



Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Roflumilast for asthma: Efficacy findings in placebo-controlled studies

E.O. Meltzer^{a,*}, P. Chervinsky^b, W. Busse^c, K. Ohta^d, P. Bardin^e, D. Bredenbröcker^f,
E.D. Bateman^g^a Department of Pediatrics, Division of Allergy and Immunology, University of California, San Diego, CA, USA^b Northeast Medical Research Associates, Dartmouth, MA, USA^c Division of Allergy and Immunology, School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA^d Department of Respiratory Medicine and Allergology, Tokyo National Hospital, Tokyo, Japan^e Monash Lung & Sleep, Monash Medical Center and University, Melbourne, Australia^f Takeda Pharmaceuticals International GmbH, Zurich, Switzerland^g Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa

ARTICLE INFO

Article history:

Received 24 July 2015

Received in revised form

15 October 2015

Accepted 17 October 2015

Available online 21 October 2015

Keywords:

Asthma

Exacerbation

FEV₁

Placebo

Roflumilast

ABSTRACT

Background: The role of roflumilast as a potential asthma treatment is not yet fully understood. A series of placebo-controlled trials were undertaken in order to investigate the safety and efficacy of roflumilast in asthma.**Aim:** To evaluate the efficacy of roflumilast in nine randomized proof-of-concept, placebo-controlled monotherapy and combination therapy phase II and III clinical studies performed between 1997 and 2005.**Methods:** The studies were conducted at sites in Europe, North and South America, Africa, Australasia and Asia and study length varied from 4 to 24 weeks. Data were analyzed from 4873 patients, 12–70 years of age, of whom 2668 received roflumilast. At randomization patients had a forced expiratory flow (FEV₁) of 45–90%. Roflumilast was investigated at doses of 125, 250 and 500 µg versus placebo. In two studies, 500 µg roflumilast was added on top of standard therapy with inhaled corticosteroids (ICS), 250 µg fluticasone propionate, or 400 µg beclomethasone dipropionate (BDP). Improvement in FEV₁ from baseline was the primary endpoint in seven studies. Key secondary endpoints included asthma symptom scores and time to first severe exacerbation.**Results:** Roflumilast consistently improved FEV₁ across the nine studies compared with placebo, reaching statistical significance in three studies. When given in addition to ICS, roflumilast provided additional improvements in FEV₁ which was statistically significant for 500 µg roflumilast/400 µg BDP versus placebo/400 µg BDP.**Conclusion:** Together these studies show that roflumilast has potential as an effective anti-inflammatory therapy for the treatment of asthma. Additional beneficial effects are observed when given in combination with ICS, which warrant further investigation.

All studies were funded by Takeda. Trial registration numbers available on ClinicalTrials.gov: NCT00073177, NCT00076076, NCT00163527.

© 2015 Published by Elsevier Ltd.

1. Introduction

The primary goals of asthma management are to achieve good

symptom control and minimize the future risk of exacerbations. The Global Initiative for Asthma (GINA) has outlined a comprehensive and integrated approach to asthma management with long-term pharmacological management anchored in a step-wise approach. In this management approach, inhaled corticosteroids (ICS) are considered to be the preferred controller therapy [1]. A failure to achieve satisfactory symptom control or prevent asthma exacerbations, particularly in severe asthma patients, together with the requirement for safer anti-inflammatory treatments, have led

* Corresponding author.

E-mail addresses: eliomeltzer@gmail.com (E.O. Meltzer), pchervinsky@gmail.com (P. Chervinsky), wwb@medicine.wisc.edu (W. Busse), kenohta@tokyo-hosp.jp (K. Ohta), philip.bardin@monash.edu (P. Bardin), dirk.bredenbroeker@takeda.com (D. Bredenbröcker), Eric.Bateman@uct.ac.za (E.D. Bateman).

to investigations into the potential use of roflumilast in asthma therapy [2,3].

Roflumilast is an oral phosphodiesterase-4 inhibitor with anti-inflammatory actions [4]. It consistently improves lung function and reduces the frequency of exacerbations in patients with severe chronic obstructive pulmonary disease (COPD), symptoms of chronic bronchitis, and a history of frequent exacerbations [5–7]. Takeda's roflumilast in asthma programme was initiated to develop a greater understanding of roflumilast and its potential treatment benefits for asthma patients and comprised a wide range of clinical studies evaluating different endpoints. This paper presents findings from all nine placebo-controlled studies within the programme on the effects of roflumilast in patients with mild to moderate asthma. As well as examining the efficacy of roflumilast in asthma, potential effects of roflumilast on reducing exacerbations and the possibility of roflumilast as an 'add-on' to ICS are explored in these placebo-controlled studies.

2. Methods

2.1. Overview of asthma studies

Nine placebo-controlled, double-blind, parallel group phase II or III studies were conducted at 985 study sites in Europe, North and South America, Africa, Australasia and Asia. The methodologies and endpoints evolved over the duration of the study programme (1997–2005). A once-daily dose of 500 µg roflumilast is approved for the treatment of COPD; additional doses of 125 µg and 250 µg were used in these early asthma studies. The efficacy of roflumilast was measured by changes in forced expiratory volume in 1 s (FEV₁) and all patients had a history of bronchial asthma with an FEV₁ of 45–90% predicted at randomization. Additional spirometric parameters and efficacy measures were examined as secondary endpoints. The studies ranged considerably in size and duration, three of the studies were conducted as small proof-of-concept studies and two of the studies assessed the efficacy of roflumilast given in addition to commonly used ICS asthma treatments.

2.2. Patients

Patients aged 12–70 years who had a history of bronchial asthma and an FEV₁ between 45 and 90% predicted at randomization were eligible for enrollment into the nine studies (Table 1). The main exclusion criteria were poorly controlled asthma four weeks prior to baseline (six weeks prior to baseline in study FK1 011), use of oral or parenteral corticosteroids in the 4 weeks prior to baseline (six weeks prior in study FK1 011, and between 4 and 12 weeks prior in studies FK1 001 and M2 012), or a diagnosis of COPD or other relevant lung disease (see companion paper in this supplement for a pooled demographics table from these studies; Chervinsky et al., Safety studies).

2.3. Interventional treatments

During the single-blind baseline run-in periods (which varied from 1 to 6 weeks duration), all asthma controller medications were withdrawn and patients received only placebo as one or two tablets taken once daily in the morning, generally after breakfast with at least 200 mL of fluid. In addition to placebo, in three studies (FK1 003, M2 013 and M2 014), patients were given 250 µg fluticasone propionate (FP), 400 µg or 500 µg beclomethasone dipropionate (BDP) as one or two puffs twice daily in the morning and evening. After baseline treatment, eligible patients were randomly allocated to receive 125 µg, 250 µg or 500 µg of roflumilast, or placebo as one or two tablets once-daily in the morning, generally

after breakfast with at least 200 mL of fluid. In three studies (FK1 003, M2 013 and M2 014), patients were given 250 µg FP, 400 µg, 500 µg or 800 µg BDP as one or two puffs twice daily in the morning and evening in addition to roflumilast and placebo. The randomization scheme was 1:1 in studies FK1 011, FK1 004 and M2 014, 2:1 in studies FK1 001 and FK1 003 and 1:1:1 in studies FK1 021, M2 012, M2 023 and M2 013. One study, FK1 021, had a 2-week wash-out period. During double-blind treatment, patients were given access to short-acting beta agonist (SABA) rescue medication, generally albuterol or salbutamol. All rescue medication was withheld for four hours before spirometric measurements.

2.4. Studies

2.4.1. Proof-of-concept monotherapy and combination therapy phase II studies (FK1 011, FK1 004 and FK1 003)

These studies were primarily designed to show the tolerability and safety (not efficacy) of roflumilast. During the short 4- or 6-week treatment period, patients in studies FK1 011 and FK1 004 received either 500 µg roflumilast or placebo once daily in the morning. Patients in study FK1 003 received 500 µg roflumilast or placebo once daily in the morning in addition to 250 µg BDP twice-daily in the morning and evening.

2.4.2. Monotherapy phase III studies (FK1 021, FK1 020, M2 012, M2 023)

Treatment effects of roflumilast 125 µg, 250 µg or 500 µg once daily in the morning versus placebo once daily in the morning were observed in larger patient populations over a treatment period of either 12 or 24 weeks to help identify the most effective dose for asthma management.

2.4.3. Combination therapy phase III studies (M2 013 and M2 014)

These studies compared the effect of roflumilast as an 'add-on' to ICS therapies over 24 weeks. Patients received 500 µg roflumilast or placebo once daily in the morning in addition to 125 µg FP twice daily in the morning and evening (M2 014) or 200 µg BDP twice-daily in the morning and evening (M2 013) to determine the effect/superiority. Once daily placebo in the morning plus 400 µg BDP twice-daily in the morning and evening was also used in study M2 013 to document the non-inferiority of roflumilast.

2.5. Endpoints

The primary endpoint in seven of the nine studies was mean change in FEV₁. In study FK1 004, the primary endpoint was diary measurement of morning peak expiratory flow (PEF_{AM}) ratio treatment Week 6/Week 0 (% of predicted), and in study FK1 011, the measurement of safety variables. Study M2 014 had co-primary endpoints of mean change in FEV₁ and rescue medication use. Key secondary endpoints are listed in Table 1.

2.6. Subgroup analyses

Change in FEV₁ from baseline was stratified by asthma severity (moderate and severe), smoking status, sex and pre-treatment history in studies FK1 003, M2 023, M2 014 and M2 013. Change in PEF_{AM} and evening peak expiratory flow (PEF_{PM}) from baseline was stratified by asthma severity in study M2 014.

2.7. Safety

Safety monitoring for all studies included adverse events (AEs), laboratory tests, physical examination findings, electrocardiograms (ECGs) and vital signs. Safety assessment continued for 30 days

Table 1

Overview of randomized, placebo-controlled, parallel group studies.

Study no. and year	Treatment period and patient population at randomization	Phase	Key inclusion criteria at randomization	Interventions	Primary endpoint	Key secondary endpoints
FK1 011 1999	4 weeks n = 47	II	• 18–70 years • Stable mild to moderate bronchial asthma • Pre-bronchodilator FEV₁ 50–80% predicted	• 500 µg rof • Placebo	Safety variables (laboratory values, physical examination: ECG, BP, HR and AE monitoring)	• Spirometry: Interim FEV₁, PEF, FVC • Morning and evening PEF from diary • PEF variation from diary • Rescue medication use from diary • Asthma symptom score from diary
FK1 004 1997–8	6 weeks n = 72	II	• 18–65 years • Stable mild to moderate bronchial asthma • Pre-bronchodilator FEV₁ 60–90% predicted	• 500 µg rof • Placebo	PEF _{AM} ratio T6/T0	• Spirometry: FEV₁, PEF, FVC • Morning and evening PEF from diary • Rescue medication use from diary • Asthma symptom score from diary
FK1 003 1997–8	6 weeks n = 257	II	• 18–70 years • Mild to moderate bronchial asthma • Pre-bronchodilator FEV₁ 50–85% predicted	• 500 µg rof + 500 µg BDP • Placebo + 500 µg BDP	FEV ₁ ratio T6/T0	• Spirometry: FEV₁, FVC, PEF, • Morning and evening PEF from diary • PEF variation from diary • Rescue medication use from diary • Asthma symptom score from diary
FK1 021 2002–4	12 weeks n = 695	III	• 18–70 years • Bronchial asthma • Pre-bronchodilator FEV₁ 50–85% predicted	• 125 µg rof • 250 µg rof • Placebo	Mean change in FEV ₁ from treatment start to end	• Spirometry: FEV₁, FVC, PEF • Morning and evening PEF from diary • Rescue medication use from diary • Asthma symptom score from diary • AQLQ(s)
FK1 020 2001–3	12 weeks n = 495	III	• 18–70 years • Bronchial asthma • Pre-bronchodilator FEV₁ 50–85% predicted	• 250 µg rof • Placebo	Mean change in FEV ₁ from treatment start to end	• Spirometry: FEV₁, FVC, PEF • Morning and evening PEF from diary • Rescue medication use from diary • Asthma symptom score from diary • AQLQ(s)
M2 012 2003–5 (NCT00073177)	24 weeks n = 849	III	• 18–70 years • Persistent bronchial asthma • Pre-bronchodilator FEV₁ 60–80% predicted	• 250 µg rof • 500 µg rof • Placebo	Mean change in FEV ₁ from baseline	• Spirometry: FEV₁, FVC, PEF • Morning PEF from diary • Rescue medication use from diary • Asthma symptom score from diary • Day/night asthma symptom score from diary • AQLQ(s)/ACQ • Time to first severe exacerbation (corticosteroid course, hospitalization or 30% PEF_{AM} decrease on 2 consecutive days) • Exacerbation variables
M2 023 2003–5 (NCT00076076)	24 weeks n = 875	III	• >18 years • Persistent chronic bronchial asthma • Pre-bronchodilator FEV₁ 45–85% predicted	• 250 µg rof • 500 µg rof • Placebo	Mean change in FEV ₁ from baseline	• Spirometry: FEV₁, FVC, PEF • Morning and evening PEF from diary • Rescue medication use from diary • Asthma symptom score from diary • Day/night asthma symptom score from diary • AQLQ(s)
M2 014 2002–3	24 weeks n = 661	IIIa	• 18–70 years • Bronchial asthma • Pre-bronchodilator FEV₁ 50–80% predicted	• 500 µg rof + 250 µg FP • Placebo + 250 µg FP	Mean change in FEV ₁ from treatment start to end; rescue medication use	• Spirometry: FEV₁, FVC, PEF • Morning and evening PEF from diary • Asthma symptom score from diary

Table 1 (continued)

Study no. and year	Treatment period and patient population at randomization	Phase	Key inclusion criteria at randomization	Interventions	Primary endpoint	Key secondary endpoints
M2 013 2003–5 (NCT00163527)	24 weeks n = 1171	III	• 12–70 years • Persistent bronchial asthma • Pre-bronchodilator FEV₁ 50–80% predicted	• 500 µg rof + 400 µg BDP • Placebo + 400 µg BDP • Placebo + 800 µg BDP	Mean change in FEV ₁ from baseline	• AQLQ(s) • Time to first severe exacerbation (corticosteroid course, hospitalization) • Spirometry: FEV₁, FVC, PEF • Morning and evening PEF from diary • Rescue medication use from diary • Asthma symptom score from diary • Day/night asthma symptom score from diary • AQLQ(s)/ACQ • Time to first severe exacerbation (corticosteroid course, hospitalization or 30% PEF_{AM} decrease on 2 consecutive days) • Exacerbation variables

rof: Roflumilast; FP: Fluticasone propionate; BDP: Beclomethasone dipropionate; T0: Treatment week 0; T6: Treatment week 6; ECG: electrocardiogram; HR: heart rate; BP: blood pressure; AE: adverse event; FEV₁: Forced expiratory volume in 1 s; FVC: Forced vital capacity; PEF: Peak expiratory flow; AQLQ: Asthma Quality of Life Questionnaire; ACQ: Asthma Control Questionnaire.

after the active treatment period. Safety findings are discussed elsewhere (see companion paper in this supplement; Chervinsky et al., Safety studies).

2.8. Statistical analysis

All analyses were performed in the intention to treat population unless otherwise specified. Change from baseline in lung function variables FEV₁, forced vital capacity (FVC) and PEF used analysis of covariance (ANCOVA) least squares (LS) means and/or repeated measurements analysis (RMA) apart from studies FK1 003 and FK1 004 which used geometric means and paired ratios. Significance was tested at the 5% level within treatments and at the 2.5% level between treatments in all studies except FK1 020 in which between treatment significance was at the 5% level. In study M2 013, the primary variable was tested in an a-priori order, so that non-inferiority of roflumilast was shown first before superiority of roflumilast was tested. Non-inferiority acceptance limits for FEV₁ were 0.1 L. Analysis of diary measurements PEF_{AM}, PEF_{PM}, asthma symptom scores and rescue medication use were undertaken using non-parametric analyses; either the Wilcoxon's signed-rank test or the Mann–Whitney U test (Study M2 023 used the Jonckheere–Terpstra test). Median days to first severe exacerbation (see Table 1 for definition) and EROS (exacerbation requiring oral or parenteral steroids) measurements of significance used the 2-sided log rank test and the 1-sided cox proportional hazard test (M2 012 and M2 013 respectively). Overall numbers of severe exacerbations/EROS were measured using the Wilcoxon rank sum test. Wilcoxon rank sum values > 0 indicate an improvement with test compared to reference. The Asthma Quality of Life Questionnaire (AQLQ) [8] and Asthma Control Questionnaire (ACQ) [9] were measured in most studies by either analysis of variance (ANOVA), paired t-test, or RMA and endpoint ANCOVA (study M2 014 also used non-parametric analyses; Wilcoxon's signed-rank test and the Mann–Whitney U test).

3. Results

3.1. Spirometric analysis, FEV₁

All studies showed a numerical increase in FEV₁ with roflumilast compared with placebo (except FK1 021, in which 125 and 250 µg doses and placebo were equivalent). This increase was statistically significant compared with placebo for the 250 µg dose in study M2 012 (0.069 L, $p = 0.0211$), and for the 500 µg dose in studies M2 023 (0.056 L, $p = 0.0163$) (Table 2). The 'add-on' studies demonstrated that when 250 µg FP was added to 500 µg roflumilast and placebo in study M2 014, roflumilast improved FEV₁ in addition to the effect from FP, this approached, but did not reach statistical significance ($p = 0.0555$). When 400 µg BDP was added to 500 µg roflumilast and placebo in study M2 013 roflumilast significantly improved FEV₁ in addition to the effect from BDP ($p = 0.0026$). In the same study, when the dose of BDP added to placebo was increased to 800 µg, the effect of roflumilast 500 µg plus 400 µg BDP still showed a relative improvement in FEV₁ which approached, but did not reach statistical significance (Fig. 1).

3.2. FEV₁ subgroup analyses

In the asthma severity subgroup analyses (M2 023, M2 014 and M2 013), roflumilast treatment significantly increased FEV₁ versus placebo in two studies in the severe asthma group (M2 023: 0.079 L, $p = 0.0075$; M2 013: 0.069 L, $p = 0.0042$), but not in the moderate asthma group. Smoking status subgroup analyses (FK1 003, M2 023, M2 014 and M2 013) were inconsistent; significant increases in FEV₁ in roflumilast groups compared to placebo, but in different subgroup combinations. In sex subgroup analyses, significant increases in FEV₁ in the 500 µg roflumilast treatment group versus placebo was observed in females (M2 023: 0.058 L, $p = 0.0216$; M2 013: 0.066 L, $p = 0.0113$) but not in males. In patients with no history of ICS use there was a significant increase in FEV₁ versus placebo with 500 µg roflumilast (M2 023 L 0.077 L, $p = 0.0150$).

Table 2Mean change in FEV₁ from baseline to treatment end in randomized, placebo-controlled, parallel group roflumilast in asthma studies, intention-to-treat population.

Study	Treatment duration/ study dates	Treatment	n	LSmean change FEV ₁ , L baseline to treatment end ± SEM (CI), p- value*	Difference vs placebo in LSmean change FEV ₁ , L baseline to treatment end ± SEM (CI) p-value†
FK1 011	4 weeks 1999	Rof 500µg Placebo	24 22 46	0.14 ± 0.09 (-0.03,0.32) 0.1102 0.06 ± 0.09 (-0.12,0.24) 0.4938	0.08 ± 0.12 (-0.17,0.33) 0.5119
FK1 004	6 weeks 1997–8	Rof 500µg Placebo	45 24 69	1.06 (1.03–1.10) [§] 0.0002 1.02 (0.97–1.07) [§] 0.3759	1.04 (0.99–1.10) [§] 0.0652
FK1 003	6 weeks 1997–8	500µg rof + 500µg BDP Placebo + 500µg BDP	170 87 257	1.12 (1.09–1.15) [§] <0.0001 1.08 (1.04–1.12) [§] 0.0001	1.04 (1.00,1.08) [§] 0.0382
FK1 021	12 weeks 2002–4	Rof 125µg Rof 250µg Placebo	221 237 234 692	0.099 ± 0.0253 (0.050,0.149) [‡] <0.001 0.101 ± 0.0242 (0.053,0.149) [‡] <0.001 0.104 ± 0.0246 (0.056,0.152) [‡] <0.001	-0.005 ± 0.0339 (-0.071,NA) 0.553 -0.003 ± 0.0333 (-0.068,NA) 0.535
FK1 020	12 weeks 2001–3	Rof 250µg Placebo	252 243 495	0.103 ± 0.0249 (0.054,0.152) [‡] <0.001 0.061 ± 0.0252 (0.012,0.111) [‡] 0.015	0.041 ± 0.0339 (-0.025,0.108) 0.224*
M2 012	24 weeks 2003–5	Rof 250µg Rof 500µg Placebo	257 257 256 770	0.203 ± 0.037 (0.131,0.276) [‡] 0.186 ± 0.038 (0.112,0.260) [‡] 0.135 ± 0.038 (0.060,0.209) [‡]	0.069 ± 0.034 (0.002,0.135) [‡] 0.0211 0.051 ± 0.034 (-0.016,0.118) [‡] 0.0661
M2 023	24 weeks 2003–5	Rof 250µg Rof 500µg Placebo	253 265 253 771	0.050 ± 0.021 (0.009,0.091) [‡] 0.0162 0.139 ± 0.022 (0.096,0.183) [‡] <0.0001 0.083 ± 0.021 (0.041,0.125) [‡] 0.0001	-0.033 ± 0.026 (-0.084,0.019) [‡] 0.8917 0.056 ± 0.026 (0.005,0.108) [‡] 0.0163
M2 014	24 weeks 2002–3	500µg rof + 250µg FP Placebo + 250µg FP	313 336 649	0.378 ± 0.035 (0.309,0.448) <0.0001 0.311 ± 0.034 (0.244,0.377) <0.0001	0.068 ± 0.043 (-0.016,0.151) 0.0555
M2 013	24 weeks 2003–5	500µg rof + 400µg BDP Placebo + 400µg BDP Placebo + 800µg BDP	374 366 384 1,124	0.099 ± 0.087 (-0.071,0.270) [‡] 0.028 ± 0.087 (-0.142,0.198) [‡] 0.053 ± 0.087 (-0.116,0.223) [‡]	0.071 ± 0.026 (0.021,0.122) [‡] 0.0026 [500µg rof + 400µg BDP vs placebo + 400µg BDP] 0.046 ± 0.025 (-0.004,0.096) [‡] <0.0001 (ni) 0.0343 (s) [500µg rof + 400µg BDP vs placebo + 800µg BDP]

ITT: Intention-to-treat; rof: roflumilast; FEV₁: Forced expiratory volume in 1 second; PEF_{AM}: Peak expiratory flow in the morning; TO: Treatment week 0; L: Litre; CI: 95% Confidence interval; SEM: Standard error of the mean; BDP: Beclomethasone dipropionate; FP: Fluticasone propionate; LS: Least squares; NA: Not applicable; ni: Non-inferiority; s: Superiority. *Analysis of covariance (ANCOVA) 2-sided 5%; †ANCOVA 1-sided for superiority 2.5%; ‡Lower and upper confidence limits; §Paired geometric mean; ¶ANCOVA Repeated Measurements Analysis (RMA). Red highlights show statistically significant results.

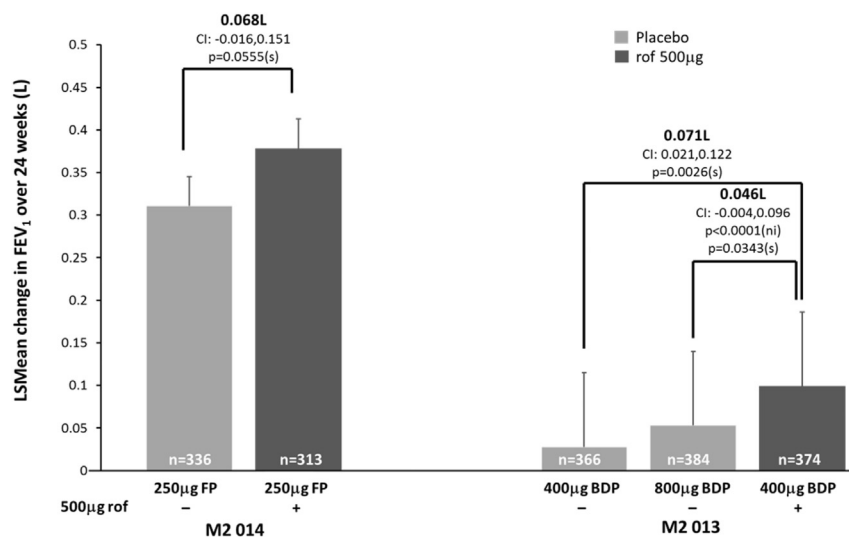


Fig. 1. Mean change in FEV₁ over 24 weeks in 'add-on' studies M2 013 and M2 014. The roflumilast 'add on' increased FEV₁ in addition to the increase by ICS. Study M2 014 used analysis of covariance (ANCOVA) endpoint analysis and study M2 013 used ANCOVA repeated measurements analysis (RMA). Error bars show the standard error of the mean. p-values are one-sided, significance level 2.5%. LSmean: Least squares mean; CI: 95% Confidence interval; FEV₁: Forced expiratory volume in 1 s; L: litre; s: Superiority; ni: Non-inferiority; FP: Fluticasone propionate; BDP: Beclomethasone dipropionate; rof: Roflumilast.

3.3. FVC

All studies showed a numerical increase in FVC compared with placebo from baseline (except M2 023 in which FVC decreased with 250 µg roflumilast compared with placebo). This increase was statistically significant compared with placebo for the 500 µg dose in study M2 023 (0.053 L, $p = 0.0249$) and M2 013 (0.092 L,

$p = 0.0015$ versus placebo plus 400 µg BDP and 0.065 L, $p = 0.0165$ versus placebo plus 800 µg BDP).

3.4. PEF

All studies showed a numerical increase in PEF measured at clinic visits, compared with placebo from baseline (except FK1 021

and M2 023 in which PEF decreased with roflumilast 250 µg compared with placebo). This increase was statistically significant compared with placebo for the roflumilast 500 µg dose in study M2 023 (9.299 L/min, $p = 0.0159$).

3.5. Diary measurements, PEF_{AM}

All studies showed a numerical increase in PEF_{AM} compared with placebo from baseline (except FK1 021 in which PEF_{AM} decreased with 125 µg and 250 µg roflumilast compared to placebo). Increases in PEF_{AM} were not statistically significant.

3.6. PEF_{AM} and PEF_{PM} subgroup analysis

In study M2 014, roflumilast 500 µg demonstrated a significant increase in PEF_{AM} and near significance with PEF_{PM} in the severe asthma subgroup versus placebo (11 L/min, $p = 0.0190$ and 10 L/min, $p = 0.0296$ respectively), but not in the moderate asthma subgroup.

3.7. Severe asthma exacerbations

Mean and median days to the first severe exacerbation were numerically higher in roflumilast treatment groups than placebo for all studies in which they were measured (M2 011, M2 014 and M2 013). This increase was statistically significant for 250 µg roflumilast versus placebo for EROS in study M2 012 (median 30 days placebo, 35 days roflumilast, $p = 0.0443$ 2-sided log rank test) and neared statistical significance for 500 µg roflumilast plus 400 µg BDP versus placebo plus 400 µg BDP for severe exacerbations in study M2 013 (median 36 days placebo plus BDP, 51 days roflumilast plus BDP, $p = 0.0259$ 1-sided cox proportional hazards model) (Fig. 2).

There were numerically fewer severe exacerbations/EROS in all roflumilast groups compared with placebo (data not shown). This reached statistical significance for EROS in study M2 012 for 250 µg roflumilast versus placebo and for severe exacerbations in study M2 013 for 500 µg roflumilast versus placebo, both plus 400 µg BDP (data not shown).

3.8. Asthma symptom scores and use of rescue medication

Asthma symptom scores improved with all treatments, but there were no statistically significant between-group differences. A similar pattern was observed for the use of rescue medication, except the percentage of rescue medication free days achieved statistical significance for 250 µg roflumilast versus placebo in study M2 012 (median 2.4% days roflumilast, 0.7% days placebo, $p = 0.0128$).

3.9. Quality of life

Mean AQLQ numerically increased in roflumilast treatment groups in all studies (FK1 021, FK1 020, M2 012, M2 023 and M2 013) compared with placebo (except 125 µg roflumilast in study FK1 021 and 500 µg roflumilast in study M2 014), but did not reach statistical significance. The only sub-score that was statistically significant was symptom score in study M2 023, in which it improved by 0.152 ($p = 0.0216$) in the 500 µg roflumilast group versus 250 µg roflumilast.

Mean ACQ improved or was equivalent compared with placebo (M2 012 and M2 013). Only 500 µg roflumilast in study M2 012 reached the minimal clinically important difference (MCID) of 0.5. The improvement was statistically significant for 500 µg roflumilast plus 400 µg BDP versus placebo plus 400 µg BDP by -0.1 in study M2 013 ($p = 0.0228$).

4. Discussion

Roflumilast consistently improved FEV_1 compared with placebo across nine studies. However, most studies did not demonstrate statistically significant differences between the effects of roflumilast and placebo. The three proof-of-concept studies (FK1 011, FK1 004 and FK1 003) were small, of short duration (4–6 weeks) and were conducted early in the study programme when it was unknown whether roflumilast had any efficacy in asthma; these studies did not produce any statistically significant findings. Further investigation in longer 12–24 week, monotherapy phase III studies (FK1 021, FK1 020, M2 012 and M2 023) showed that 250 µg and 500 µg doses of roflumilast consistently improved FEV_1 over

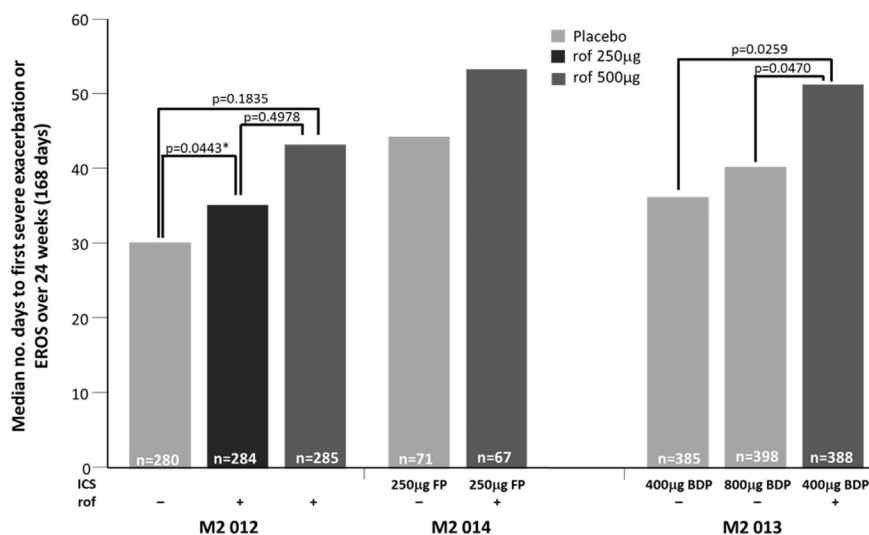


Fig. 2. Median number of days to first severe exacerbation/EROS over 24 weeks (168 days) in studies M2 012, M2 013 and M2 014. Patients receiving roflumilast took longer to incur a severe exacerbation/EROS. *Significant p-value; Study M2 014: significance was not measured; Study M2 012: log rank test, two-sided p-value, significance level 5%; Study M2 013: cox proportional hazard model, one-sided p-value, significance level 2.5%; Study M2 012: number of days to first EROS; Studies M2 014 and M2 013: number of days to first severe exacerbation; EROS: Exacerbation requiring oral/parenteral steroids; FP: Fluticasone propionate; BDP: Beclomethasone dipropionate; rof: Roflumilast; ICS: Inhaled corticosteroid.

time and a statistically significant difference was demonstrated for 250 µg roflumilast versus placebo (M2 012) and 500 µg roflumilast versus placebo (M2 023) in the 24-week studies.

Two further combination therapy phase III studies investigated the effects of 500 µg roflumilast in addition to ICS therapy for 24 weeks. These studies showed that the combination of roflumilast/400 µg BDP had a statistically significant increase in FEV₁ compared to placebo/400 µg BDP (M2 013) and roflumilast/250 µg FP had a near statistically significant increase in FEV₁ compared with placebo/250 µg FP (M2 014). Taking all measurements of asthma into account, doses of 125 µg and 250 µg roflumilast generally showed less improvement, suggesting that 500 µg is the most efficacious dose. Other spirometric variables, including FVC and PEF, showed similar results to FEV₁. Diary observations of asthma scores and rescue medication appeared to support the FEV₁ data, but similarly no consistent effects were observed. Lack of a consistent effect on spirometric measures of asthma symptoms is not surprising – roflumilast reduces future exacerbation risk in COPD [5] rather than having a direct effect on symptoms (as do bronchodilators), and it can be hypothesized that it is likely to have similar long-term effects in asthma.

Roflumilast is known to significantly reduce exacerbation rates in patients with COPD [5], but the studies conducted in the asthma programme were not all of sufficient duration or size to observe a consistent effect on asthma exacerbations. However, the time to first severe asthma exacerbation was significantly longer (five days) with 250 µg roflumilast treatment compared to placebo in study M2 012 and approached statistical significance (15 days longer) for 500 µg roflumilast/400 µg BDP compared with placebo/400 µg BDP in study M2 013. One quality of life measure, ACQ, which measures the adequacy of asthma control, improved significantly more in 500 µg roflumilast/400 µg BDP treated patients than in those treated with placebo/400 µg BDP (M2 013).

ICS are the foundation of therapy for patients with persistent asthma [1], they control airway inflammation, reduce symptoms and improve lung function [10]. However, the Gaining Optimal Asthma control (GOAL) study has shown that treatment with ICS alone results in well-controlled asthma in only 68% of patients [11], paving the way for additional therapies to provide additive benefits. Since roflumilast has a different anti-inflammatory mechanism of action to ICS, this approach appears logical. The beneficial effects of roflumilast on the disease mechanisms of COPD are thought to be cellular, acting on neutrophils, monocytes, macrophages, smooth muscle cells and other cell types [12]. Since many of these cells are also involved in asthma [13], it can be speculated that the effects of roflumilast in asthma are conferred through similar mechanisms. The mechanism of action of roflumilast in asthma is explored more in the companion paper in this supplement (Bardin et al., Mechanism of action studies).

Study M2 013 provides evidence that roflumilast can be added to the ICS BDP to give additional improvements in lung function and also shows that adding roflumilast to the commonly used low dose of ICS (400 µg BDP) [3] delivers similar efficacy to that provided by 800 µg BDP. Two further studies reported in a companion paper in this supplement (Bateman et al., non-placebo studies) showed that roflumilast 500 µg is non-inferior to BDP. There is some evidence that FP is more effective than BDP [14,15], regardless, near significant changes in lung function were also seen when roflumilast was added to the ICS FP at the 250 µg dose in study M2 012 compared to placebo/250 µg FP. Together, these data suggest that addition of roflumilast is a promising alternative to increasing ICS dose for refractory asthma, which can be associated with increased risk of side effects [1]. Thus, the addition of roflumilast should be investigated as an alternative treatment at Step 3 of the GINA report, where adding a LABA is the preferred treatment if

asthma symptoms are not controlled with ICS alone, other options being adding a leukotriene modifier or theophylline [1].

The severity and incidence of AEs reported from these placebo-controlled studies are reported separately in a companion paper in this supplement; Chervinsky et al., Roflumilast for asthma: Safety findings from a pooled analysis of ten clinical studies. This pooled safety analysis confirms that roflumilast is generally well tolerated by patients with asthma and reflects the overall safety profile seen previously in patients with COPD.

Interpretation and significance of the results varied according to the study design. Limiting factors included small study populations, especially in subgroup analyses, use of a low dose of roflumilast and short duration. Patient numbers were not equal in subgroups (for example, in the severe asthma subgroup there was a maximum of 357 patients in the studies analyzed, whereas in the moderate subgroup the largest group comprised 63 patients). With regard to exacerbations, in COPD the effect of roflumilast in reducing exacerbation rates has been observed in patients with severe or very severe COPD in studies of one year duration [5]. The longest study among those reported here was 24 weeks, and the patients had only mild to moderate asthma. These factors may explain the failure to reach statistical significance in some of the endpoint analyses. They point to the need for further studies of longer duration using the currently approved dose of roflumilast for COPD (500 µg/once daily), in more homogeneous patient groups (for some endpoints), in patients with more severe asthma.

5. Conclusion

Together these studies show that roflumilast may have potential as an anti-inflammatory therapy for the treatment of asthma. The studies conducted in this asthma programme were not of sufficient duration or size to observe a conclusive roflumilast effect, however, when given in addition to ICS (400 µg BDP and 250 µg FP) in two of the larger studies, roflumilast provided additional improvements in lung function. This finding is important as it indicates that roflumilast may confer added benefits in patients receiving ICS, which are considered to be the mainstay of asthma therapy, and these findings warrant further investigation.

Role of the funding source

These studies were funded by Takeda Pharmaceuticals International GmbH, who was responsible for oversight and overall project management. Medical writing support was provided by Ella Palmer of Synergy Vision (United Kingdom) and was funded by Takeda.

Conflicts of interest

E. O. Meltzer received a grant to his institution, Allergy & Asthma Medical Group & Research Center, for clinical trial and Investigator meeting expenses from Takeda. He reports personal fees for consulting from AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Meda, Merck, Regeneron/Sanofi, Sunovion and Teva; grants to the Allergy & Asthma Medical Group & Research Center from AstraZeneca, Boehringer Ingelheim and Teva; and personal fees for lectures from Meda, Merck, Sunovion, Takeda and Teva.

P. Chervinsky received a grant for conducting research studies from Northeast Medical Research.

W. Busse reports personal fees for consulting from Aerocrine, AstraZeneca, Boehringer-Ingelheim, Genentech, Gilead, Glaxo SmithKline, Merck, Novartis, Pfizer, Roche, Sanofi, Takeda and Teva; personal fees for Data Safety Monitoring Board membership from

Boston Scientific and Circassia; and personal fees for Study Oversight Committee membership from ICON.

K. Ohta received personal grants from AstraZeneca (2012), Glaxo SmithKline (2012) and MSD and an honorarium for lectures from Astellas, AstraZeneca, Boehringer Ingelheim Glaxo SmithKline, Kyorin and MSD.

P. Bardin reports no conflicts of interest.

D. Bredenbröker is an employee of Takeda Pharmaceuticals International GmbH.

Eric D Bateman reports personal fees for consulting and advisory board membership from Actelion, Almirall, AstraZeneca, Boehringer Ingelheim, and Hoffman la Roche; personal fees for advisory board membership from ALK-Abello, Chiesi, Elevation Pharma, Forest, Glaxo SmithKline, Napp Pharma, Navigant Consulting, Novartis, Pfizer, IMS Consulting Group, Takeda, and ICON; personal fees for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, Glaxo SmithKline, Merck, Novartis, Pfizer and Takeda; personal fees for educational materials from PeerVoice and Indegene; and grants to his institution for participation in clinical trials sponsored by Actelion, Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Cephalon, Chiesi, Glaxo SmithKline, Hoffman la Roche, Merck, Nycomed, Takeda, TEVA and Sanofi-Aventis outside the submitted work. He has membership of the Board of the Global Initiative for Asthma.

Acknowledgments

All authors participated in development of the final manuscript. Medical writing support was provided by Ella Palmer of Synergy Vision (United Kingdom) and funded by Takeda.

References

- [1] Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2014. Available from: <http://www.ginasthma.org/>.
- [2] E.D. Bateman, J.L. Izquierdo, U. Harnest, et al., Efficacy and safety of roflumilast in the treatment of asthma, *Ann. Allergy Asthma Immunol.* 96 (2006) 679–686.
- [3] J. Bousquet, M. Aubier, J. Sastre, et al., Comparison of roflumilast, an oral anti-inflammatory, with beclomethasone dipropionate in the treatment of persistent asthma, *Allergy* 61 (2006) 72–78.
- [4] D.C. Grootendorst, S.A. Gauw, R.M. Verhoosel, et al., Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD, *Thorax* 62 (2007) 1081–1087.
- [5] P.M. Calverley, K.F. Rabe, U.M. Goehring, et al., Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials, *Lancet* 374 (2009) 685–694.
- [6] L.M. Fabbri, P.M. Calverley, J.L. Izquierdo-Alonso, et al., Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials, *Lancet* 374 (2009) 695–703.
- [7] S.I. Rennard, P.M. Calverley, U.M. Goehring, et al., Reduction of exacerbations by the PDE4 inhibitor roflumilast—the importance of defining different subsets of patients with COPD, *Respir. Res.* 12 (2011) 18.
- [8] E.F. Juniper, G.H. Guyatt, R.S. Epstein, et al., Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials, *Thorax* 47 (1992) 76–83.
- [9] E.F. Juniper, P.M. O'Byrne, G.H. Guyatt, et al., Development and validation of a questionnaire to measure asthma control, *Eur. Respir. J.* 14 (1999) 902–907.
- [10] R. Djukanovic, J.W. Wilson, K.M. Britten, et al., Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma, *Am. Rev. Respir. Dis.* 145 (1992) 669–674.
- [11] E.D. Bateman, H.A. Boushey, J. Bousquet, et al., Can guideline-defined asthma control be achieved? The gaining optimal asthma control study, *Am. J. Respir. Crit. Care Med.* 170 (2004) 836–844.
- [12] A. Hatzelmann, E.J. Morcillo, G. Lungarella, et al., The preclinical pharmacology of roflumilast—a selective, oral phosphodiesterase 4 inhibitor in development for chronic obstructive pulmonary disease, *Pulm. Pharmacol. Ther.* 23 (2010) 235–256.
- [13] P.J. Barnes, Immunology of asthma and chronic obstructive pulmonary disease, *Nat. Rev. Immunol.* 8 (2008) 183–192.
- [14] N. Adams, T.J. Lasserson, C.J. Cates, et al., Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children, *Cochrane Database Syst. Rev.* (2007 Oct 17) (4):CD002310.
- [15] S.J. Szefler, R.J. Martin, T.S. King, et al., Significant variability in response to inhaled corticosteroids for persistent asthma, *J. Allergy Clin. Immunol.* 109 (2002) 410–418.

[1] Global Strategy for Asthma Management and Prevention, Global Initiative for