2 SYNOPSIS OF STUDY REPORT, No. D-13.085 (AC-058A201)

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:	
Ponesimod	Type … *(ONLY DRA)*	
NAME OF ACTIVE SUBSTANCE(S):	Page:	
ACT-128800	Type … *(ONLY DRA)*	

TITLE OF THE STUDY	A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of two doses of ponesimod (ACT-128800), an oral $S1P_1$ receptor agonist, administered up to twenty-eight weeks in patients with moderate to severe chronic plaque psoriasis.		
STATUS OF STUDY / TYPE OF REPORT	Final clinical study report		
INDICATION	Moderate to severe chronic plaque psoriasis		
INVESTIGATORS / CENTERS AND COUNTRIES	58 centers in 15 countries: Austria (3), Belgium (1), Bulgaria (4), Czech Republic (4), Denmark (1), Estonia (3), Hungary (6), Italy (3), Latvia (3), Lithuania (1), Romania (5), Russia (7), Slovakia (4), Switzerland (2), and Ukraine (11).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL (first patient first visit to last patient last visit)	22 September 2010 to 24 October 2012	CLINICAL PHASE	2
OBJECTIVES	The primary objective was to demonstrate at Week 16 (end of the induction period) the efficacy of at least one of two doses of ponesimod (20 mg or 40 mg) compared to placebo in patients with moderate to severe chronic plaque psoriasis, based on the proportion of patients with at least 75% improvement of Psoriasis Area and Severity Index (PASI75) from baseline to Week 16.		

	The secondary objective was to assess at Week 16 (end of the induction period) the efficacy of two doses of ponesimod compared to placebo, based on the improvement of Physician's Global Assessment (PGA) from baseline to Week 16. Other objectives of the study were: • To assess the maintenance of treatment response from Week 16 to Week 28 (end of the maintenance period). • To evaluate the safety and tolerability of ponesimod. • To investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of ponesimod.
STUDY DESIGN	This was a prospective, multicenter, multinational, double-blind, randomized, placebo-controlled, three-arm, parallel group, dose-finding study that evaluated the efficacy, safety and tolerability of two oral once-daily doses of ponesimod (20 mg and 40 mg) versus placebo for a duration of 28 weeks. The study included a screening period of up to 35 days for patients' eligibility assessments prior to randomization (stratified by center) to the study drug or placebo. The treatment duration of the study was 28 weeks divided into two periods: induction (16 weeks) and maintenance (12 weeks). **Induction period** (first day of study drug administration up to Week 16): Eligible patients were randomized in a 2:2:1 ratio to ponesimod 20 mg, ponesimod 40 mg, or placebo. Patients were initially administered ponesimod 10 mg or placebo on Day 1 of the treatment period and were up-titrated at weekly intervals to achieve 20 mg (Day 8) or 40 mg (Day 15) dose levels. Thereafter, patients remained on their respective doses of ponesimod or placebo until Week 16. **Maintenance period** (Week 16 to Week 28): Patients who achieved at least 50% improvement from baseline in PASI (PASI50) at Week 16 were re-randomized in a

	1:1 ratio, either to continue on the same dose of ponesimod or placebo or to switch to placebo, thus resulting in five treatment groups for the maintenance period as follows: **Induction period** / **Maintenance period** Ponesimod 20 mg / Ponesimod 20 mg[1] or Placebo[2] Ponesimod 40 mg / Ponesimod 40 mg[3] or Placebo[4] Placebo / Placebo Hereafter referred to as:[1] Ponesimod 20/20; [2] Ponesimod 20/placebo; [3] Ponesimod 40/40; [4] Ponesimod 40/placebo. Patients who did not achieve at least PASI50 at Week 16 did not enter the maintenance period and completed the end-of-treatment (EOT) visit and a follow-up period that ended with an end-of-study (EOS) visit. All patients had an EOT visit and a follow-up period that ended with an EOS visit 8 days after the last study drug intake. A safety follow-up was performed for all patients by a telephone call 30 days after the last study drug intake. Additional urine pregnancy tests were performed for women of childbearing potential 30 days and 8 weeks after study drug discontinuation.
NUMBER OF PATIENTS	For the induction period (up to Week 16), a total of 320 patients were planned to be randomized. A total of 326 patients were actually randomized in a 2:2:1 ratio to ponesimod 20 mg (126 patients), ponesimod 40 mg (133 patients), or placebo (67 patients). A total of 219 patients entered the maintenance period (Week 16 to Week 28). Patients who received ponesimod in the induction period were re-randomized in a 1:1 ratio (ponesimod:placebo) to ponesimod 20/20 (49 patients), ponesimod 20/placebo (45 patients), ponesimod 40/40 (53 patients), and ponesimod 40/placebo (47 patients), and patients who received placebo in the induction period were mock re-randomized to placebo (25 patients).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients aged 18 to 60 years with moderate to severe plaque psoriasis with body surface area (BSA) involvement > 10%, PASI score > 10 at screening and randomization, and requiring systemic treatment were eligible to enter the induction period of the study. Patients achieving at least PASI50 at Week 16 were eligible to enter the maintenance period of the study.
TRIAL DRUG / BATCH No.	Ponesimod 10, 20, and 40 mg ACT-128800 free base polymorphic form C as tablets. • Ponesimod 10 mg tablets: PD09059, PD10141 and PD11058 • Ponesimod 20 mg tablets: PD09060, PD10142 and PD11059 • Ponesimod 40 mg tablets: PD09061, PD10143 and PD11060
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	Patients received ponesimod 20 or 40 mg, or matching placebo tablets once daily for a period of up to 28 weeks. A two-step up-titration scheme was used during the first 2 weeks of the induction period.
REFERENCE DRUG / BATCH No.	Matching placebo tablets of identical appearance and formulation, but without ponesimod. Placebo tablets: PD09056, PD10075 and PD11057
REFERENCE DRUG DOSE / ROUTE / REGIMEN / DURATION	Patients received matching placebo tablets once daily for a period of up to 28 weeks. A two-step (mock) up-titration scheme was followed during the 2-week induction period.
CRITERIA FOR EVALUATION	
EFFICACY:	The primary efficacy endpoint was the proportion of patients with PASI75 at Week 16. The secondary efficacy endpoint was the proportion of patients with “clear” or “almost clear” on PGA at Week 16. Exploratory efficacy endpoints investigated during both induction and maintenance periods included the proportion of patients achieving specific PASI improvement from baseline, PGA and Patient’s Global Psoriasis Assessment (PGPA) improvements of at least

	two levels relative to baseline and 'no signs of psoriasis' or 'almost no signs of psoriasis' (i.e., 0–1 on PGPA) at individual visits. In addition, changes in psoriatic-arthritis-related joint pain and skin biopsy histology relative to baseline at Week 16 and Week 28 were investigated. The proportion of patients free of relapse (i.e., reduction of the maximum achieved PASI improvement within the induction period by > 50% during the maintenance period) and rebound (PASI deterioration to ≥ 125 % of baseline or any psoriasis serious adverse event [SAE], or any severe generalized pustular, erythrodermic, or inflammatory psoriasis adverse event [AE] occurring within the maintenance period) and the time to loss of PASI75 were investigated only for the maintenance period. Quality of life (QoL) was evaluated by the change from baseline in Dermatology Life Quality Index (DLQI) and Short-Form-36 (SF-36) scores at Week 8, 16, and 28.
PHARMACOKINETICS AND PHARMACODYNAMICS:	• Pre-dose (trough) concentrations of ponesimod in plasma on Days 8 and 15, and at Weeks 3, 8, 16, 22, 28 (EOT), and 29 (EOS) • Steady-state concentrations of ponesimod (from Week 3 onwards for all dose groups) averaged across steady-state visits (Weeks 3, 8 and 16) by patient • The total and percent change in lymphocyte count at steady-state concentrations of ponesimod averaged across steady-state visits (Weeks 3, 8 and 16) by patient • The relationship between total lymphocyte count and PASI score (observed score and percent change from baseline and PASI50, 75, and 90)
SAFETY:	Safety endpoints determined the proportion of patients who died, experienced SAEs and AEs and AEs leading to premature discontinuation of study treatment up to 7 days after EOT. In addition, change in laboratory variables, vital signs and electrocardiogram (ECG: 12-lead and Holter) were investigated. Pre-defined marked laboratory abnormalities and clinically relevant

	ECG and Holter abnormalities, vital signs and pulmonary abnormalities were determined. Additional specific safety endpoints included in this study based on the previous clinical experience with ponesimod were: • The nadir (lowest) post-dose heart rate (HR) and the change to nadir (12-lead ECG) at each day with multiple post-dose assessments compared to pre-dose on the same day; • Changes in pulmonary function test (PFT) parameters (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and FEV_1 and FVC in percent of predicted value) from baseline to all assessed timepoints during the study.

STATISTICAL METHODS:

The global null hypothesis was that none of the two ponesimod dose groups differed from placebo in the probability of reaching at least PASI75 at Week 16. The alternative hypothesis was that the probability of reaching PASI75 differed from placebo for at least one of the ponesimod dose groups.

All efficacy analyses for the induction period were performed using All-randomized set (intention-to-treat [ITT]), which included all randomized patients who had signed the informed consent. Exploratory efficacy analyses for the maintenance period were performed using the Maintenance set, which included all patients in the ITT set who were re-randomized and received at least one dose of study drug in the maintenance period.

The main analysis of the primary endpoint was performed using Fisher's exact test of two independent binominal probabilities to test the null hypothesis. The Bonferroni-Holm procedure was adopted to control the global type I error rate ($\alpha = 0.05$, 2-sided) with the most extreme difference between ponesimod dose groups and placebo to be tested at a 2-sided significance level of 0.025.

The secondary endpoint was analyzed using Fisher's exact test as for the primary endpoint, adopting the Bonferroni-Holm procedure.

The change from baseline in QoL measures at Week 16 was analyzed using Wilcoxon rank sum test. Other exploratory endpoints were analyzed descriptively

Safety data were analyzed descriptively using the Safety set (i.e., all patients in the ITT set who received at least one dose of the study drug), except for the data from the

maintenance period for which the Maintenance set was used.

The anticipated sample size of the study was 320 patients (128 for each ponesimod group and 64 for placebo) considering Fisher's exact test for comparison of two probabilities from independent binominal distributions (nQuery Advisor) for each of the tested ponesimod doses versus placebo at a significance level of 0.025. For the sample size estimation, it was assumed that 35% and 10% of patients would reach PASI75 in the ponesimod and placebo groups, respectively. The experiment-wise type I error was set to 0.05 (2-sided). The type II error was set to 0.05 (i.e. power 0.95).

PATIENT DISPOSITION:

A total of 326 patients were randomized in a 2:2:1 ratio to ponesimod 20 mg (n = 126) and ponesimod 40 mg (n = 133) and placebo (n = 67) groups. All randomized patients received study treatment. Of the 278 patients (85.3%) who completed the induction period, 219 patients (78.8% of those who completed the induction period) entered the maintenance period, and 59 (21.2%) did not enter the maintenance period as 54 patients (19.4%) did not reach at least PASI50 and 5 patients did not enter based on their or investigator's decision. A total of 203 patients (92.7% of those who entered the maintenance period) completed the 28-week treatment up to the end of the maintenance period.

A total of 292 patients (89.6%) undertook their EOS visit.

Of the 326 patients in the All-randomized set, 48 (14.7%) prematurely discontinued study drug during the induction period (13.5% ponesimod 20 mg, 15.0% ponesimod 40 mg, 16.4% placebo), most frequently due to AEs (both ponesimod 20 mg and 40 mg groups) or patient's decision to discontinue the study drug (placebo group). Of the 219 patients in the Maintenance set, 16 (7.3%) discontinued study drug prematurely during the maintenance period (6.1% ponesimod 20/20, 6.7% ponesimod 20/placebo, 3.8% ponesimod 40/40, 14.9% ponesimod 40/placebo, 4.0% placebo/placebo). Across the groups, loss to follow-up, AEs, administrative reason and withdrawal of consent most commonly led to study drug discontinuation.

Baseline demographic characteristics across the three treatment groups were matched. There was a predominance of males (75.2%), and the median age was approximately 40 years. Mean total body mass index (BMI) was 27.7 kg/m^2 with approximately 30% of patients having a BMI ≥ 30 kg/m^2. The majority of patients were from the Ukraine (26.7%) and the region of Czech Republic, Hungary and Slovakia (26.1%). The majority of patients were either smoking at the start of this study or were former smokers (51.8%).

Baseline disease characteristics were well-balanced across the three treatment groups. The median time since the initial diagnosis of psoriasis at randomization was 14.8 years (range: 0.1 to 50.8 years). The mean PASI score at baseline was 22.0. The majority of

patients were assessed as 'moderate to severe' (53.7%) on PGA, and 96.9% of patients had PGPA scores of 3 or above (ranging from 0 [no signs of psoriasis] to 5 [worst severity of disease]) at baseline.

EFFICACY RESULTS:

Induction period: The proportion of patients reaching at least PASI75 at Week 16 (primary efficacy endpoint) was higher in both ponesimod 20 mg (46.0%) and 40 mg (48.1%) groups than in the placebo group (13.4%). The treatment effect (difference in proportions vs placebo) of ponesimod 20 mg (32.6%, 95% confidence limits [CLs] 19.9%, 45.3%) and ponesimod 40 mg (34.7%, 95% CLs 22.1%, 47.3%) was clinically relevant and statistically significant ($p < 0.0001$, Fisher's exact test). Results of all sensitivity analyses performed on the primary endpoint were consistent with those of the main analysis.

The proportion of patients with "clear" or "almost clear" on PGA at Week 16 (secondary efficacy endpoint) was higher in ponesimod 20 mg (27.8%) and 40 mg (32.3%) groups than in the placebo group (4.5%). The treatment effect (difference in proportions vs placebo) of ponesimod 20 mg (23.3%, 95% CLs 13.3%, 33.3%) and ponesimod 40 mg (27.9%, 95% CLs 17.7%, 38.0%) was clinically relevant and statistically significant ($p < 0.0001$, Fisher's exact test).

The treatment effect of ponesimod on the primary and secondary endpoints was similar with the two doses tested. However, PASI90 responses at Week 16 appeared to be dose-related (14.3% ponesimod 20 mg, 24.8% ponesimod 40 mg, 3.0% placebo, All-randomized set).

PASI and PGA scores improved similarly over time in both ponesimod dose groups. Improvement in PASI score started to diverge from placebo at Week 3 and increased further up to the end of the induction period (Week 16). At Week 16, the mean percent change in the PASI score (± standard deviation [SD]) from baseline was greater in the ponesimod 20 mg (–63.7% ± 28.88) and ponesimod 40 mg groups (–66.4% ± 29.65) than in the placebo group (–29.6% ± 37.22).

Efficacy results during the induction period were supported by changes in patient-assessed outcomes including PGPA, DLQI, and SF-36:

- At Week 16, the proportion of patients with improvements in PGPA scores ('no signs of psoriasis' or 'almost no signs of psoriasis') was higher in the ponesimod 20 mg (34.1%) and 40 mg (33.8%) groups than in the placebo group (6.0%). The proportion of patients achieving at least two levels of improvement in PGPA scores at Week 16 was higher in the ponesimod 20 mg (51.6%) and ponesimod 40 mg (52.6%) groups than in the placebo group (16.4%).
- At Week 8 and Week 16, the mean change (± SD, i.e. improvement) from baseline in the total DLQI score was greater in the ponesimod 20 mg (–4.5 ± 5.01 and

–6.6 ± 5.97, respectively) and ponesimod 40 mg groups (–5.0 ± 5.71 and –6.9 ± 6.61, respectively) than in the placebo group (–2.2 ± 4.37 and –3.0 ± 5.91, respectively). The treatment difference (versus placebo) in the mean change (i.e., improvement) in total DLQI score at Week 16 was –3.4 (95% CLs –5.2, –1.6, p = 0.0003, Wilcoxon rank sum test) for ponesimod 20 mg and –3.7 (95% CLs –5.6, –1.9, p = 0.0004, Wilcoxon rank sum test) for ponesimod 40 mg. The proportion of patients achieving an absolute DLQI score of 0 or 1 at Week 16 and at least a 5-point decrease in DLQI score from baseline at Week 16 (*post-hoc* analyses) was higher in the ponesimod 20 mg group (31.0% and 51.6%, respectively) and ponesimod 40 mg group (27.1% and 50.4%, respectively) than in the placebo group (6.0% and 28.4%, respectively).

- On both doses of ponesimod, statistically significant treatment effects (vs placebo) were observed for the mean change from baseline to Week 16 in all SF-36 domains (norm-based), except physical functioning and bodily pain (both doses) and mental health (ponesimod 20 mg).

Consistent with the effect observed on PASI and PGA at Week 16, the treatment effect of ponesimod on patient-assessed outcomes was similar with two doses tested.

The treatment effect of ponesimod (vs placebo) for PASI75 response at Week 16 was consistent across all subgroups (prior systemic treatment, geographical region, baseline PASI, psoriatic arthritis, and age), except BMI on ponesimod 20 mg dose. In the ponesimod 20 mg group, the treatment effect (vs placebo) in the subgroup of patients with BMI $\geq$ 30 kg/m^2 was lower (3.3%, 95% CLs –22.8%, 29.4%) than in the subgroup of patients with BMI < 30 kg/m^2 (44.6%, 95% CLs 30%, 59.3%).

Maintenance period: Data from Week 16 to Week 28 indicated that maximum efficacy is achieved beyond 16 weeks of treatment with ponesimod:

- Among patients who continued on 20 mg and 40 mg, 71.4% and 77.4%, respectively, achieved PASI75 and 42.9% and 50.9%, respectively, achieved PASI90 at Week 28. In contrast, among patients who switched from ponesimod 20 mg and 40 mg to placebo, 42.2% and 40.4%, respectively, achieved PASI75, and 20.0% and 23.4%, respectively, achieved PASI90 at Week 28.
- The proportion of patients with "clear" or "almost clear" on PGA further increased from Week 16 to Week 28 in the ponesimod 20/20 (49.0%) and ponesimod 40/40 groups (50.9%), while it decreased in the ponesimod 20/placebo (20.0%) and ponesimod 40/placebo groups (23.4%).

Higher proportions of patients lost PASI75 response and/or experienced relapses after switching to placebo as compared to patients who continued to receive ponesimod:

- The proportion of patients with loss of PASI75 at any time between Week 16 to 28 was higher in the ponesimod 20/placebo (48.0%) and ponesimod 40/placebo groups (50.0%) than in the ponesimod 20/20 (31.3%) and ponesimod 40/40

groups (12.1%).

- The proportion of patients free of relapse at any time between Week 16 to 28 was higher in ponesimod 20/20 (93.5%) and ponesimod 40/40 (98.0%) groups than in the ponesimod 20/placebo (69.0%) and ponesimod 40/placebo (65.0%).

These results were generally supported by data obtained from other exploratory endpoints including PGA, PGPA, DLQI, and SF-36 scores, for which further improvements were usually observed during the maintenance period.

Up to the end of the maintenance period, rebound was only reported for two patients in the ponesimod 20/placebo group (4.4%) and for one patient in the ponesimod 40/placebo group (2.1%), all of which were PASI deterioration to ≥ 125% of baseline. No patients were reported with any new form of psoriasis.

Other efficacy endpoints: Pain related to psoriatic arthritis was assessed for the 44 patients who were diagnosed with psoriatic arthritis at randomization. At the end of the induction period, the proportion of patients with improvements in psoriatic arthritis pain was higher in the ponesimod 20 mg (56.3%) and ponesimod 40 mg (65.0%) groups than in the placebo group (37.5%). No patients experienced worsening of psoriatic arthritis pain.

A total of 55 patients participated in the skin biopsy substudy conducted at selected centers. Overall, the results were highly variable across the parameters (acanthosis and papilomatosis indices, Total T Cell, Dermal T Cell, and Epidermal T cell), and no specific pattern could be identified.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

The mean steady-state concentrations (from trough samples) for patients in the induction period at Week 3 were 122 ng/mL and 239 ng/mL ponesimod for the 20 mg and 40 mg ponesimod groups, respectively. Similar concentrations were observed at Week 3 for the subset of patients who entered the maintenance period, showing that these patients were no different (in terms of drug exposure) to those who only completed the induction period. This suggests that the average steady-state concentration was not the only determining factor for a patient to achieve PASI50 by Week 16 and thus enter the maintenance period. Concentrations at subsequent visits after reaching steady-state (Week 3) remained stable up to Week 16 (for patients in the induction period) and up to Week 28 (for patients who entered the maintenance period).

There was no relevant influence of BMI, age, or sex on the mean plasma concentrations in either the induction or the maintenance period. The variability in mean concentrations was moderate in both ponesimod 20 mg (CV: 32.5–47.4%) and 40 mg (CV:42.1–51.2%) during the induction period. Similar variability was observed for 20 mg (CV: 39.6–55.1%) and 40 mg (CV: 38.8–56.9%) for patients who entered the maintenance period.

The PK/PD modeling showed that PASI score, percent change from baseline in PASI score, and the dichotomized PASI measures (PASI75, PASI90, and PASI50) were characterized reasonably well by average steady-state drug concentration. Similarly, PASI outcome was characterized reasonably well by total lymphocyte count steady-state average, but in almost all models, average steady-state drug concentration was identified as being a statistically more significant covariate than total lymphocyte count (as indicated by lower p-values). The only other covariate that was found to be statistically significant towards modeling the PASI score at Week 16 was the PASI baseline score. Age, sex, body weight, BMI, and total lymphocyte count steady-state average were found to be not statistically significant. No covariates were found to be systematically significant in the modeling of PASI score change, PASI50, PASI75, and PASI90 at Week 16.

The longitudinal PK/PD modeling showed that the Hutmacher model characterizes the data obtained in this study well. The model comprised baseline PASI score, time, and steady-state trough concentrations as predictive covariates. The model suggests that the expected difference in response (PASI percent change from baseline, PASI50, PASI75, and PASI90) between active doses and placebo is larger for lower PASI baseline scores.

SAFETY RESULTS:

The median overall duration of exposure to study treatment was approximately 16 weeks in all groups. For patients randomized to ponesimod and subsequently re-randomized to placebo in the maintenance period, exposure to placebo treatment was not included in the overall duration of exposure to study treatment. The proportion of patients with more than 24 weeks of exposure to study treatment (37.3% ponesimod 20 mg, 38.3% ponesimod 40 mg, 35.8% placebo, based on Safety set [n = 326] for the overall treatment duration) was similar across the groups.

In the following descriptions, data is presented for treatment-emergent events, unless otherwise specified, for the overall treatment period in the Safety set (n = 326), i.e., the period from study drug start date/time to study drug end date + 7 days. For patients who received ponesimod treatment during the induction period and were re-randomized to receive placebo in the maintenance period, the overall treatment period was from the study drug start date/time up to the date of last dose of study drug in the induction period + 7 days.

The proportion of patients who experienced at least one AE was 57.9% in the ponesimod 20 mg group, 74.4% in the ponesimod 40 mg group and 50.7% in the placebo group. The most frequently reported AEs that occurred at a higher incidence in the ponesimod 20 mg or 40 mg groups compared to placebo included (overall incidence $\geq$ 2% in any group) dyspnea (11.1% ponesimod 20 mg, 26.3% ponesimod 40 mg, 1.5% placebo), increased alanine aminotransferase (ALT; 14.3% ponesimod 20 mg, 10.5% ponesimod 40 mg, 3.0% placebo), increased aspartate aminotransferase (AST; 5.6% ponesimod

20 mg, 6.8% ponesimod 40 mg, 3.0% placebo), dizziness (5.6% ponesimod 20 mg, 4.5% ponesimod 40 mg, 1.5% placebo), and hypertension (3.2% ponesimod 20 mg, 3.8% ponesimod 40 mg). Incidences of dyspnea were dose-related.

No patient died during the study. One patient (2002/13105, ponesimod 40 mg) died due to unexplained causes, after study completion, approximately 7 weeks after the last study drug intake.

A total of 11 patients experienced at least one SAE (4.0% ponesimod 20 mg, 3.8% ponesimod 40 mg, 1.5% placebo). A higher proportion of patients in the ponesimod 20 mg (7.9%) and 40 mg groups (10.5%) discontinued study treatment due to AEs than in the placebo group (1.5%).

AEs of special interest were defined on the basis of nonclinical and clinical findings and comprised certain cardiovascular disorders (HR and rhythm-related, cardiac and hypertension-related AEs), liver abnormalities, pulmonary disorders, eye disorders, infection-related AEs, and skin and non-skin malignancy AEs.

Cardiovascular safety topics of special interest: Atrioventricular (AV) block (second-degree) and cardiac failure in the context of hypertensive crisis (one patient each) were reported as SAEs on ponesimod treatment only. Cardiovascular AEs led to discontinuation of study treatment in 6 patients. AV block (second-degree; 4 patients) and non-sustained ventricular tachycardia (single episode, one patient) that resulted in discontinuation of study treatment were reported on Day 1 (ponesimod 10 mg). Right bundle branch block resulted in the discontinuation of study treatment in one patient on Day 29 (ponesimod 40 mg). No treatment was required for any of these patients who discontinued study treatments, and the events resolved spontaneously.

Ponesimod treatment was associated with a transient first-dose effect on HR and AV conduction. Based on 1–6 h post-dose 12-lead ECG measurements following the administration of ponesimod 10 mg on Day 1, the maximum mean HR (± SD) change from pre-dose levels (approx 70 bpm) ranged was –13.2 ± 9.43 bpm in the ponesimod 20 mg group and –13.5 ± 8.78 bpm in the ponesimod 40 mg group (2 h post-dose), compared to 1.7 ± 9.44 bpm on placebo (1 h post-dose). Following up-titration to 20 mg and 40 mg on Day 8 and Day 15, respectively, the maximum mean (± SD) HR reduction was smaller. HR reduction to values < 40 bpm (individual HR decreases of 11–26 bpm) was reported for 4 patients (all ponesimod) on Day 1 at 2–3 h post-dose. Prolongation of PR to > 200 ms with increases in PR from baseline of > 20 ms was reported for 19 patients on ponesimod 10 mg on Day 1 (out of 259, 7.34%) versus none on placebo. During the course of the study, PR prolongations were sporadic, without association with ponesimod treatment, and of no clinical relevance . Holter monitoring confirmed these first-dose effects of ponesimod on HR and AV conduction.

Based on Holter monitoring, Mobitz I (Wenckebach) second-degree AV block was

reported for 4 patients (3 ponesimod, one placebo) at screening. A total of 15 cases of Mobitz I (Wenckebach) second-degree AV block were reported during the study (13 on ponesimod, 2 on placebo). Twelve cases of Mobitz I (Wenckebach) second-degree AV block were reported on ponesimod 10 mg treatment on Day 1, which in one case was also reported at screening. One patient (ponesimod 40 mg) had an episode of Mobitz I (Wenckebach) second-degree AV block on Day 15. No recurrence of Mobitz I (Wenckebach) second-degree AV block was reported in any of the patients who continued treatment with ponesimod. Two patients in the placebo group experienced Mobitz I (Wenckebach) second-degree AV block, one on Day 1 and one on Day 8, respectively.

Hypertension was reported as an AE only in the ponesimod groups (3.2% ponesimod 20 mg, 3.8% ponesimod 40 mg). The overall mean change in systolic blood pressure (SBP) / diastolic blood pressure (DBP) from baseline to the end of overall treatment period in the ponesimod 20 mg (0.6/1.3 mmHg) and 40 mg groups (0.8/–0.5 mmHg) and placebo group (–3.2/–2.9 mmHg) were small. The proportion of patients with SBP $\geq$ 140 mmHg or 160 mmHg, both accompanied by increase of $\geq$ 20 mmHg and DBP $\geq$ 90 mmHg or 100 mmHg, both accompanied by increase of $\geq$ 15 mmHg were generally higher in the ponesimod groups (20 mg and 40 mg) than in the placebo group.

Liver abnormalities: The incidence of hepatobiliary disorders or liver enzyme abnormality-related AEs in the overall treatment period was higher in the ponesimod groups (15.9% on 20 mg, 11.3% on 40 mg) than in the placebo group (3.0%) with no relation between AE onset and duration of treatment. None of the liver abnormality AEs were reported as SAEs. The proportion of patients with ALT elevations > 3 × upper limit of normal (ULN) was higher on ponesimod 20 mg (11.3%) and 40 mg groups (8.4%) than in the placebo group (3.1%); all were asymptomatic. ALT elevations > 5 × ULN (2.4% ponesimod 20 mg, 3.8% ponesimod 40 mg) were reported only on ponesimod treatments, and in 3 cases exceeded 8 × ULN. None of the patients had ALT or AST elevations > 3 × ULN and total bilirubin (TBIL) > 2 × ULN. Of the 10 patients with ALT or AST elevations > 5 × ULN with ponesimod (induction or maintenance periods), liver enzymes normalized in 3 patients while on ponesimod treatment. In the remaining 7 patients, elevations resolved either after switching to placebo or after study completion or premature treatment discontinuation. A total of 3 patients discontinued ponesimod treatment due to liver enzyme elevations.

Pulmonary findings: The incidence of pulmonary AEs of special interest was higher in the ponesimod groups (12.7% 20 mg, 30.8% 40 mg) than in the placebo group (3.0%) predominantly due to dose-related incidences of dyspnea in the ponesimod groups (11.1% 20 mg, 26.3% 40 mg) compared to the placebo group (1.5%). None of the pulmonary AEs of special interest were reported as SAEs. AEs of dyspnea (one patient 20 mg, 6 patients, 40 mg), wheezing (2 patients 40 mg), decreased FEV_1 and FVC (one

patient, 40 mg) led to treatment discontinuation.

The mean percent change (± SD) in FEV_1 and FVC from baseline to the end of the overall treatment period was greater in the ponesimod 20 mg ($-4.9\% \pm 7.86$ and -0.5 ± 12.88, respectively) and 40 mg groups ($-8.3\% \pm 9.17$ and -3.3 ± 8.23, respectively) than in the placebo group ($-1.6\% \pm 4.64$ and 0, respectively). The decreases in the ponesimod groups were dose dependent. The decrease from baseline in FEV_1 at Week 16 was stable up to Week 28 in the ponesimod 20/20 and ponesimod 40/40 groups, while FEV_1 returned to baseline in the ponesimod 20/placebo and ponesimod 40/placebo groups.

A higher proportion of patients in the ponesimod groups had FEV_1 and FVC < 80% of their baseline measurements (5.8% and 2.5%, respectively, 20 mg; 23.2% and 5.6%, respectively, 40 mg) compared to placebo (1.6% and 0%). FEV_1 and FVC < 70% of the predicted normal value were reported only in the ponesimod groups (2.5% and 0, respectively, 20 mg and 11.2% and 4.0%, respectively, 40 mg).

Other safety findings: Marked decreases in lymphocyte count (i.e., $< 0.2 \times 10^9$/L) were only reported on a single occasion among patients in the ponesimod group (one patient 20 mg, 4 patients 40 mg). None of these patients discontinued the study treatment due to lymphopenia.

Of the 4 patients reported with eye-disorder-related AEs of special interest (3 patients ponesimod 40 mg, one patient placebo), one confirmed case of macular edema (ponesimod 40 mg) was reported as an SAE and resulted in treatment discontinuation.

Infection-related AEs of special interest (i.e., preferred terms from the system organ class 'Infections and Infestations', only if reported as serious or severe) were reported only in the ponesimod groups (3 patients). Pneumonia (one patient on ponesimod 40 mg) and severe-intensity acute viral infection concomitant with worsening of Gilbert's syndrome (one patient on ponesimod 20 mg) were reported as SAEs and resulted in treatment discontinuation.

Malignancy-related AEs of special interest were reported only in the ponesimod 40 mg group (2 patients), one of which was reported as an SAE (Hodgkin's disease) and one (basal cell carcinoma) resulted in treatment discontinuation.

CONCLUSIONS:

The results of this study suggest that modulation of the $S1P_1$ receptor with ponesimod may be an effective treatment for patients with chronic plaque psoriasis. The primary objective of demonstrating the efficacy at Week 16 (the end of the induction period) for at least one of the two doses of ponesimod compared to placebo in patients with moderate to severe chronic plaque psoriasis was met, with a statistically significant higher proportion of patients achieving PASI75 at Week 16 for each ponesimod dose

compared to placebo. Consistent and clinically relevant improvements on ponesimod treatment were observed on physician and patient-rated disease severity and health-related QoL scores at Week 16. Improvements in PASI score were observed early with treatment and the response continued to increase for both ponesimod doses when treatment was continued beyond Week 16, reaching a plateau of efficacy after 24 weeks. Both doses appear to be similarly effective.

Similar effects were observed with the two doses tested on efficacy outcomes including PASI, PGA, PGPA, DLQI, and SF-36, suggesting that a plateau of efficacy is approached with a dose of 20 mg. After discontinuation of ponesimod therapy, there was a gradual loss of clinical benefit, which is consistent with the natural course of psoriasis and supports the need for continuous therapy with ponesimod to provide optimal control of psoriasis.

The nature and severity of AEs reported in this study were consistent with the known safety profile of ponesimod and with the underlying conditions of the investigated population. Ponesimod 40 mg was associated with reduced tolerability due to an increased incidence of AEs of dyspnea and pulmonary-related AEs. Ponesimod 20 mg was well tolerated.

In view of the efficacy and safety data observed in this study, the benefit/risk profile of ponesimod 20 mg may be suitable for the systemic treatment of patients with moderate to severe chronic plaque psoriasis.

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