one in the placebo arm.

Cardiac disorders were reported as AEs in 6 (13.3%) ACT-128800-treated subjects and in 1 (4.8%) placebo-treated subject. The most frequent cardiac disorders reported in ACT-128800-treated subjects were bradycardia (8.9%) and first-degree AV block (6.7%).

HR reduction was observed in the ACT-128800 group. As recorded by 12-lead ECG, in the active treatment group, the median nadir HR recorded on Day 1 was 54 bpm (range 44–86 bpm) and the median time to nadir was 3 h post-dose. PR prolongation (defined as PR interval > 200 ms) occurred in 5 subjects treated with ACT-128800 compared with 2 subjects on placebo. No relevant changes were observed in the mean and median QTcB, QTcF and QRS intervals. ECG Holter assessments performed on Day 1–2 and Day 5–6 over 30 h and on Day 42 over 6 h confirmed the transient nature of ACT-128800 effects on HR observed with 12-lead ECG. The results showed that the circadian pattern of HR was not affected by ACT-128800. Intermittent second-degree AV block was recorded in 3 subjects (2 treated with ACT-128800 and 1 with placebo). In addition, 5 subjects treated with ACT-128800 had a single asymptomatic episode of a self-terminating short run of 3-4 ventricular ectopic beats, assessed as "non-sustained ventricular tachycardia".

No significant changes/effects of ACT-128800 on lung function changes and respiratory side effects were observed in the present study.

Overall, these results indicate that ACT-128800 is adequately tolerated in subjects with psoriasis.

CONCLUSIONS:

This study did not demonstrate the efficacy of ACT-128800 20 mg once daily on PASI at Week 6 in subjects with moderate to severe chronic plaque psoriasis. The primary efficacy endpoint, defined as mean PASI percent change from BL to Week 6 showed a placebo-corrected treatment effect of 10%, which was not statistically significant. Nevertheless, it is important to note that all primary and exploratory efficacy assessments of this study

provided indications of an effect of ACT-128800 20 mg once daily vs placebo from Week 5 of treatment onwards. Although none of these observations were statistically significant, the results of the study (taken together) suggest that a clinically important therapeutic effect might be observed after longer treatment duration and/or with a higher dose of ACT-128800.

The pharmacokinetic assessement indicated that peak concentrations of ACT-128800 are reached between 3 and 6 h post-dose and steady state conditions are attained on Day 14. ACT-128800 progressively decreases total lymphocyte counts during the first 2 weeks of treatment before inducing a plateau with lymphocyte counts increasing back toward pre-treatment values within a week following treatment end.

The study supports an acceptable safety profile of ACT-128800 20 mg in subjects with moderate to severe chronic plaque psoriasis. The assessment of the clinical relevance of the Holter findings (intermittent second-degree AV block and non-sustained ventricular tachycardia) will require collection of additional data.

DATE OF THE REPORT:

18 January 2011