Respiratory Medicine 134 (2018) 143–149

Contents lists available at ScienceDirect

Respiratory Medicine

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

Efficacy and safety of lebrikizumab in adult patients with mild-to-moderate asthma not receiving inhaled corticosteroids

Philip Korenblat[a], Edwin Kerwin[b], Igor Leshchenko[c], Karl Yen[d], Cecile T.J. Holweg[d], Judith Anzures-Cabrera[e], Carmen Martin[e], Wendy S. Putnam[d], Laura Governale[d], Julie Olsson[d], John G. Matthews[d,*]

[a] The Clinical Research Centre LLC, St Louis, MO, USA
[b] Clinical Research Institute of Southern Oregon PC, Medford, OR, USA
[c] Ural State Medical University, Yekaterinburg, Russia
[d] Genentech, Inc., South San Francisco, CA, USA
[e] Roche Products Limited, Welwyn Garden City, UK

ARTICLE INFO

Keywords:
Mild
Moderate
Asthma
Lebrikizumab

ABSTRACT

Background: Asthma is a heterogeneous and complex disease in both its clinical course and response to treatment. IL-13 is central to Type 2 inflammation and contributes to many features of asthma. In a previous Phase 2 study, lebrikizumab, an anti-IL-13 monoclonal antibody, did not significantly improve FEV_1 in mild-to-moderate asthma patients not receiving ICS therapy. This Phase 3 study was designed to further assess the efficacy and safety of lebrikizumab in adult patients with mild-to-moderate asthma treated with daily short-acting β_2-agonist therapy alone.

Methods: Adult patients with mild-to-moderate asthma were randomised to receive lebrikizumab 125 mg subcutaneously (SC), placebo SC, or montelukast 10 mg orally for 12 weeks, with an 8-week follow-up period. The primary efficacy endpoint was absolute change in pre-bronchodilator FEV_1 from baseline at Week 12.

Findings: A total of 310 patients were randomised and dosed in the study. The mean absolute change in FEV_1 from baseline at Week 12 was higher in the lebrikizumab-treated arm compared with placebo (150 mL versus 67 mL); however, this improvement did not achieve statistical significance (overall adjusted difference of 83 mL [95% CI: −3, 170]; p = .06). Montelukast did not improve FEV_1 as compared with placebo. Lebrikizumab was generally safe and well tolerated during the study.

Interpretation: Lebrikizumab did not significantly improve FEV_1 in mild-to-moderate asthma patients at a dose expected to inhibit the IL-13 pathway. Inhibiting IL-13 in this patient population was not sufficient to improve lung function. These data support the findings of a previous trial of lebrikizumab in patients not receiving ICS.

Clinical Trials Registry number: This trial was registered under NCT02104674 at http://www.clinicaltrials.gov.

1. Introduction

Asthma is a complex heterogeneous disease characterised by chronic airway inflammation and marked variability in its clinical course and response to treatment [1–3]. Inhaled corticosteroids (ICS) and β_2-agonists are the mainstay of asthma therapy and provide effective control in the majority of patients [4]. However, further understanding of the disease and new treatment options across the range of asthma severityis needed.

Lebrikizumab is a humanised monoclonal antibody that binds to soluble interleukin (IL)-13 with high affinity and blocks signalling through the active IL-4 receptor (R)α/IL-13Rα1 heterodimer. Lebrikizumab has been investigated for the treatment of asthma, primarily in patients with moderate-to-severe asthma that was uncontrolled despite treatment with ICS and a second controller [5–7]. There is some evidence that ICS can reduce IL-13 activity; therefore, to understand the effects of treatment with lebrikizumab, it is important to understand the effects of blocking IL-13 in patients who are not being

Abbreviations: AE, adverse event; AQLQ(S), Standardised Asthma Quality of Life Questionnaire; ATA, anti-therapeutic antibodies; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; HLGT, high level group term; HLT, high level term; ICS, inhaled corticosteroids; IL, interleukin; ISR, injection site reaction; IxRS, interactive voice/web-based response system; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; PEF, peak expiratory flow; PK, pharmacokinetics; PT, preferred term; SABA, short-acting β_2-agonist; SOC, system organ class

* Corresponding author. Senior Group Medical Director, OMNI Early Clinical Development, Genentech, Inc. A member of the Roche Group, USA.
E-mail address: matthews.john@gene.com (J.G. Matthews).

https://doi.org/10.1016/j.rmed.2017.12.006
Received 21 July 2017; Received in revised form 27 October 2017; Accepted 10 December 2017
Available online 13 December 2017

treated with ICS [8].

In a previous Phase 2 study, lebrikizumab attenuated the late-phase response to allergen challenge by 48% compared with placebo in patients with mild asthma (not taking ICS therapy), without a demonstrable effect on the early-phase response [9]. A post-hoc analysis showed the greatest benefit in patients with evidence of Type 2 disease, which was based on higher levels of serum periostin. A subsequent Phase 2 study (MOLLY) of patients with asthma who were not being treated with ICS therapy showed that treatment with lebrikizumab was associated with a small (but not statistically significant or clinically meaningful) relative increase in forced expiratory volume in 1 s (FEV_1) compared with placebo [10]. Taken together, these studies did not provide adequate characterisation of lebrikizumab's efficacy in the mild-to-moderate patient population. Therefore, the current trial was designed to provide a definitive efficacy estimate of lebrikizumab in mild-to-moderate asthma patients who are not receiving ICS.

This study evaluates the efficacy of lebrikizumab in the overall enrolled population and when stratified by biomarker status (high serum periostin or high blood eosinophil counts). Previously in patients with moderate-to-severe asthma treated with background ICS, lebrikizumab showed the greatest treatment benefit in patients with biomarker evidence of Type 2 asthma, e.g., high periostin [5,7]. In recent Phase 3 trials in patients with uncontrolled asthma despite treatment with ICS and a second controller medication, both serum periostin levels and blood eosinophil counts were used to enrich for treatment benefit [6].

Here we report the results from a Phase 3, randomised study (STRETTO) to assess the efficacy and safety of lebrikizumab in adult patients with mild-to-moderate asthma treated with daily short-acting β_2-agonist (SABA) therapy alone. Montelukast was included as an active comparator to provide information about the sensitivity of the study to detect a small increase in FEV_1. In published studies, montelukast has been associated with a statistically significant benefit on FEV_1, but the effect was numerically lower than the effect of ICS [11–13].

2. Methods

2.1. Study design and participants

STRETTO (NCT02104674) was a Phase 3, randomised, double-blinded, placebo-controlled multicentre study. Enrolment commenced in June 2014 and was completed in August 2015. The study consisted of a 2-week screening period, a 12-week treatment period, and an 8-week safety follow-up period. Eligible patients were aged 18–75 years, with an asthma diagnosis for ≥12 months at screening and a pre-bronchodilator FEV_1 of 60–85% predicted. Patients were required to demonstrate a bronchodilator response during screening, defined as a ≥15% relative improvement in FEV_1 after bronchodilator administration. ICS treatment was not permitted for at least 30 days prior to enrolment and during the 12-week placebo-controlled period. Patients treated with ICS must not have been discontinued from ICS therapy expressly to meet study eligibility. Patients were also required to have stable asthma during the screening period, as defined by stable FEV_1, peak expiratory flow (PEF), and daily SABA use. Exclusion criteria included current smoker or former smoker with more than 10 pack-years history, parasitic infection within the preceding 6 months, and clinically significant lung disease other than asthma. All patients provided written informed consent.

2.2. Randomisation and masking

Patients were randomised in a 1:1:1 ratio to receive blinded lebrikizumab 125 mg SC, placebo SC, or open-label Singulair® (montelukast sodium) 10 mg orally in the evening (Fig. 1).

Randomisation was stratified by serum periostin level, baseline percentage of predicted FEV_1, and geographical region, and was performed through an interactive voice/web-based response system (IxRS) using a permuted block design method [14]. Lebrikizumab and placebo were identical in appearance and were supplied by Roche in prefilled syringes. Patients either received an injection from the prefilled syringe or they received montelukast. The spirometry technician was blinded to study treatment, and patients were asked not to discuss study treatment assignment with the spirometry technician.

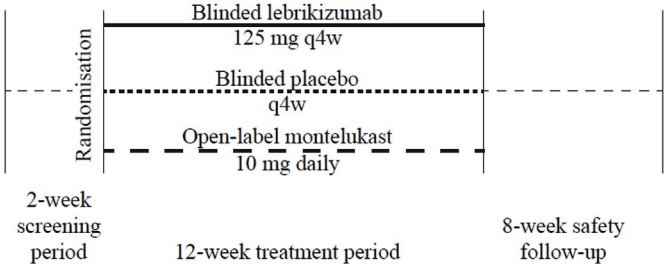

Fig. 1. Study design schematic.

2.3. Procedures

Lebrikizumab or placebo was administered subcutaneously every 4 weeks during the 12-week placebo-controlled period, or one 10 mg tablet of montelukast was self-administered orally by the patient once daily in the evening with no subcutaneous injections. Pill counting was performed each month. Assessments included measurement of FEV_1, patient-reported outcome measures (e.g., Standardised Asthma Quality of Life Questionnaire [AQLQ(S)]), adverse events (AEs), biomarkers (fractional exhaled nitric oxide [FeNO], blood eosinophils, periostin), pharmacokinetics (PK), and anti-therapeutic antibodies (ATA). Patients were provided with the In2itive e-Diary to record daily PEF measurements and montelukast compliance, daytime asthma symptoms, nighttime awakenings, and daily SABA use.

2.4. Outcomes

The primary efficacy endpoint was the absolute change in pre-bronchodilator FEV_1 from baseline at Week 12. Secondary efficacy endpoints included absolute change in pre-bronchodilator PEF from baseline at Week 12, time to treatment failure, change in SABA use, and change in asthma-specific health-related quality of life, as assessed by the overall score of the AQLQ(S). Treatment failure was defined as a worsening of asthma symptoms in association with one or more of the following: relative decrease in pre-bronchodilator FEV_1 ≥ 20% from baseline; 20% decline in morning pre-bronchodilator PEF on two consecutive days compared with baseline values; use of 10 or more inhalations of albuterol (or equivalent), or two or more additional administrations (or any new use) of nebulised SABA therapy in a single day; or need for any inhaled, oral, or parenteral corticosteroid or other controller medication (e.g., long-acting muscarinic antagonists, long-acting β_2-agonists, leukotriene modifiers, theophylline).

2.5. Pharmacokinetic analyses

Blood samples were taken at baseline and throughout the study, and serum lebrikizumab concentrations were measured (see supplement for further details).

2.6. Pharmacodynamic analyses

Details of pharmacodynamic analyses are included in the online supplement.

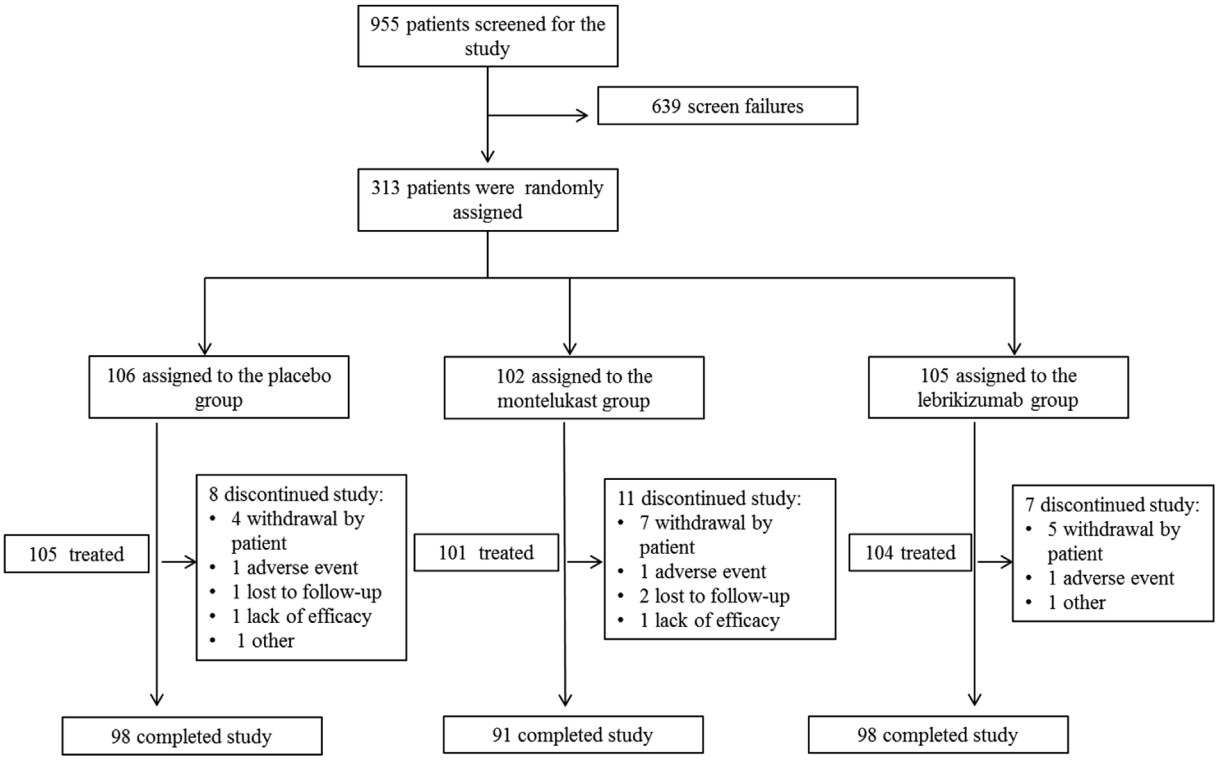

Fig. 2. Patient disposition.

2.7. Safety

Safety assessments consisted of monitoring and recording treatment-emergent AEs, including their severity. AEs of special interest included the following: local injection site reactions (ISRs); anaphylactic, anaphylactoid, and serious hypersensitivity reactions; infections; and malignancies. Infections were evaluated in the categories of infections broad and infections narrow. Infections broad included preferred terms (PT) under the MedDRA System Organ Class (SOC) "Infections and Infestations." Infections narrow included PTs in the High Level Group Terms (HLGT) "Helminthic Disorders," "Mycobacterial Infectious Disorders," "Protozoal Infectious Disorders," or High Level Term (HLT) "Listeria Infections." A masked anaphylaxis adjudication committee reviewed potential cases of anaphylaxis.

2.8. Statistical analyses

The sample size of 100 patients per treatment arm (a total of 300 patients) was selected for the primary efficacy endpoint of the study. With approximately 100 patients per arm (lebrikizumab and placebo), the study had 80% power to detect a difference in absolute change in FEV_1 from baseline to Week 12 between lebrikizumab and placebo of 120 mL (approximately 5% change from baseline). Data from the montelukast treatment arm were used to evaluate the assay sensitivity of the study because montelukast-treated patients were expected to demonstrate an increase in FEV_1 over the 12-week treatment period [11–13]. The standard deviation for the absolute change from baseline to Week 12 was 300 mL for both comparisons (i.e., lebrikizumab and placebo, and montelukast and placebo). A two-sided significance was considered at 0.05. A prespecified population of montelukast compliant patients was defined by detectable plasma montelukast concentrations at 3 or more visits during the treatment period to mitigate a risk that open-label montelukast was not taken (results in supplement). With approximately 100 patients per arm, the study had > 90% power to detect a difference in absolute change of FEV_1 from baseline to Week 12 between montelukast and placebo of 160 mL (approximately 6.7% change from baseline).

The efficacy analyses were performed in the modified intent-to-treat (mITT) population, consisting of all patients who were randomised and received at least one dose of study drug (lebrikizumab, placebo, or montelukast), i.e., all randomised and treated patients. As prespecified in the protocol, analysis of the primary efficacy endpoint was also conducted separately in the biomarker-high (serum periostin ≥ 50 ng/mL or baseline blood eosinophil count ≥ 300 cells/μL) and biomarker-low (serum periostin < 50 ng/mL and baseline blood eosinophil count < 300 cells/μL) subgroups. Continuous efficacy endpoints were analysed with the use of a mixed model for repeated measures (MMRM) and descriptive statistics as appropriate, with both models adjusted based on covariates. The MMRM model included the following covariates for adjustment: screening values for periostin and eosinophil levels with four categories (high/high, high/low, low/high, and low/low), geographical region (United States or Rest of World), week of treatment (as a categorical factor), treatment group, and the interaction of treatment with week. The model also included baseline FEV_1 as a continuous covariate and its interaction with week of treatment. Time-to-treatment failure was analysed using a Cox proportional hazards model. The safety analyses were performed on patients grouped according to the treatment received.

2.9. Role of funding source

The funder of the study contributed to study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

3. Results

3.1. Disposition and demographics

A total of 313 patients were randomised to one of the three treatment arms (n = 105 lebrikizumab, n = 102 montelukast, and n = 106

Table 1
Patient demographics.

	Montelukast (n = 101)	Placebo (n = 105)	Lebrikizumab (n = 104)
Age, years	44.2 ± 13.3	44.7 ± 14.0	42.9 ± 13.8
Sex			
Female, n (%)	61 (60.4%)	66 (62.9%)	63 (60.6%)
Male, n (%)	40 (39.6%)	39 (37.1%)	41 (39.4%)
Race, n (%)			
American Indian	1 (1.0%)	0	1 (1.0%)
Asian	5 (5.0%)	4 (3.8%)	2 (1.9%)
Black or African American	10 (9.9%)	20 (19.0%)	13 (12.5%)
White	84 (83.2%)	81 (77.1%)	88 (84.6%)
Multiple	1 (1.0%)	0	0
Body mass index, kg/m^2	27.80 ± 5.27	27.62 ± 4.81	27.13 ± 4.99
Former smoker, n (%)	20 (19.8%)	19 (18.1%)	20 (19.2%)
Pre-bronchodilator FEV_1			
Absolute, litres	2.38 ± 0.57	2.31 ± 0.63	2.39 ± 0.59
% predicted	71.71 ± 6.57	71.81 ± 6.47	72.32 ± 6.91
Reversibility, %	21.75 ± 10.64	24.17 ± 10.62	24.44 ± 13.36
AQLQ(S) score	5.01 ± 1.16	5.27 ± 1.09	5.03 ± 1.08
Median serum periostin, ng/mL[a]	52.14 (26.9–110)	51.57 (32.8–160.6)	50.95 (27.2–104.6)
Median FeNO, ppb[a]	41 (7–373)	37 (6–232)	34 (6–242)
Median blood eosinophil count, cells per μL[a]	210 (0–1060)	220 (0–800)	200 (20–680)
Biomarker high (periostin ≥ 50 ng/mL or blood eosinophils ≥ 300 cells per μL), n[a]	61	75	67
Biomarker low (periostin < 50 ng/mL or blood eosinophils < 300 cells per μL), n[a]	40	30	37
SABA puffs per day at baseline	1.76 ± 1.7	1.59 ± 1.79	1.73 ± 1.84

Unless otherwise stated, data are expressed as mean ± SD. Biomarker data expressed as median (min–max).
AQLQ(S), Standardised Asthma Quality of Life Questionnaire; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume SABA, short-acting β2-agonist.
[a] Baseline at day −14.

placebo; Fig. 2).

Three patients were randomised but not dosed. One patient did not meet the requirement of daily SABA use (stable asthma during screening criterion) and was discontinued by the site prior to receiving study treatment, one patient experienced an adverse event of "vasovagal" during sample collection prior to study drug administration and refused participation in the study, and one patient was randomised using a periostin value from a previous screening and subsequently not treated and discontinued from the study. These patients were not included in the data analyses. Treatment arms were generally balanced with respect to demographic and baseline characteristics such as age, sex, baseline FEV_1, periostin, and blood eosinophils (Table 1). Approximately 58% of patients had a history of allergic rhinitis and the prevalence of allergic rhinitis was balanced across treatment arms. Nasal and/or sinus polyps were reported in 4% of patients, with slightly more patients in the montelukast arm compared to the lebrikizumab and placebo arms (7% in the montelukast arm, 3% in the lebrikizumab arm, and 3% in the placebo arm).

A total of 287 patients (91.7%) completed the study; a patient was considered to have completed the study if the last safety follow-up visit was completed, regardless of whether the patient completed treatment. The proportion of patients discontinuing the study prematurely was 7.5% in the placebo arm, 6.7% in the lebrikizumab arm, and 10.8% in the montelukast arm. The most common reason for discontinuation from the study was "withdrawal by patient" (overall 5.1%; Fig. 2). Some patients who discontinued the study early were patients who were withdrawn from treatment due to protocol-defined treatment failure and declined to complete the safety follow-up period.

3.2. Primary and secondary endpoints

3.2.1. Absolute change in FEV_1

For the primary efficacy endpoint, the adjusted mean absolute change in pre-bronchodilator FEV_1 at Week 12 was 150 mL in the lebrikizumab arm compared with 67 mL in the placebo arm (overall adjusted difference of 83 mL [95% CI: −3, 170]; p = .06). When analysed by biomarker status, the biomarker-high group (n = 75 placebo arm; n = 67 lebrikizumab arm) showed similar results to the overall mITT population. In these biomarker-high patients, at Week 12, the mean absolute changes from baseline in FEV_1 were 157 mL and 92 mL in the lebrikizumab and placebo arms, respectively (overall difference of 65 mL [95% CI: −42, 171]; Fig. 3).

In the biomarker-low subgroup (n = 30 placebo arm; n = 37 lebrikizumab arm), the mean difference between lebrikizumab and placebo was 148 mL (95% CI: −5, 300). Consistent with the overall mITT population, these differences were not statistically significant (Fig. 3). In the montelukast arm, the adjusted mean absolute change in FEV_1 at Week 12 was 52 mL compared with 69 mL in the placebo arm, resulting in an overall difference of −17 mL (95% CI: −101, 68; p = .6954; Fig. 3). Similar effects of montelukast on FEV_1 were seen when analysed by biomarker status (see supplement).

3.2.2. Treatment failure

Nine patients in the lebrikizumab arm and 11 in the placebo arm met the definition of treatment failure. The hazard ratio from the Cox proportional hazards model comparing the risk of treatment failure for the lebrikizumab-treated patients versus the placebo-treated patients was 1.06 (95% CI: 0.47, 2.42; Fig. S1). Evidence for proportional hazards was explored by including a time by treatment interaction term in an extended Cox proportional hazards model. The coefficient for this interaction was not statistically significant (p = .9966), suggesting that there is no evidence against proportional hazards.

3.2.3. Other secondary endpoints

Other secondary endpoints, including absolute change in pre-bronchodilator PEF, absolute change in asthma reliever medication use, and change in AQLQ(S), did not show a statistically significant treatment effect of lebrikizumab versus placebo (Table 2).

3.3. Pharmacokinetic anales

Serum lebrikizumab trough concentrations were consistent with those observed in previous Phase 2 and recent Phase 3 lebrikizumab trials [5,6,10]. The observed mean ± SD concentrations increased

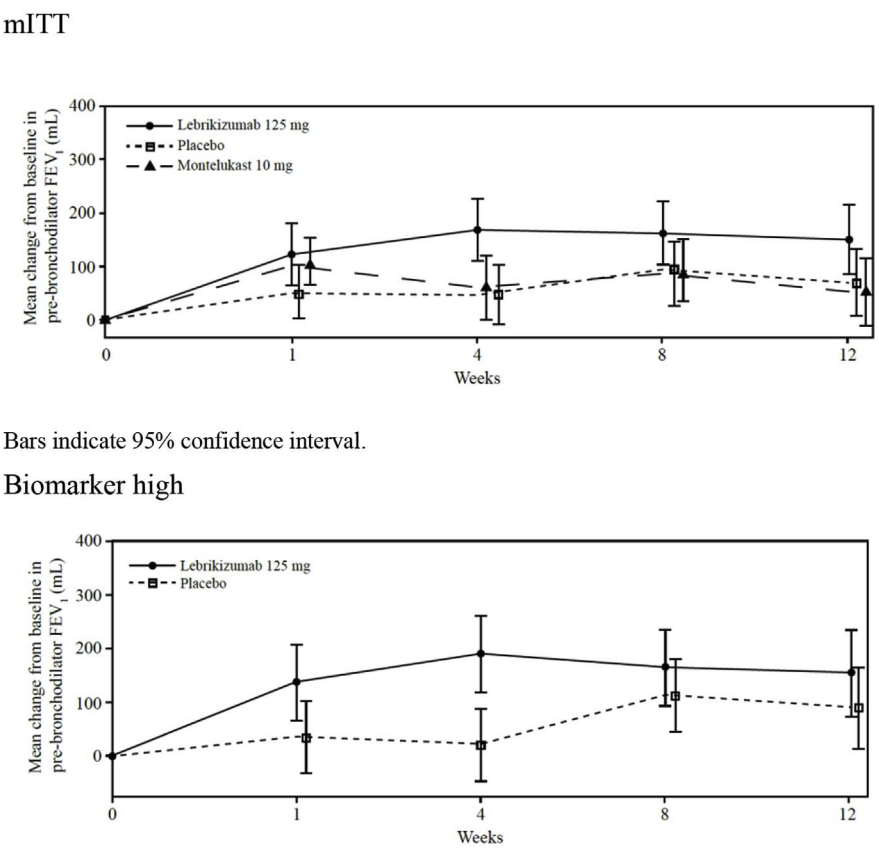

Fig. 3. Absolute change in FEV_1 from baseline at Week 12, mITT patients (top), biomarker-high group (middle), biomarker-low group (bottom). FEV_1, forced expiratory volume in 1 s; mITT, modified intent-to-treat.

Table 2
Changes in other secondary endpoints at Week 12.

Secondary endpoint	Placebo (n = 105)	Lebrikizumab (n = 104)
Absolute change in morning pre-bronchodilator PEF (L/min)		
Adjusted mean ± SE	5.25 ± 5.57	1.63 ± 5.51
Difference in means (95% CI)		−3.61 (−18.46, 11.23)
Absolute change in asthma reliever medication use (puffs/day)		
Adjusted mean ± SE	−0.55 ± 0.11	−0.51 ± 0.11
Difference in means (95% CI)		0.04 (−0.25, 0.32)
Absolute change in AQLQ(S) score		
Adjusted mean ± SE	0.68 ± 0.09	0.62 ± 0.09
Difference in means (95% CI)		−0.06 (−0.29, 0.17)

AQLQ(S), Standardised Asthma Quality of Life Questionnaire; PEF, peak expiratory flow.

from 9.58 ± 4.12 μg/mL at Week 4 to 14.2 ± 5.81 μg/mL at Week 8 and then 18.1 ± 6.46 μg/mL at Week 12 as the lebrikizumab concentrations approached steady state. The mean terminal elimination $t_{1/2}$ was approximately 24 days (Table 3).

3.3.1. *Pharmacodynamic biomarkers*

Mean FeNO levels declined with lebrikizumab treatment by −31.9 ppb from baseline to Week 12 versus placebo −10.9 ppb, while minimal changes relative to placebo were observed with montelukast treatment (montelukast change from baseline at Week 12, −13.2 ppb; Fig. S2). Mean periostin levels decreased to a lesser extent upon lebrikizumab treatment relative to placebo at Week 12 (lebrikizumab −3.9 ng/mL versus placebo 0.3 ng/mL). Changes in periostin in the

Table 3
Lebrikizumab pharmacokinetic parameters.

	$C_{max,\ Wk1}$ (μg/mL)	$T_{max,\ Wk1}$ (Day)	$C_{min,\ Wk4}$ (μg/mL)	$C_{min,\ Wk8}$ (μg/mL)	C_{Wk12} (μg/mL)	$t_{1/2}$ (Day)
N	103	103	101	90	82	90
Mean ± SD	14.9 ± 5.91	7.04 ± 1.17	9.58 ± 4.12	14.2 ± 5.81	18.1 ± 6.46	23.7 ± 7.24

$C_{max,\ Wk1}$, maximum observed concentration at Week 1; $C_{min,\ Wk4}$, minimum serum concertation at Week 4; $C_{min\ Wk8}$, minimum serum concertation at Week 8; C_{Wk12}, serum concentration at Week 12; $t_{1/2}$, mean elimination half-life; $T_{max,\ Wk1}$, time at which maximum serum concentration is observed.

montelukast arm were minimal (1.3 ng/mL; Fig. S3). Lebrikizumab treatment was associated with a small increase in mean eosinophil count (55 cells/μL) relative to placebo (34 cells/μL). Montelukast was associated with a reduction in eosinophil counts relative to placebo from baseline at Week 12 (montelukast change, −32 cells/μL; Fig. S4).

3.3.2. Safety

The proportion of patients who experienced at least one AE during the treatment period was 44% in the placebo arm, 40% in the lebrikizumab arm, and 41% in the montelukast arm. Three patients experienced 4 serious AEs during the treatment period: a subdural haematoma and a cerebrospinal fluid leakage in a placebo-treated patient; one event of anaphylaxis attributed to peanuts occurred in a lebrikizumab-treated patient with a known history of peanut allergy; and a single case of malignancy (melanoma in situ) occurred in a lebrikizumab-treated patient. No deaths were reported in this study (Table 4).

The rate of infections was higher in the placebo-treated arm (25%) when compared with the lebrikizumab- (20%) and montelukast-treated arms (20%). There were no events in the infections narrow category. The percentage of patients experiencing at least one ISR was the same (3%) for both the placebo and lebrikizumab arms, and no patients discontinued early from the treatment due to an ISR. Six patients in the placebo arm, 7 patients in the lebrikizumab arm, and 6 patients in the montelukast arm discontinued from study treatment due to AEs. Most AEs were mild-to-moderate in intensity: 2% of patients in each of the placebo and lebrikizumab arms experienced severe AEs, and no patients experienced severe AEs in the montelukast arm during the treatment period.

4. Discussion

In patients with mild-to-moderate asthma who were not receiving ICS, lebrikizumab treatment resulted in a small increase in FEV_1 that was not statistically significant. Overall, FEV_1 results are consistent with the previous lebrikizumab Phase 2 study in mild-to-moderate asthma patients [10].

Table 4
Overview of adverse events.

	Placebo (n = 103)	Montelukast (n = 103)	Lebrikizumab (n = 104)
Total number of AEs	74	63	72
Total number of serious AEs	2	0	2
Total number of deaths	0	0	0
Total number of patients with at least one:			
AE	45 (43.7%)	42 (40.8%)	42 (40.4%)
Severe AE	2 (1.9%)	0	2 (1.9%)
Serious AE	1 (1.0%)	0	2 (1.9%)
AE leading to discontinuation from study treatment	6 (5.8%)	6 (5.8%)	7 (6.7%)
ISR	3 (2.9%)	0	3 (2.9%)
Anaphylaxis per Sampson's criteria	0	0	1 (1.0%)
Infection (broad)	26 (25.2%)	21 (20.4%)	21 (20.2%)
Infection (narrow)	0	0	0
Malignancy	0	0	1 (1.0%)

AE, adverse event; ISR, injection-site reaction.

The intention of this study was to evaluate a mild-to-moderate patient population not treated with ICS, because of the potential ICS IL-13 interaction and to characterize lebrikizumab across a range of asthma severity. This patient population receiving only SABA treatment may not be as clinically relevant as the mild-to-moderate patient population treated with a controller medication, as illustrated by two countries that expressed ethical concerns regarding the study enrolling a population that should be receiving standard of care treatment. Potentially enrolling a patient population taking low-dose ICS would have been more clinically relevant. However, the patient subset enrolled allowed the appropriate characterisation of lebrikizumab treatment benefit without background ICS, and therefore was not confounded by the potential impact of ICS on IL-13 activity.

This study suggests that IL-13 may not be a dominant driver of lung function in asthmatic patients who have mild-to-moderate disease. The improvement in FEV_1 following lebrikizumab treatment in a Phase 2 study (MILLY) of patients who were uncontrolled despite ICS treatment led to the hypothesis that these patients likely had residual IL-13 activity that ICS was not able to suppress or fully suppress. Thus, patients might have had a relative steroid insensitivity and enrolling patients who were uncontrolled on ICS enriched for an ICS-resistant population that was more likely to benefit from anti-IL-13 therapy. Inhibiting IL-13 in these steroid-insensitive patients may have a more pronounced effect on FEV_1.

The recent Phase 3 LAVOLTA I and II studies in patients with uncontrolled asthma despite ICS and second controller therapy failed to show the expected effect of lebrikizumab on asthma exacerbations in the pre-specified biomarker subgroup, but did show improvements in FEV_1 in both trials [6]. Results of the current study are consistent with the lower efficacy observed in the previous trial in mild-to-moderate asthma that also evaluated an all-comers patient population with respect to biomarkers [6].

Lebrikizumab inhibited the IL-13 pathway, as shown by a decrease in FeNO and, to a lesser extent, periostin levels and a small increase in blood eosinophil counts. These changes were observed after the first dose and were sustained throughout the treatment period. Serum concentrations of lebrikizumab were consistent with those in previous studies [5,6,10]. The small increase in mean blood eosinophils has previously been observed with lebrikizumab, tralokinumab, and dupilumab, and it is thought to relate to blocking of the induction of adhesion molecules by IL-13, such as P-selectin and chemokines with a coiled-coiled motif that binds to chemokine receptor 3 [15,16]. These chemokines and adhesion molecules can serve as chemo-attractants for eosinophils, and if eosinophils do not translocate to areas of inflammation, they will remain in the blood.

Lebrikizumab was generally safe and well tolerated during the study, and no new safety concerns were identified. There were no deaths during the study, and of the four serious AEs experienced during the treatment period, none were considered by the investigators to be related to the study drugs. The incidence of patients experiencing at least one injection reaction was the same for both the placebo and lebrikizumab groups.

The current study has some limitations. The positive control of montelukast did not achieve improvement on FEV_1, despite evidence of adherence to the treatment (assessed by montelukast concentration in

the blood and by pill counting). Previous trials conducted in the 1990's have shown an effect of montelukast on lung function in adults, but more recent trials have failed to show a consistent benefit on FEV_1 in adults with asthma [11,12,17]. It is possible that the lower symptom burden and SABA use among patients enrolled in this trial compared with the pivotal montelukast trials conducted when the standard of care for asthma treatment was different and ICS were not widely used contributed to this different result. It was also not possible to implement blinded montelukast due to difficulties in manufacture of placebo tablets in the time window of the study start. A placebo response to blinded treatment was observed in this trial with FEV_1 improvement in the placebo group. The magnitude of the placebo response was generally consistent with the placebo response observed in previous trials in mild-to-moderate asthma patients and was considered in the planning of the study design and sample size [12,13].

In conclusion, these data contribute to the characterisation of the efficacy of lebrikizumab over the entire spectrum of asthma severity. In patients not receiving ICS, inhibiting IL-13 was not sufficient to significantly improve FEV_1.

Declaration of interests

Disclosure forms provided by the authors are available with the full text of this article.

Funding

F. Hoffmann-La Roche Ltd.

Acknowledgements

This research was supported by Genentech Inc., a member of the Roche Group. We thank the patients who participated in this trial, the investigators, and staff at all study sites.

Support for third-party writing assistance for this manuscript, furnished by Manminder Kaur, PhD, of MediTech Media, was provided by Genentech Inc., a member of the Roche Group.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2017.12.006.

References

[1] E.H. Bel, Clinical phenotypes of asthma, Curr. Opin. Pulm. Med. 10 (1) (2004) 44–50.
[2] P. Haldar, I.D. Pavord, D.E. Shaw, et al., Cluster analysis and clinical asthma phenotypes, Am. J. Respir. Crit. Care Med. 178 (3) (2008) 218–224.
[3] S.E. Wenzel, Asthma: defining of the persistent adult phenotypes, Lancet 368 (9537) (2006) 804–813.
[4] Global initiative for asthma (GINA). Global strategy for asthma management and prevention - updated 2017. http://ginasthma.org/gina-reports. Updated 2017. Accessed October, 2017.
[5] N.A. Hanania, M. Noonan, J. Corren, et al., Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies, Thorax 70 (8) (2015) 748–756.
[6] N.A. Hanania, P. Korenblat, K.R. Chapman, et al., Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials, Lancet Respir. Med. 4 (10) (2016) 781–796.
[7] J. Corren, R.F. Lemanske, N.A. Hanania, et al., Lebrikizumab treatment in adults with asthma, N. Engl. J. Med. 365 (12) (2011) 1088–1098.
[8] T. Naseer, E.M. Minshall, D.Y. Leung, Expression of IL-12 and IL-13 mRNA in asthma and their modulation in response to steroid therapy, Am. J. Respir. Crit. Care Med. 155 (1997) 845–851.
[9] H. Scheerens, J.R. Arron, Y. Zheng, et al., The effects of lebrikizumab in patients with mild asthma following whole lung allergen challenge, Clin. Exp. Allergy 44 (1) (2014) 38–46.
[10] M. Noonan, P. Korenblat, S. Mosesova, et al., Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids, J. Allergy Clin. Immunol. 132 (3) (2013) 567–574 e12.
[11] K. Malmstrom, G. Rodriguez-Gomez, J. Guerra, et al., Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. montelukast/beclomethasone study group, Ann. Intern. Med. 130 (6) (1999) 487–495.
[12] T.F. Reiss, L.C. Altman, P. Chervinsky, et al., Effects of montelukast (MK-0476), a new potent cysteinyl leukotriene (LTD4) receptor antagonist, in patients with chronic asthma, J. Allergy Clin. Immunol. 98 (3) (1996) 528–534.
[13] R.A. Baumgartner, G. Martinez, J.M. Edelman, et al., Distribution of therapeutic response in asthma control between oral montelukast and inhaled beclomethasone, Eur. Respir. J. 21 (1) (2003) 123–128.
[14] D.F. Signorini, O. Leung, R.J. Simes, E. Beller, V.J. Gebski, T. Callaghan, Dynamic balanced randomization for clinical trials, Stat. Med. 12 (24) (1993) 2343–2350.
[15] C.E. Brightling, P. Chanez, R. Leigh, et al., Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial, Lancet Respir. Med. 3 (9) (2015) 692–701.
[16] S. Wenzel, M. Castro, J. Corren, et al., Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial, Lancet 388 (10039) (2016) 31–44.
[17] R.M. Follows, N.G. Snowise, S.Y. Ho, C.L. Ambery, K. Smart, B.A. McQuade, Efficacy, safety and tolerability of GSK2190915, a 5-lipoxygenase activating protein inhibitor, in adults and adolescents with persistent asthma: a randomised dose-ranging study, Respir. Res. 14 (2013) 54–9921-14-54.