2 SYNOPSIS OF STUDY REPORT, No. D-12.506 (AC-060A201)

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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ACT-129968	Type … *(ONLY DRA)*	

TITLE OF THE STUDY	A multi-center, double-blind, placebo-controlled, randomized, multiple dose, 2-period cross-over, Phase IIa study to investigate the pharmacodynamics, tolerability and safety, and pharmacokinetics of ACT-129968 in subjects with mild to moderate allergic asthma		
INDICATION	Allergic Asthma		
INVESTIGATORS / CENTERS AND COUNTRIES	Zuzana Diamant (Leiden, the Netherlands) Brian O'Connor (London, UK) Dave Singh (Manchester, UK)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	13 Aug 2008 to 15 Jan 2009	CLINICAL PHASE	2a
OBJECTIVES	**Primary objective** To demonstrate the effect of ACT-129968 versus placebo on forced expiratory volume, measured in 1 second (FEV_1) during the late allergic reaction (3–10 hours) after a bronchial allergen challenge. **Secondary objectives** • To investigate the effect of ACT-129968 on airway inflammation and airway hyperresponsiveness (AHR) after a bronchial allergen challenge. • To investigate the tolerability and safety of multiple oral doses of ACT-129968.		

	• To investigate the pharmacokinetics (PK) of ACT-129968 in subjects with mild to moderate allergic asthma.
STUDY DESIGN	Prospective, multi-center, double-blind, placebo-controlled, randomized, multiple-dose, 2-period cross-over, Phase 2a proof-of-mechanism study. The washout-period between two treatment periods was at least 21 days.
NUMBER OF PATIENTS	The study required 12 evaluable subjects. It was planned to randomize at least 18 subjects to allow for up to 6 non-evaluable subjects. 18 subjects were recruited in this study and 15 were analyzed for the primary endpoint.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	**Main inclusion criteria** • Men and women not of childbearing potential 18–55 years of age (inclusive). • Signed informed consent prior to any study-mandated procedure. • Having stable, mild to moderate allergic asthma for at least 1 year and fulfilling the following criteria at screening: – AHR to inhaled methacholine (Mch) with the provocative concentration of Mch causing a fall in baseline FEV_1 of 20% ($PC_{20}FEV_1$ [Mch]) < 16 mg/mL Mch chloride. – Early and late allergic reaction (EAR, LAR) airway response with ≥ 15% minimal reduction in FEV_1 during LAR (3–10 h) following a standardized bronchial allergen challenge with house dust mite (HDM) extract. **Main exclusion criteria** • Ongoing or recent treatment with medications for allergic airway disease (either prescribed or over-the counter [OTC]) other than short-acting, inhaled $beta_2$ agonist on infrequent, as needed basis. • Smoking within the last year or life-time consumption > 10 pack-years

TRIAL DRUG / BATCH No.	ACT-129968, 200 mg capsule. Batch no.: HC108 001 Retest date: March 2009
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	Oral ACT-129968, at multiple doses of 1,000 mg administered as five capsules of 200 mg twice daily on an empty stomach starting with the evening dose on Day 1 and ending with the morning dose on Day 5 of each treatment period.
REFERENCE DRUG / BATCH No.	Matching placebo capsules. Batch no.: HC104 001 Retest date: March 2009
REFERENCE DRUG DOSE / ROUTE / REGIMEN / DURATION	Oral placebo, at multiple doses of 1,000 mg administered as five capsules of 200 mg twice daily on an empty stomach starting with the evening dose on Day 1 and ending with the morning dose on Day 5 of each treatment period.
CRITERIA FOR EVALUATION EFFICACY:	**Primary endpoint** • The baseline-corrected area under the FEV_1 reduction curve from 3 to 10 hours after allergen challenge ($AUC_{3–10h}$) on Day 4 of each treatment period. Baseline was defined as the value measured pre-allergen and post-diluent on Day 4 of each treatment period. **Exploratory endpoints** • Maximum % FEV_1 reduction from baseline during EAR (0–3 h) and LAR (3–10 h) on Day 4 of each treatment period. Baseline was defined as the value measured pre-allergen and post-diluent on Day 4 of each treatment period. • The $AUC_{0–3h}$ on Day 4 of each treatment period**.** Baseline was defined as the value measured pre-allergen and post-diluent on Day 4 of each treatment period. • Differential cell count (eosinophils, neutrophils, lymphocytes, macrophages, mast cells, ciliated epithelial cells) expressed as a percentage of nucleated non-squamous cells in induced sputum

	24 h post-allergen challenge on Day 5 of each treatment period. • Change in mean exhaled nitric oxide (eNO) from baseline to end of EAR (3 h, Day 4), end of LAR (10 h, Day 4), and 24 h post-allergen challenge (Day 5) of each treatment period. Baseline was defined as the value measured pre-allergen and pre-diluent on Day 4 of each treatment period. • Ratio of 24 h post-allergen challenge (Day 5) over 24 h pre-allergen (Day 3) in $PC_{20}FEV_1$(Mch) of each treatment period. • Change from baseline to end of LAR (10 h, Day 4) in nasal brush (NAB) markers (eosinophils, neutrophils, lymphocytes, macrophages, mast cells, ciliated epithelial cells expressed as a percentage of nucleated non-squamous cells). Baseline was defined as the value measured pre-allergen and pre-diluent on Day 4 of each treatment period. • Change from 24 h pre-allergen (Day 3) to 10 h and 24 h post-allergen challenge in peripheral blood eosinophils and basophils expressed as a percentage of white blood cells. • Change from 24 h pre-allergen (Day 3) to 10 h and 24 h post-allergen challenge in interleukin (IL)-3, IL-4, IL-5, IL-13, and IgE.
SAFETY:	• Change from baseline (defined as the value measured immediately prior to the first drug administration during each treatment period) to Day 5 of each treatment period for vital signs parameters (supine systolic and diastolic blood pressure and heart rate). • Change from baseline (defined as the value measured immediately prior to the first drug administration during each treatment period) to Day 5 of each treatment period for electrocardiogram (ECG) parameters. • Change from baseline (defined as the value

	measured at screening) to End-of-Study (EOS) for clinical laboratory tests. • Change from baseline (defined as the value measured at screening) to EOS in body weight. • Treatment-emergent ECG abnormalities and treatment-emergent adverse events (AEs) up to 4 days after last drug administration during each treatment period. • AEs leading to premature discontinuation of study drug. • Treatment-emergent serious adverse events (SAEs) up to 4 days after last drug administration during each treatment period.
PHARMACOKINETICS	• Trough (pre-morning dose) plasma concentrations of ACT-129968.

STATISTICAL METHODS:

The paired Student's t-test was used to test the null hypothesis of no difference between ACT-129968 and placebo for the primary pharmacodynamic endpoint at the overall type-I error probability $\alpha = 0.10$.

With a sample size of at least 12 evaluable subjects and based on the assumptions for the primary endpoint (normal distribution with a standard deviation [SD] of the differences of 1,342 L·h), the study would detect a difference exceeding 1,500 L·h between the mean values of the primary endpoint measured under ACT-129968 treatment and under placebo treatment with 94% power. The abovementioned SD of the difference was derived from the expected SD of the primary parameter (1,500 L·h) and the expected correlation coefficient between paired observations (0.6).

No correction for multiple testing was applied for the exploratory parameters. These were analyzed using appropriate statistical methodology considering the specificity of the study design.

The Per-protocol set was used for all the analyses of pharmacodynamic endpoints.

The Safety set was used to perform all safety analyses.

Tolerability and safety endpoints were listed and summarized descriptively considering the specificity of the design of the study.

The PK set was used to perform all PK and possible PK/pharmacodynamic analyses.

PK endpoints were listed and analyzed descriptively

PATIENT DISPOSITION:

Eighteen subjects were enrolled into the study after signing the informed consent and complying with the inclusion criteria. Enrollment was evenly distributed over the centers, with each center enrolling 6 subjects. Of the 18 subjects, two discontinued treatment with the study medication, one each due to unstable disease and common cold. One additional subject did not have valid data, resulting in a total of 15 subjects in the Per-protocol set for assessment of the primary endpoint.

The number of subjects in Per-protocol sets for the sputum induction, eNO, $PC_{20}FEV_1$, NAB, and PK were 5, 12, 14, 6, and 15 subjects, respectively.

All subjects completed an EOS visit and were evaluable for safety.

EFFICACY RESULTS:

The primary endpoint was the baseline-corrected $AUC_{3–10h}$ on Day 4 of each treatment period. A statistically significant decrease ($p = 0.006$) in $AUC_{3–10h}$ was found when comparing ACT-129968 to placebo. The difference in AUC, when treated with ACT-129968 was 1.278 L·h, which represented a 25.6% change compared to placebo.

The supplementary analysis revealed no period or carry-over effects, indicating that the wash-out period was adequate.

Maximal decrease in FEV_1 and AUC during the allergen-induced EAR (0–3 h) did not differ between treatments.

The results of the statistical analysis did not reveal a significant difference between treatments in the $PC_{20}FEV_1$ ratio of Day 5 and Day 3. However, review of the data indicated an improvement of $PC_{20}FEV_1$ during treatment with ACT-129968 but not with placebo. This was confirmed by additional analyses that showed a statistically significant difference in the $PC_{20}FEV_1$ ratio of Day 5 and Day 1 between ACT-129968 and placebo using baseline as covariate.

There was a statistically significant difference between treatments in the change of mean eNO levels from baseline to end of EAR (3 h, Day 4), end of LAR (10 h, Day 4), and 24 h post-allergen challenge (Day 5) of each treatment period. ACT-129968 appeared to increase eNO levels compared to placebo. However, review of the data indicated that this was due to a difference in baseline values between treatments. Using a statistical model that included baseline as a covariate, no differences between treatments were shown.

In this study, the quality and number of collected sputum and NAB samples was inadequate and only a small number of analyzable samples (5 and 6 subjects, respectively) were provided. No statistically significant differences between treatments were found.

Blood eosinophil levels were low and did not change markedly over time. No differences

between treatments were observed.

Most of the serum cytokine levels (i.e., IL-3, IL-4, IL-5, and IL-13) were below the limit of quantification for all subjects. Only incidental measurements were above the limit of quantification. No differences in IgE levels were observed between treatments.

PHARMACOKINETIC RESULTS:

Review of the individual plasma concentration-time curves indicated large inter-individual variability in plasma concentrations. No correlation between plasma concentration and effect on the primary efficacy endpoint could be detected.

SAFETY RESULTS:

One subject discontinued the study treatment due to common cold. ACT-129968 was well tolerated at the dose regimen of 1,000 mg twice daily during 4.5 days. The overall frequency of AEs reported during treatment with ACT-129968 was similar to that observed with placebo. Dyspnea, fatigue, and headache were the most frequently reported AEs in the study. Several airway-related AEs were reported (dyspnea, asthma exacerbation, chest discomfort, bronchospasm, cough, productive cough). Review of the individual data suggested that these AEs were related to the nature of this study, most likely the study-mandated tests performed (i.e., allergen challenge, $PC_{20}FEV_1$ [Mch], sputum induction). No treatment-related effects were observed for clinical laboratory, vital signs, body weight, or ECG variables.

CONCLUSIONS:

- Compared to placebo, ACT-129968 inhibited the late allergic reaction to a statistically significant degree, both in terms of FEV_1 $AUC_{3–10h}$, and maximal percentage fall in FEV_1 from baseline.
- No statistically significant difference was detected in $PC_{20}FEV_1$ ratio of Day 5 and Day 3. However, additional analyses indicated a clinically relevant improvement of $PC_{20}FEV_1$ ratio of Day 5 and Day 1 in favor of ACT-129968 compared to placebo.
- The sputum, blood, and NAB inflammatory markers could not be evaluated in this study due to small numbers of analyzable/eligible samples.
- The ACT-129968 plasma concentrations of subjects with allergic asthma were highly variable between subjects and were comparable to those measured in healthy subjects. No correlation between plasma concentration and effect on the primary efficacy endpoint could be detected.
- The dose of 1,000 mg twice a day ACT-129968 was well tolerated in this study. The overall frequency of AEs was similar to that observed with placebo. Several AEs indicating bronchial effects were reported mainly during ACT-129968 treatment. However, review of the data suggested that they were most likely related to study-mandated tests performed in the study.

DATE OF THE REPORT:

15 October 2012