1 Title Page	Health Economic Report No. 382/2006	Version (1.0)

Title: A randomized, controlled study of roflumilast (250 mcg and 500 mcg) versus placebo in patients with asthma. A 24-week, multicentre, multinational, double-blind parallel group clinical study A health economic evaluation of the FLASH-Study.	Study Protocol No.: **BY217/M2-023** INN: Roflumilast Project No. / List No.: BY217 Compound No.: B9302-107 Batch No.: roflumilast (500 mcg) 320190, 320200, 420210 roflumilast (250 mcg) 120190 placebo 130280, 420240
Version date: 23-Jan-2007	Development phase: IIIb
Study initiation date: 05-Dec-2003 (FPI)	Indication studied: Bronchial asthma
Study completion date: 10-Jun-2005 (LPO)	Date of early termination: not applicable
Summary of Modifications to the final report:	not applicable

Name and country of investigators:
Investigators at 135 sites in Russia (10 sites), Ukraine (9 sites), and the United States (116 sites).

Coordinating investigator:
[redacted] Allergy & Asthma Medical Group & Research Center, 9610 Granite Ridge Drive, San Diego, California, 92123, United States

Name of sponsor's responsible medical officer:

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Person(s) responsible for HE study report:

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Sponsors contact persons:

See accompanying letter of the regulatory approval application

Statement of GCP compliance:

This study was performed in accordance with Good Clinical Practice regulations as set forth in the ICH Consolidated Guideline E6 (CPMP/ICH/135/95)

Archiving responsibility for essential documents:

Department RCO/CT at ALTANA Pharma AG, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6

2 SYNOPSIS

Title of the study:

A randomized, controlled study of roflumilast (250 mcg and 500 mcg) versus placebo in patients with asthma. A 24-week, multicentre, multinational, double-blind parallel group clinical trial.

Investigators:

See report of the clinical study **BY217/M2-023 (**report no. 225/2005).

Study centers:

See report of the clinical study **BY217/M2-023 (**report no. 225/2005).

Publication (reference):

Not applicable

Study period (years):

Duration of the study: December 2003 to June 2005
Recruitment period: December 2003 to December 2004

Clinical Phase: III

Objectives:

The objective of the health economic analysis of the trial BY217/M2-023 was:

- to assess the direct and indirect costs associated with the treatment of 250 mcg and 500 mcg oral roflumilast compared with placebo for the US from the Medicare perspective
- to assess the cost effectiveness of 250 mcg and 500 mcg oral roflumilast compared with placebo for the US from the Medicare perspective

Health economic methodology:

The health economic study was performed as a piggy-back study to the clinical study BY217/M2-023. The observation period covered the complete duration of the clinical study, i.e. a 2-4 weeks single-blind placebo baseline period (visit B0, B2, B3, B4) and a treatment phase of 24 weeks (visits T0, T2, T4, T8, T12, T18 and T24). Resource use data were collected using a specific health economic case report form. Health economic analyses were conducted for the subgroup of US patients only.

Number of patients:

Full analysis US subset with health economic data available	n = 587
Placebo	n = 184
Roflumilast 250 mcg	n = 199
Roflumilast 500 mcg	n = 204

Diagnosis and criteria for inclusion and randomization:

Inclusion:	Persistent chronic bronchial asthma acc. to GINA (Global Initiative for Asthma) 2002; For other inclusion criteria see study protocol BY217/M2-023, section 7
Randomization	see study protocol BY217/M2-023, section 7

Duration of treatment: 24 weeks

Test product, dose, mode of administration, batch no.:

Test product:	Roflumilast, 500 mcg, one tablet once daily, by mouth in the morning after breakfast
Dose:	One tablet once daily in the morning
Batch numbers:	320190, 320200, 420210
Test product:	Roflumilast, 250 mcg, one tablet once daily, by mouth in the morning after breakfast
Dose:	One tablet once daily in the morning
Batch numbers:	120190

Reference therapy, dose, mode of administration, batch no.:

Reference product:	Matched placebo, one tablet once daily, by mouth in the morning after breakfast
Dose:	One tablet once daily in the morning
Batch numbers:	130280, 420240

Criteria for evaluation:

Effectiveness evaluation:	FEV_1 (forced expiratory volume in one second) [l] (mean change in FEV_1 from baseline to final visit using ANCOVA (analysis of covariance)) Asthma symptom score (sum) Proportion and number of symptom-free days / rescue medication-free days Number of worsenings of asthma Proportion of patients without worsening of asthma Time to first worsening of asthma [days] AQLQ(S) (asthma quality of life questionnaire, standardized version) total score and domain scores at all timepoints (B0/2/3/4, T4, T12, T24) Mean change in AQLQ(S) total score and domain scores from Blast to Tlast Proportion of patients with a clinically relevant improvement in

	AQLQ(S) total score and domain scores from Blast to Tlast. These are further referred to as AQLQ(S) responders.
	AQLQ(S) total score and domain scores for AQLQ(S) responders
	AQLQ(S) total score and domain scores for patients with / without worsening of asthma
	EQ-5D (EuroQol 5 dimensions) total score, domain scores and VAS at all timepoints (B0/2/3/4, T4, T12, T24)
	Mean change in EQ-5D total score, domain scores and VAS (visual analogue scale) from Blast to Tlast
	QALYs (quality-adjusted life years) gained under roflumilast as compared to placebo
Costs evaluation:	Number of ambulatory care contacts
	Number and duration of relevant hospitalizations
	Number of ambulance transportations
	Number of relevant procedures
	Study medication, rescue medication and other relevant medication
	Number of work / school/ university days lost

Data analysis:

The health economic analyses were performed based on the subset of US patients using descriptive statistics. Data are presented by treatment group as well as overall for the full analysis subset with health economic data available (full analysis set defined as in the analysis of the clinical trial). The resource use related to asthma and the resource use related to relevant adverse events (as defined in the health economic analysis plan (Appendix III) were evaluated separately. The resource use was calculated for the 3 months prior to study start (baseline) as well as for the treatment period.

Unit costs for the US were assigned to the resource use of the treatment phase. Based on the resource use of the treatment phase (T0 to T24) multiplied by the unit costs, the total costs under roflumilast 250 mcg, roflumilast 500 mcg and placebo, respectively, were calculated from the Medicare perspective. The direct and indirect costs of the treatment groups were considered separately.

The effectiveness of roflumilast 500 mcg was significantly better than the effectiveness of placebo with respect to mean change in FEV_1 from baseline to study end. For roflumilast 250 mcg, no advantages in effectiveness could be observed compared to placebo. Therefore, cost-effectiveness analyses were only conducted comparing roflumilast 500 mcg versus placebo.

SUMMARY – CONCLUSIONS

In the treatment of persistent chronic asthma, roflumilast 500 mcg was more effective in terms of mean change in FEV_1 from baseline to study end. Costs for patients treated with roflumilast 500 mcg were significantly higher than costs for patients treated with placebo due to study medication cost itself. However, cost-effectiveness analysis with respect to costs per 100 ml FEV_1 gained showed a clear advantage of roflumilast 500 mcg compared to placebo.

Roflumilast 250 mcg showed no statistically significant advantages in terms of effectiveness compared to placebo and higher costs, therefore, no cost-effectiveness analyses were performed for this treatment arm.

The main cost drivers were costs for study medication, rescue medication and hospitalizations. Generally, only limited other resource use could be observed (e.g. ambulatory care contacts, work days lost). The low resource use during the treatment period of 24 weeks corresponds to low resource use reported for the three months prior to study start.

Health related quality of life and health status was assessed using the AQLQ(S) and the EQ-5D. Neither the AQLQ(S) nor the EQ-5D showed clear advantages for any of the treatment arms. Due to the short study period, QALYs gained during the treatment period were generally low, but comparable for all treatment groups.