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

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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

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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.

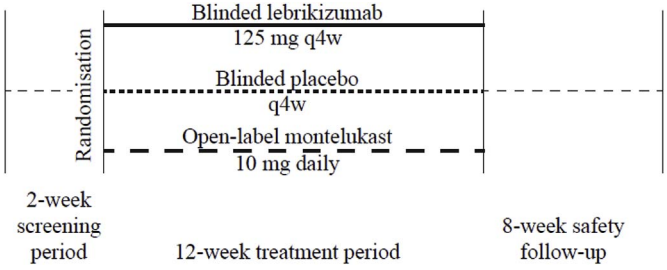

Fig. 1. Study design schematic.

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.