2 SYNOPSIS OF STUDY REPORT, NO. D-12.733 (AC-060A202)

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:	
Setipiprant	Type … *(ONLY DRA)*	
NAME OF ACTIVE SUBSTANCE(S):	Page:	
ACT-129968	Type … *(ONLY DRA)*	

TITLE OF THE STUDY	CONTROL: CRTH2 antagONist TReatment to contrOL asthma A multicenter, double-blind, placebo-controlled, parallel-group study to establish proof-of-concept and explore the efficacy of different doses of ACT-129968 (setipiprant) in adult patients with partly controlled asthma		
INDICATION	Asthma		
INVESTIGATORS / SITES AND COUNTRIES	The study was conducted at 97 sites in 13 countries with 83 sites enrolling patients. A pharmacokinetic–cardiac-monitoring (PK–CM) sub-study was conducted at 50 sites with 27 sites enrolling patients into the sub-study. Prinicipal/Coordinating Investigator: Eric Bateman		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	3 November 2010 to 12 January 2012	CLINICAL PHASE	2b
OBJECTIVES	The primary objective was to demonstrate the efficacy of 1000 mg twice a day (b.i.d.) setipiprant versus placebo on change from baseline to Week 12 in forced expiratory volume in 1 second (FEV_1). Other objectives were to explore the efficacy of different doses of setipiprant on the change in lung function and		

	asthma control, and to assess the pharmacokinetics (PK), safety, and tolerability of setipiprant. The maintenance of treatment effect on symptoms and inflammatory markers was to be explored during the run-out period.
STUDY DESIGN	This was a prospective, multicenter, randomized, double-blind (DB), placebo-controlled, multiple-dose, parallel-group, Phase 2b study in adult patients with partly controlled asthma on reliever-only therapy. The study included a screening period of approximately 2 weeks followed by a 12-week DB treatment period during which patients were treated with placebo or setipiprant 100, 500, or 1000 mg b.i.d. (1:1:1:1 randomization). The DB treatment period was followed by a 2-week run-out period, which concluded with the end-of-study visit. Safety follow-up was conducted for all patients by telephone 30 days after the last intake of the study drug. Morning pre-dose PK samples for investigation of steady-state trough setipiprant concentrations were taken at Week 1 (Visit 3) to Week 12 (Visit 7). A PK–CM sub-study was conducted to investigate the effect of food on steady-state setipiprant exposure. Setipiprant was dosed in the fasted state at Week 2 (Visit 4) and with food at Week 4 (Visit 5). The sub-study also investigated the relationship between plasma setipiprant concentrations and ECG measurements. At both Week 2 and Week 4, 12-h PK profiling was performed concurrently with 12-h 12-lead Holter monitoring.
NUMBER OF PATIENTS	A total of 412 eligible patients were planned to be randomized. A total of 438 patients were actually randomized. Of these, 121 patients were randomized into the PK–CM sub-study. The modified intention-to-treat (mITT) set was used for the efficacy analysis and comprised 98.9% of randomized patients (setipiprant 100, 500, and 1000 mg b.i.d.: 106, 108, and 108; placebo: 111). All but one randomized patient were included in the Safety set (setipiprant 100, 500, and 1000 mg b.i.d.: 109, 108, and

	109; placebo: 111). For the PK trough analysis (main study), trough concentrations from 305 patients on setipiprant were used in the summary statistical analysis. For the fed/fasted investigation (PK–CM sub-study), PK profiles of 39 patients on setipiprant were used in the summary statistical analysis.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male or female patients aged 18 to 65 years diagnosed with asthma at screening according to the Global Initiative for Asthma Guidelines. Patients were required to have met the following inclusion criteria: • Pre-bronchodilator $FEV_1 \leq 85\%$ of the predicted normal value measured at least 6 h after the last intake of a short-acting inhaled β2 agonist. • Reversibility of airway obstruction ≥ of 12% and ≥ 200 mL from the pre-bronchodilator FEV_1 value measured 15–45 min after administration of 400 µg salbutamol using a valved spacer device. • Asthma Control Questionnaire (ACQ) score ≥ 1.5 • Positive reaction to a skin prick test (wheal diameter ≥ 3 mm greater than saline control) or increased specific IgE (radioallergosorbent test) to common allergens.
TRIAL DRUG / BATCH No.	[redacted]
[redacted]	
DRUG DOSE / ROUTE / REGIMEN / DURATION	[redacted] 12-week DB period (1:1:1:1 randomization ratio): Placebo Setipiprant 100 mg b.i.d. Setipiprant 500 mg b.i.d.

	Setipiprant 1000 mg b.i.d. Two week run-out: No study drug was administered (short-acting β2 agonist was the only allowed asthma treatment).
CRITERIA FOR EVALUATION EFFICACY:	The primary efficacy endpoint of the study was the change from baseline to Week 12 in pre-bronchodilator FEV_1 percent of predicted (FEV_1% predicted) in the setipiprant 1000 mg b.i.d. group. The secondary efficacy endpoints of the study included • Change from baseline to Week 12 in pre-bronchodilator FEV_1% predicted in the 100 and 500 mg b.i.d. dose groups of setipiprant. • Change from baseline to Week 12 in ACQ score. • Change from baseline to each week during treatment and run-out periods in the morning and evening Peak Expiratory Flow (PEF), and diurnal PEF variation. • Change from baseline to each week during treatment and run-out periods in asthma symptoms score (daytime, night-time, and total daily asthma symptoms score). • Change from baseline to each week during treatment and run-out periods in the use of asthma reliever medication. • Time to discontinuation from the study drug due to lack of efficacy (i.e., need for additional asthma treatment or the occurrence of a clinical asthma exacerbation) up to the end of treatment (EOT) • Time to first clinical asthma exacerbation (i.e., deterioration of asthma requiring treatment with oral corticosteroids, hospital admission, or emergency room visit) up to EOT. Exploratory efficacy endpoints further investigated the effects of setipiprant treatment on the changes from baseline in pre- and post-bronchodilator FEV_1 and forced vital capacity (FVC, absolute and % predicted), ACQ and asthma symptoms at individual weeks of the DB treatment period, and over the 2–week run-out period.

PHARMACOKINETICS AND PHARMACODYNAMICS:	The PK endpoints of the study were trough (morning pre-dose sample) plasma concentration of setipiprant at Weeks 1, 2, 4, 8, and 12 and the attainment of steady-state conditions in all setipiprant treatment groups. Within the PK–CM sub-study, the effect of food (Week 2 / Visit 4, fasted condition, and Week 4 / Visit 5, fed condition) on the PK of setipiprant was investigated. The PK/pharmacodynamic (PD) relationship between the morning trough plasma concentration of setipiprant and FEV_1 (absolute and % predicted), ACQ, and total daily asthma symptoms score was evaluated through a population PK/PD approach, and is summarized separately.
SAFETY:	Safety was evaluated on the basis of the incidence of serious adverse events (SAEs), adverse events (AEs), and AEs leading to premature discontinuation of study drug. In addition, assessments of laboratory variables, vital signs, 12-lead ECG (all patients) and Holter monitoring (patients participating in PK–CM sub-study), physical condition and body weight were performed. Daily electronic diary and PEF contributed to the ongoing safety monitoring of the patients.

STATISTICAL METHODS:

The null hypothesis was that there was no difference between setipiprant 1000 mg b.i.d. and placebo for change from baseline to Week 12 in pre-bronchodilator FEV_1% predicted. The alternative hypothesis was that there was a difference between the two treatments. A difference of 6% predicted (pre-bronchodilator FEV_1% predicted) versus placebo was to be detected at Week 12, if change from baseline in % predicted in both groups was normally distributed with a standard deviation (SD) of 13% predicted.

No imputation of missing data was done in the presentation of summary statistics in tables, listings and graphs for any of the endpoints in this study. For endpoints on which a formal statistical analysis was performed for the change from baseline to Week 12 / over 12 weeks (i.e., primary endpoint, secondary endpoints: pre-bronchodilator FEV_1% predicted, ACQ, morning and evening PEF, diurnal PEF variation, and total daily asthma symptoms score, and exploratory endpoints: nasal symptoms visual analog scale, pre-bronchodilator FEV_1 and pre-bronchodilator FVC), the last-observation-(post-baseline)-carried-forward (LOCF) method was used to impute missing Week 12 data.

Efficacy analyses were performed using the mITT set, which included all randomized patients who received at least one dose of study drug and had at least one valid post-baseline assessment of the primary endpoint. The change from baseline to Week 12 in pre-bronchodilator FEV_1% predicted in the setipiprant 1000 mg b.i.d. (primary endpoint) was compared with placebo using analysis of covariance (ANCOVA), with pre-bronchodilator FEV_1% predicted at baseline and the treatment arm as independent variables (covariates) and the change from baseline to Week 12 in pre-bronchodilator FEV_1% predicted as response variable.

[redacted]

Subgroup analyses based on subgroups of gender, pre-bronchodilator FEV_1% predicted at baseline ($\leq$ 60, 60–80, $\geq$ 80) and inhaled corticosteroids (ICS) as previous asthma-specific treatment administered within 6 months prior to study entry (presence, absence) were performed on the primary endpoint and selected secondary endpoints (total ACQ score, total daily asthma symptoms score, and diurnal PEF variation) using the mITT set.

A dose-response relationship for change from baseline to the mean over 12 weeks in pre-bronchodilator FEV_1% predicted, change from baseline to Week 12 in pre-bronchodilator FEV_1% predicted, FVC, diurnal PEF variation, total daily asthma symptoms score, and ACQ was explored through modeling techniques that involved a combination of parametric models and multiple comparisons. The procedure selected the model most likely to represent the true underlying dose-response curve, while preserving the family-wise error rate. The selected model was used to provide inference on the adequate doses.

PK endpoints were analyzed descriptively using the PK set which included all

randomized patients who received at least one dose of study drug and had at least one valid post-dose assessment. Attainment of steady-state conditions was determined by visual inspection of the plasma trough concentration–time profile.

Safety data were analyzed descriptively using the Safety set that included all randomized patients who received at least one dose of study drug.

PATIENT DISPOSITION:

A total of 826 patients were screened. Of the 438 patients randomized to one of the four treatment groups (setipiprant 100, 500, and 1000 mg b.i.d.: 109, 108, and 110; placebo: 111), 437 patients received study drug. One patient was inadvertently randomized to setipiprant 1000 mg b.i.d. instead of being listed as a screen failure and therefore prematurely discontinued from the study prior to receiving study drug.

A total of 358 (81.7%) randomized patients completed the DB treatment period. The proportion of patients discontinuing study drug was 18.3%, 17.6%, and 15.6% in the setipiprant 100, 500, and 1000 mg b.i.d. groups, respectively, and 20.7% in the placebo group. The most commonly reported reasons for discontinuation of study drug among all patients were lack of efficacy (5.0%) (a composite of 'clinical asthma exacerbation' [4.1%] and 'need for additional asthma treatment' [0.9%]), occurrence of AEs (4.8%) and withdrawal from treatment (3.4%). For all but one patient, premature discontinuation of study drug also resulted in discontinuation from the study.

The study (including the run-out period) was completed by 352 (80.4%) randomized patients (setipiprant 100, 500, and 1000 mg b.i.d.: 88, 86, and 91; placebo: 87).

DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

Demographic and baseline characteristics were generally balanced across the four treatment groups. Females represented 53.1% of the study population, and the median age of all patients was 44 years (range: 18-65 years). Mean body mass index (BMI) was 27.7 kg/m^2. The majority (87.3%) of the patients were Caucasian / White. There were no between-group differences in mean FEV_1% predicted (setipiprant groups: 66.53–67.77; placebo: 65.55), mean % reversibility (24.43–29.52; 28.65), mean ACQ score (2.45–2.50; 2.47), mean use of reliever medication (2.38–2.72; 2.63 number of occasions per day), or the prevalence of symptoms during the day (mean score: 1.44–1.60; 1.46) or at night (mean score: 0.81–0.90; 0.86). The median duration since initial diagnosis of asthma ranged from 15.84 to 17.39 years (range: 0.01–58.92 years) in the setipiprant groups, compared to 15.86 years (range: 0.30–58.53 years) in the placebo group. The proportion of patients reported to concomitantly suffer from allergic rhinitis at study entry ranged from 33 to 38% in the setipiprant groups, compared to 32% in the placebo group.

EFFICACY RESULTS:

Primary endpoint: The main analysis (LOCF, mITT set) did not show a difference between setipiprant 1000 mg b.i.d. and placebo for the mean change from baseline to Week 12 in pre-bronchodilator FEV_1% predicted (placebo-corrected treatment effect: 2.14, 95% confidence limits [CLs]: −1.32, 5.60, p = 0.2251). Consistent results were observed for the sensitivity analyses performed with and without imputation for missing data.

Results of the subgroup analyses performed on the primary endpoint were generally consistent with the results described for the overall group.

Dose-response analyses based on mean change from baseline to Week 12 in pre-bronchodilator FEV_1% predicted did not show a significant trend across dose groups, for any of the candidate models.

Secondary endpoints: Secondary endpoint analyses provided no consistent support for a benefit of the different doses of setipiprant (100, 500, and 1000 mg b.i.d.) versus placebo.

Results for primary and secondary endpoints are summarized below:

Endpoint	**Setipiprant b.i.d.**		
	100 mg	**500 mg**	**1000 mg**
	Mean treatment effect (95% CL) versus placebo*		
Pre-bronchodilator FEV_1% predicted	−1.22 (−4.70, 2.25)	1.61 (−1.85, 5.06)	2.14 (−1.32, 5.60)†
ACQ score	0.02 (−0.20, 0.25)	−0.05 (−0.27, 0.18)	0.00 (−0.23, 0.22)
PEF			
Morning, *L/min*	8.75 (−9.92, 27.41)	11.18 (−7.45, 29.82)	26.06 (7.44, 44.69)
Evening, *L/min*	−5.87 (−24.15, 12.41)	5.87 (−12.29, 24.03)	25.72 (7.55, 43.89)
Diurnal variation	−1.70 (−4.88, 1.49)	−1.21 (−4.39, 1.97)	−2.53 (−5.72, 0.65)
Total daily asthma symptoms score	−0.12 (−0.46, 0.22)	−0.11 (−0.45, 0.23)	−0.01 (−0.35, 0.32)

Endpoint	Setipiprant b.i.d.			Placebo
	100 mg	500 mg	1000 mg	
	Mean change (95% CLs) from baseline to Week 12			
Day-time asthma symptoms score	−0.61 (−0.81, −0.42)	−0.54 (−0.70, −0.38)	−0.57 (−0.74, −0.40)	−0.44 (−0.58, −0.30)
Night-time asthma symptoms score	−0.29 (−0.42, −0.15)	−0.32 (−0.44, −0.20)	−0.30 (−0.41, −0.19)	−0.23 (−0.34, −0.13)
Use of reliever medication, *occasions per day*	−0.81 (−1.15, −0.47)	−0.87 (−1.22, −0.52)	−0.82 (−1.15, −0.49)	−0.52 (−0.88, −0.16)
	K-M estimate at Day 84			
Study drug discontinuation due to lack of efficacy, *cumulative % (KM) with events*	4.0	6.1	3.8	7.8
First clinical asthma exacerbation, *cumulative % (KM) with events*	4.1	7.1	2.9	8.8

*Values shown are the placebo-corrected mean treatment effects (95% CLs) for the change from baseline to Week 12. For all values shown, $p > 0.1$, except for morning PEF, $p = 0.0062$ and for evening PEF, $p = 0.0056$ for the setipiprant 1000 mg b.i.d. group.
†Primary endpoint.

No evidence of a difference between any of the setipiprant treatment groups (100, 500, and 1000 mg b.i.d.) and placebo was observed for the change from baseline in pre-bronchodilator FEV_1% predicted, ACQ score, asthma symptoms score, diurnal PEF variation, and use of reliever medication. For morning and evening PEF, a treatment difference between setipiprant 1000 mg b.i.d. and placebo was observed (morning PEF: 26.06 L/min, 95% CLs: 7.44, 44.69, $p = 0.0062$; evening PEF: 25.72 L/min, 95% CLs: 7.55, 43.89, $p = 0.0056$).

K-M curves associated with both time to permanent discontinuation from study drug due to lack of efficacy up to EOT, and time to first clinical asthma exacerbation event up to EOT, appear to show separations between setipiprant groups and placebo. These separations were observed within the first 28 days of start of treatment; however, the event rates were low and the findings are not conclusive.

Exploratory endpoints: Since the primary and the secondary efficacy endpoints did not show efficacy of setipiprant, the results for the exploratory efficacy endpoints are not described. [redacted]

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Similar mean setipiprant plasma trough concentrations were observed between Visits 3 and 7, suggesting that steady-state was achieved by Visit 3 and was sustained at Visit 7 (EOT).

The results suggest that following 1000 mg of setipiprant, food does not influence the rate of absorption (no difference in median time to reach maximum plasma concentration [t_{max}]), whereas food delayed the rate of absorption at lower doses (later median t_{max}). Following the 500 and 1000 mg doses there was a reduction, up to approximately 1.5-fold, in the total amount of setipiprant absorbed.

SAFETY RESULTS:

A total of 326 patients received at least one dose of setipiprant. One patient randomized to setipiprant 1000 mg b.i.d. did not receive study drug. The median duration of exposure was 12.0 weeks in all three setipiprant treatment groups and 11.9 weeks in the placebo group, with 57.8-62.0% of the patients in the setipiprant groups and 49.5% of patients in the placebo group receiving treatment for the full 12–week period.

The proportion of patients with at least one treatment-emergent AE was 41.3%, 55.6%, and 42.2% in the setipiprant 100, 500, and 1000 mg b.i.d. group, respectively, and 49.5% in the placebo group. The most frequently reported AEs by preferred term were asthma (setipiprant 100, 500 and 1000 mg b.i.d.: 7.3%, 7.4% and 4.6%; placebo: 10.8%), headache (6.4%, 0% and 5.5%; 8.1%) and nasopharyngitis (4.6%, 8.3% and 1.8%; 4.5%). The majority of treatment-emergent AEs were of mild to moderate intensity across all treatment groups. AEs considered to be severe in intensity were reported for 3 (2.8%), 4 (3.7%) and 2 (1.8%) patients in the setipiprant 100, 500 and 1000 mg b.i.d. groups, respectively, and for 5 (4.5%) patients in the placebo group. Overall, there was no clear pattern or dose relationship in the incidence or severity of any AE reported across the setipiprant treatment groups.

There was one death reported during the study. The patient had been exposed to setipiprant 500 mg b.i.d. for 4 days and died of ‘ovarian cancer with metastases to the liver’ 50 days after the last intake of study drug. The SAE resulting in the death of the patient was judged by the investigator as unrelated to study drug.

During the study, a total of 12 SAEs were reported in 11 (2.5%) patients [setipiprant 100, 500 and 1000 mg b.i.d.: 2 (1.8%), 4 (3.7%) and 2 (1.8%), respectively; placebo: 3 (2.7%)]. All SAEs were judged by the investigator as unrelated to study drug. One pregnancy was reported in each of the setipiprant 100, 500 mg b.i.d. and placebo groups. Of these, two resulted in abortion, of which one was elective (setipiprant 100 mg b.i.d.) and one spontaneous (setipiprant 500 mg b.i.d.). The placebo-treated patient gave birth to a healthy baby girl via normal delivery at 39 weeks’ gestation.

AEs leading to discontinuation of study drug were reported in 10.1%, 11.1% and 5.5% of

patients in the setipiprant 100, 500, and 1000 mg b.i.d. groups, respectively, and in 11.7% of patients in the placebo group.

Mean changes from baseline to the assessed time points (Weeks 1, 2, 4, 8, 12 and 14) in hematology variables and clinical chemistry variables were unremarkable in all treatment groups. During the study, increases in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN) were observed in 5 setipiprant-treated patients (1, 2 and 2 patients in the 100, 500 and 1000 mg b.i.d. groups, respectively) and in 2 placebo-treated patients. None of these patients had concomitant increases in bilirubin > 2 × ULN. Four patients (3 and 1 patient in the setipiprant 500 and 1000 mg b.i.d. groups, respectively) had clinically relevant increases in triglycerides (values > 5.7 mmol/L).

No clinically relevant mean changes from baseline in vital signs were observed in the four treatment groups. None of the treatment-emergent ECG abnormalities (12-lead ECG and Holter) were considered by the investigator to be clinically significant.

CONCLUSIONS:

The primary endpoint of demonstrating efficacy of 1000 mg b.i.d. setipiprant versus placebo on the change in FEV_1% predicted from baseline to Week 12 was not met. Secondary endpoint evaluations provided no consistent support of a benefit of different doses of setipiprant (100, 500, and 1000 mg b.i.d.) versus placebo on lung function, asthma control, and asthma symptoms. Treatment differences were observed with setipiprant 1000 mg b.i.d. versus placebo for PEF (morning and evening) and asthma exacerbation, which could point to a pharmacological effect; however, no firm conclusions can be drawn. Overall, all doses of setipiprant were well tolerated.

DATE OF THE REPORT:

27 May 2013