2 SYNOPSIS OF STUDY REPORT, No. D-10.888 (AC-058B201)

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, dose-finding study to evaluate the efficacy, safety, and tolerability of three doses of ponesimod (ACT-128800), an oral $S1P_1$ receptor agonist, administered for twenty-four weeks in patients with relapsing-remitting multiple sclerosis		
INDICATION	Relapsing-remitting multiple sclerosis		
INVESTIGATORS / CENTERS AND COUNTRIES	94 centers in 23 countries randomized patients Coordinating investigator: Tomas Olsson, MD, PhD		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	23 Aug 2009 to 17 June 2011 (first patient, first visit to last patient, last visit)	CLINICAL PHASE	Type 2b
OBJECTIVES	The primary objective was to demonstrate the efficacy of at least one of three doses of ponesimod as compared to placebo in patients with relapsing-remitting multiple sclerosis (RRMS) on the cumulative number of new gadolinium-enhancing (Gd+) lesions per patient, recorded on T_1-weighted magnetic resonance imaging (MRI) scans at Weeks 12, 16, 20 and 24 after study drug initiation. Secondary objectives were: • To evaluate the effects of ponesimod on the annualized confirmed relapse rate within 24 weeks of study drug initiation.		

	• To evaluate the effects of ponesimod on time to first confirmed relapse within 24 weeks of study drug initiation. • To evaluate the safety and tolerability of ponesimod.
STUDY DESIGN	Phase 2b, prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, four-arm, parallel-group, dose-finding study. Screening was performed 21 to 35 days prior to randomization. The baseline visit was performed within 3 days prior to randomization. Patients were randomized in a 1:1:1:1 ratio (10 mg ponesimod: 20 mg ponesimod: 40 mg ponesimod: placebo), with stratification by center. Study drug was administered for a period of 24 weeks. A two-step up-titration scheme was followed during the treatment period. Up-titration scheme:

		Ponesimod once daily (o.d.)			
	Period	**Placebo**	**10 mg**	**20 mg**	**40 mg**
Dose level 1	Day 1–7 (initial dose)	0 mg	10 mg	10 mg	10 mg
Dose level 2	Day 8–14 (first up-titration)	0 mg[1]	10 mg[1]	20 mg	20 mg
Dose level 3[2]	Day 15–Week 24 (second up-titration)	0 mg[1]	10 mg[1]	20 mg[1]	40 mg

[1] mock up-titration; [2] maintenance phase

The first dose of study drug on Day 1 and the first dose on up-titration Days 8 and 15 was administered at the investigational site, and patients [redacted]. From Week 4 onwards, site visits were performed every 4 weeks up to the end of the 24-week treatment period or up to study drug discontinuation. The end-of-treatment (EOT) visit was performed at Week 24 (i.e., Day 168 ± 5) or following premature discontinuation of study drug.

Two safety follow-up visits were performed, 7 ± 1 days and 30 ± 5 days (end-of-study [EOS] visit) after the last

	intake of study drug for patients who prematurely discontinued study drug and for those who completed 24 weeks of treatment but chose not to enter the extension study. For patients who entered the extension study at Week 24, the EOS visit coincided with the EOT visit at Week 24.
NUMBER OF PATIENTS	[redacted] 464 patients were randomized. Of these, 462 patients received study treatment and were included in the All-treated set. Of the patients randomized, 97.0% (450/464) were included in the modified intent-to-treat (mITT) set and 83.8% (389/464) in the Per-protocol set. The Per-protocol set was used for the primary analysis.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult male and female patients aged 18 to 55 years (inclusive), with a diagnosis of RRMS according to the revised (2005) McDonald Diagnostic Criteria for multiple sclerosis (MS). Patients were required to be in a stable clinical condition (without a clinical exacerbation of MS for at least 30 days prior to randomization), ambulatory and with an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 (inclusive). Patients were required to have had documented relapses (at least one within 12 months prior to screening or at least 2 within 24 months prior to screening) or to have at least one Gd+ lesion on T_1-weighted MRI (central reading) at screening.
TRIAL DRUG / BATCH No.	Ponesimod: 10, 20 or 40 mg ACT-128800 free base as hard gelatin capsules. Batch Numbers: PD07071 & PD08129 for 10 mg ACT-128800 10 capsules & 36 capsules per bottle; PD07072 & PD08130 for 20 mg ACT-128800 10 capsules & 36 capsules per bottle; PD07073 & PD08131 for 40 mg ACT-128800 36 capsules per bottle.

TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	Ponesimod 10, 20 or 40 mg, or matching placebo capsules once daily for a period of 24 weeks. A two-step up-titration scheme was followed.
REFERENCE DRUG / BATCH No.	Matching placebo capsules of identical appearance. Batch Numbers: PD07069 & PD08127 for Placebo 10 capsules & 36 capsules) per bottle.
REFERENCE DRUG DOSE / ROUTE / REGIMEN / DURATION	Matching placebo capsules once daily for a period of 24 weeks. A two-step (mock) up-titration scheme was followed.
CRITERIA FOR EVALUATION EFFICACY:	The primary efficacy endpoint was the cumulative number of new T_1 Gd+ lesions at Weeks 12, 16, 20, and 24 after study drug initiation. [redacted] The secondary endpoints were: • Annualized confirmed relapse rate within 24 weeks of study drug initiation. • Time to first confirmed relapse within 24 weeks of study drug initiation. The exploratory endpoints were: *Other MRI-related variables*: • [redacted] • Cumulative number of new or enlarged T_2 lesions from Weeks 12 to 24. • Cumulative number of total T_1 Gd+ lesions from Weeks 12 to 24. • [redacted] • Cumulative number of combined unique active lesions (new T_1 Gd+ lesions plus new or enlarged

T_2 lesions) from Weeks 12 to 24.

- [redacted]
- Percentage change from baseline to Week 24 in brain volume.

[redacted]

Neurological assessments:

- Absolute change from baseline in EDSS scores and categorical change (improved, stable or worsened) from baseline to Week 24 in EDSS.

Ophthalmological assessments:

- Change from baseline to Week 24 in average retinal nerve fiber layer (RNFL) thickness, central foveal thickness, and total macular volume as measured by optical coherence tomography (OCT) at selected centers.
- Change from baseline to Week 24 in average number of letters correctly read in a best corrected visual acuity test (recorded only at centers that also performed OCT).

	Quality of life: • Change from baseline in quality of life based on two questionnaires (Multiple Sclerosis Impact Scale 29 [MSIS-29] and modified Fatigue Impact Scale [mFIS]) completed by the patients at baseline, Week 12 and Week 24 (only in those countries where verified translations were available). [redacted]
PHARMACOKINETICS AND PHARMACODYNAMICS:	The pharmacokinetic endpoints were: • Plasma concentrations of ponesimod at trough level (pre-dose) on Days 8 and 15, at Weeks 4, 12 and 24, and on days (all) of re-initiation and re-up-titration of study drug following drug interruption. • Plasma concentrations of ponesimod at 2.5 h post-dose on Days 1, 8 and 15, and on days (all) of re-initiation and re-up-titration of study drug following drug interruption. The pharmacodynamic endpoints were: • Peripheral blood lymphocyte count as a function of ponesimod dose and plasma concentration at trough (pre-dose) on Days 8 and 15, and at Weeks 4, 12 and 24. • Post-treatment lymphocyte count recovery, one and four weeks (30 days) after study drug discontinuation. • [redacted]
SAFETY:	The safety endpoints were: • Occurrence of adverse events (AEs), and serious adverse events (SAEs) during the treatment period and the follow-up period, and AEs leading to premature discontinuation of study drug. • Occurrence of AEs of special interest (i.e.,

cardiovascular AEs, hepatobiliary disorders/liver toxicity, pulmonary AEs, eye disorders, and infection-related AEs reported as severe or as serious by the investigator) during the treatment and follow-up periods.

- Change from baseline to all assessed time points in:
  - ECG variables (heart rate [HR], PR, QRS, QT, QTc);
  - Pulmonary function tests (PFTs) (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC ratio, and FEV_1 and FVC in percent of predicted value and percent change from baseline);
  - Ophthalmological exam (best corrected visual acuity, and OCT [at selected centers only]);
  - Blood pressure (systolic [SBP]/diastolic [DBP]);
  - Laboratory variables.
- Change in ECG variables (HR, PR, QRS, QT, QTc) from pre-dose to post-dose at selected time points during the study.
- Occurrence of clinically relevant ECG abnormalities as assessed by 12-lead ECG, based on central reading.
- Occurrence of clinically relevant ECG abnormalities as assessed by 24-hour Holter ECG monitoring (based on central reading), for all patients enrolled after the approval of Global protocol Amendment 2.
- Change in left ventricular (LV) ejection fraction as assessed by Standard 2D echocardiography from screening to Week 12 and Week 24 (at selected centers).
- Occurrence of clinically relevant cardiac abnormalities as assessed by Standard 2D/Doppler echocardiography (at selected centers).
- Occurrence of elevated liver function tests, hematological abnormalities and metabolic abnormalities as defined by sponsor guidelines.
- Change in body weight from baseline to EOT.

STATISTICAL METHODS:

The primary endpoint was the cumulative number of new T_1 Gd+ lesions between

Weeks 12 and 24, i.e., the sum of new T_1 Gd+ lesions reported at Weeks 12, 16, 20, and 24. The primary analysis was performed using the Per-protocol (MRI) set. The global null hypothesis was expressed as a family of null hypotheses. The test of the null hypotheses was based on a negative binomial (NB) regression model with treatment group as a four-level covariate. Each dose of ponesimod was compared to placebo.

Based on the assumption of [redacted] a 50% reduction in the cumulative number of new Gd+ lesions in at least one of the ponesimod groups, a study with 90 evaluable patients per treatment group had 90% power to detect a significance difference at an alpha of 0.0167 applying Bonferroni-Holm adjustment.

The time to first confirmed relapse was analyzed using the Kaplan-Meier (K-M) method and log rank test. The treatment effects vs placebo were described by the hazard ratios and their 95% confidence limits (CLs) derived from a Cox proportional regression model with the treatment group (a four-level variable) as explanatory variable.

The annualized relapse rate (ARR) was calculated on treatment group and patient level. [redacted]

PATIENT DISPOSITION:

A total of 621 patients were screened. Of these, 464 patients were randomized in the study; 108, 116, 119, and 121 patients randomized to the ponesimod 10 mg, 20 mg and 40 mg, and placebo groups, respectively. All but two randomized patients (ponesimod 20 mg) received treatment with study drug.

In the ponesimod 10 mg, 20 mg and 40 mg groups, 16.7%, 13.2%, and 21.0% of patients, respectively, prematurely discontinued study treatment, compared to 9.1% in the placebo group. In the ponesimod 10 mg, 20 mg and 40 mg groups, 11.1%, 5.3%, and 13.4% of the patients, respectively, discontinued study treatment due to AEs compared to 2.5% on placebo. Discontinuation of treatment due to withdrawal of consent was reported in 1.9%, 0.9%, 2.5%, and 0.8% of the patients in the ponesimod 10 mg, 20 mg and 40 mg, and placebo groups, respectively. One patient (0.9%) in the ponesimod 10 mg group was lost to follow-up.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

The majority of patients treated in the study were female (67.5%). The mean age was 36.4 years (range: 18–55 years). The patient population was predominantly Caucasian (96.3%). The demographic and baseline disease characteristics were similar across the four treatment groups.

The median time since initial diagnosis of MS was 2.3 years (mean: 4.2 years, range: 0–23.3 years). The median time since the first symptoms of MS was 5.2 years (mean: 7.2 years, range: 0.2–35.8 years). The median time since the most recent documented relapse

prior to screening was 4.1 months (mean: 5.3 months, range: 0–50 months).

[redacted]

Gd+ T_1 lesions on the baseline MRI scan were observed in 46.3% of patients. The mean number of T_1 Gd+ lesions at baseline (MRI scan) was 2.1 (range 0–59).

Prior to randomization into the study, 81.5–83.3% and 77.7% of the patients in the three ponesimod groups and placebo, respectively, had received at least one medication for the treatment of MS.

EFFICACY RESULTS:

In the ponesimod groups, the mean cumulative number of new T_1 Gd+ lesions at Weeks 12 to 24 (primary efficacy endpoint) ranged from 1.1–3.5 compared to 6.2 in the placebo group. In the primary analysis (NB regression analysis with imputation for missing data) of the cumulative number of new T_1 Gd+ lesions at Weeks 12 to 24 using the Per-protocol set, a statistically significant treatment effect was demonstrated for each ponesimod group. The treatment effect (ratio) vs placebo with ponesimod 10 mg was 0.566 (95% CLs: 0.337, 0.952, P = 0.0318), with ponesimod 20 mg 0.170 (95% CLs: 0.100, 0.289, P < 0.0001), and with ponesimod 40 mg 0.226 (95% CLs: 0.133, 0.384, P < 0.0001).

A significant dose-response relationship (P < 0.0001) was identified for the primary endpoint using a multiple comparison modeling technique (MCP-Mod). A mean reduction of 70% was estimated with the 20 mg dose. Only a minor further increase in the effect was projected for doses greater than 20 mg.

Results of the other MRI-related endpoints are summarized below:

MRI-related endpoint	Treatment effect (ratio)* ponesimod vs placebo		
	Ponesimod 10 mg	Ponesimod 20 mg	Ponesimod 40 mg
[redacted]			
Cumulative total number of T_1 Gd+ lesions at Weeks 12 to 24	0.734 (0.426, 1.263, P = 0.2637)	0.288 (0.168, 0.492, P < 0.0001)	0.294 (0.171, 0.507, P < 0.0001)
Cumulative number of new or enlarged T_2 lesions at Weeks 12 to 24	0.694 (0.353, 1.367, P = 0.2914)	0.443 (0.223, 0.883, P = 0.0208)	0.657 (0.336, 1.284, P = 0.2194)

* NB regression analysis using the Per-protocol set; estimated treatment effect ratio and 95% CLs.

At Week 24/EOT, a greater proportion of patients in the ponesimod groups was free of active lesions compared to placebo.

The estimated ARR (confirmed relapses) within 24 weeks of study drug initiation was lower in the ponesimod groups compared to placebo (see below). The estimated (K-M) percentage of patients free of confirmed relapses at Week 24 was higher in the

ponesimod groups compared to placebo (see below):

Relapse endpoint	Ponesimod 10 mg	Ponesimod 20 mg	Ponesimod 40 mg	Placebo
Annualized (confirmed) relapse rate				
		ARR estimate[¥]		
ARR (confirmed relapses) within 24 weeks of study drug initiation	0.332 (0.198, 0.557)	0.417 (0.266, 0.653)	0.251 (0.141, 0.446)	0.525 (0.358, 0.770)
		Treatment effect (rate ratio)[Ψ] ponesimod vs placebo		
	0.632 (0.332, 1.202, P = 0.1619)	0.793 (0.440, 1.432, P = 0.4420)	0.478 (0.240, 0.954, P = 0.0363)	
Time to first confirmed relapse				
		K-M estimate[#]		
Patients free of confirmed relapses at Week 24	85.6% (78.59%, 92.60%)	83.9% (76.90%, 90.96%)	90.6% (84.97%, 96.16%)	78.5% (70.98%, 85.96%)
		Treatment effect (hazard ratio)[§] ponesimod vs placebo		
	0.64 (0.33, 1.22, P = 0.1744)	0.79 (0.43, 1.45, P = 0.4529)	0.42 (0.20, 0.87, P = 0.0189)	

Analysis set: All-treated set
[¥] ARR estimate with 95% CLs from NB regression analysis
[Ψ] Treatment effect (rate ratio) with 95% CLs from NB regression analysis
[#] K-M estimates with 95% CLs (log-rank test)
[§] Treatment effect (hazard ratio) with 95% CLs derived from Cox proportional hazards model

Overall, 55.6%, 59.6% and 68.9% of the patients in the ponesimod 10 mg, 20 mg and 40 mg groups, respectively, were free from inflammatory disease activity (i.e., experienced no confirmed relapses and had no T_1 Gd+ lesions) at Week 24/EOT compared to 50.4% on placebo.

Optical coherence tomography (a substudy with a total of 162 patients in the OCT analysis set) showed a mean (± standard deviation [SD]) decrease of 1.8 ± 10.28 µm from baseline (92.7 µm) in average RNFL thickness at EOT in the ponesimod 10 mg group compared to no change in the placebo group. In the ponesimod 20 mg and 40 mg groups, a mean increase from baseline was observed. Mean increases from baseline in central foveal thickness at EOT in the ponesimod groups ranged from 1.4 ± 18.25 µm to 6.7 ± 41.32 µm compared to 1.0 ± 16.00 µm on placebo. Change from baseline of > 40 µm in central foveal thickness were reported for 11.1% of the patients in the ponesimod 10 mg group compared to 7.3% in the placebo group. In the ponesimod 20 mg and 40 mg groups, the incidences were 4.2% and 4.4%, respectively.

PHARMACOKINETIC RESULTS:

Low variability in arithmetic mean and median plasma concentrations of ponesimod was observed between Week 4 and Week 24 for the three ponesimod groups. The mean concentrations of ponesimod at Week 24 were 57.1 ng/mL, 111.7 ng/mL, and 199.7 ng/mL in the 10 mg, 20 mg, and 40 mg dose groups, respectively, indicating a near dose-linear relationship.

SAFETY RESULTS:

During the study, patients in the ponesimod groups and the placebo group received study treatment for a median duration (including interruptions) of 167–168 days.

The proportion of patients who had at least one treatment-emergent AE was similar across the ponesimod groups (73.9–77.2%) and placebo (74.4%). Frequently reported AEs that occurred at a higher incidence in the three ponesimod groups compared to placebo were dyspnea (ponesimod 10 mg group: 4.6%, ponesimod 20 mg group: 6.1%, ponesimod 40 mg group: 14.3%, placebo: 3.3%), peripheral edema (ponesimod 10 mg group: 1.9%, ponesimod 20 mg group: 2.6%, ponesimod 40 mg group: 10.9%, placebo: 1.7%) and dizziness (ponesimod 10 mg group: 7.4%, ponesimod 20 mg group: 6.1%, ponesimod 40 mg group: 9.2%, placebo: 2.5%). Incidences of dyspnea and peripheral edema appeared to be dose-related. Most cases of dyspnea were reported within the first four weeks of treatment.

No patient died during the study. During the treatment period, 6.5%, 6.1%, 2.5% and 4.1% of the patients in the ponesimod 10 mg, 20 mg and 40 mg, and placebo groups, respectively, had at least one SAE. In the ponesimod 10 mg, 20 mg, and 40 mg groups, 11.1%, 5.3%, and 13.4% of the patients, respectively, discontinued study treatment due to AEs compared to the placebo group (3.3%).

AEs of special interest were defined on the basis of preclinical and clinical findings and comprised certain cardiovascular disorders, hepatobiliary disorders/liver toxicity, pulmonary disorders, eye disorders, and infection-related AEs.

[redacted]

Bradycardia AEs were reported on Day 1 by 2.0% (7/341) of the patients treated with ponesimod 10 mg. Two of these cases resulted in discontinuation of study treatment. No AE of bradycardia was reported following up-titration to 20 mg and 40 mg on Day 8 and Day 15, respectively. Treatment with ponesimod was associated with a transient first-dose effect on HR. [redacted]

On Day 1, a total of seven cases (7/341, 2.0%) of second-degree AV-block Mobitz I were

Echocardiography reports during the study were read centrally and assessed by an expert. Based on the available data it was concluded by the expert that no differences in echocardiography morphological or functional variables were apparent between ponesimod and placebo groups. Taking into consideration the low incidence of observed changes, it was concluded that these findings do not carry any prognostic significance.

A transient decrease in mean SBP/DBP was observed both with ponesimod 10 mg and placebo during the first five hours following administration of the first dose of study drug on Day 1.

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations ≥ 3 × upper limit of normal (ULN) were reported only with ponesimod treatment.

[redacted] Hepatobiliary AEs of special interest were reported at a higher incidence in the ponesimod groups (6.1%–9.2%) compared to placebo (1.7%), with no correlation between AE onset and duration of treatment. None of the patients in the four treatment groups had total bilirubin elevations > 2 × ULN. Three cases of increased ALT resulted in discontinuation of study treatment (one case in each of the three ponesimod groups). No cases of suspected drug induced liver injury were reported in the study.

Pulmonary AEs of special interest were reported in a higher proportion of patients in the ponesimod groups (ponesimod 10 mg: 9.3%, ponesimod 20 mg: 16.7%, ponesimod 40 mg: 31.9%) compared to the placebo group (6.6%), with most of the AEs reported within the first four weeks of treatment. This was predominantly due to dyspnea, which was experienced by 4.6%, 6.1% and 14.3% of the patients in the ponesimod 10 mg, 20 mg and 40 mg groups, respectively, compared to 3.3% in the placebo group. Discontinuation of study treatment due to dyspnea was only reported in the ponesimod 10 mg (one patient, 0.9%) and ponesimod 40 mg groups (four patients, 3.4%). In the ponesimod 40 mg group, two additional patients discontinued study treatment due to exertional dyspnea and one patient discontinued study treatment due to decreased PFTs. Dose-dependent decreases from baseline in PFTs [redacted] were observed in the ponesimod groups. [redacted]

Ocular AEs of special interest were reported for 4.4% and 0.8% of the patients in the ponesimod 20 mg and 40 mg groups, respectively, and 0.8% in the placebo group. The higher incidence of eye disorder-related AEs of special interest in the ponesimod 20 mg group was due to macular edema (three cases, 2.6%) and one case each of papilledema and retinal exudates. [redacted]

[redacted] Based on expert assessment, only one case of reported macular edema in the ponesimod 20 mg group was considered confirmed. The [redacted] three cases, which were diagnosed by ophthalmoscopy were not confirmed by OCT and resolved without sequelae.

Due to the pharmacological effect of ponesimod, mean lymphocyte count decreased (on Day 8) during treatment with ponesimod. [redacted] In patients in the ponesimod groups who performed follow-up visits after EOT, the mean lymphocyte count returned to within baseline range by the time of the follow-up visit 1 (8 days after EOT) [redacted] No patient discontinued study treatment due to lymphopenia.

Infection-related AEs reported as severe or serious (SAEs) included one case of severe intensity viral gastroenteritis (ponesimod 40 mg group) and one case of measles reported as serious (placebo group). No cases of serious viral infections and no cases of opportunistic infections were reported in the ponesimod groups.

Two cases of malignancy were reported in the study, one in the ponesimod 10 mg group (breast cancer [redacted] and one in the placebo group (cervix carcinoma).

CONCLUSIONS:

The primary objective of demonstrating the efficacy of at least one of the three doses of ponesimod in patients with RRMS was met with a statistically significant decrease in the cumulative number of new T_1 Gd+ lesions on MRI at Weeks 12–24 for each ponesimod dose compared to placebo. There was clear dose-dependent relationship for the effect on the primary endpoint with a plateau of efficacy achieved with the 20 mg dose.

The two-step study drug dose up-titration scheme was successful in minimizing the first-dose effect of ponesimod on heart rhythm and conduction. The peripheral lymphocyte count reduction (mean % decrease of 46%–70%) was not associated with the occurrence of severe or serious infections during the treatment period. Treatment with ponesimod was associated with dose-dependent decreases from baseline in PFTs, which were reversible upon treatment discontinuation. The magnitude of this decrease was highest in the 40 mg dose group and was associated with reduced tolerability due to dyspnea leading to treatment discontinuation in several patients.

Based on the comprehensive analysis of efficacy, safety, and tolerability results of this

Phase 2b study, further supported by modeling of dose/concentration-response relationships, a maintenance dose of 20 mg appears the most appropriate ponesimod dose for treatment of MS patients.

DATE OF THE REPORT:

31 January 2013