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Early View

Study protocol

Long-term effect of dupilumab on prevention of lung function decline in patients with uncontrolled moderate-to-severe asthma: ATLAS trial design

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Title: Long-term effect of dupilumab on prevention of lung function decline in patients with uncontrolled moderate-to-severe asthma: ATLAS trial design

Lucia De Prado Gomez[1], Ian Pavord[2], William Busse[3], Christopher E Brightling[4], Michael E Wechsler[5], Klaus F Rabe[6,7], Mei Zhang[8], Jun Xing[8], Juby A Jacob-Nara[8], Paul J Rowe[8]

[1]Sanofi, Reading, UK; [2]NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK; [3]UW Allergy, Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [4]Institute for Lung Health, NIHR Leicester Biomedical Research Center, Department of Respiratory Sciences, University of Leicester, Leicester, UK; [5]National Jewish Health, Denver, CO, USA; [6]LungenClinic Grosshansdorf (member of the German Center for Lung Research [DZL]), Airway Research Center North (ARCN), Grosshansdorf, Germany; [7]Christian-Albrechts University (member of the German Center for Lung Research [DZL]), Airway Research Center North (ARCN), Kiel, Germany; [8]Sanofi, Bridgewater, NJ, USA

Corresponding author

Lucia De Prado Gomez

Sanofi, Reading, UK

Lucia.DePradoGomez@sanofi.com

+44 7793 286 919

Take home message

The ATLAS trial is designed to establish the role of dupilumab in preventing long-term loss of lung function in patients with moderate-to-severe asthma, and its potential effect on disease modification.

ABSTRACT (250/250 words)

Background: Many patients with asthma experience loss of lung function over time, and in certain patients this can lead to progressive obstructive patterns. similar to chronic obstructive pulmonary disease. Patients with severe asthma may experience accelerated lung function decline (LFD). However, characteristics and risk factors for LFD in asthma have not been well described. Dupilumab may prevent or slow the rate of LFD in patients with uncontrolled, moderate-to-severe asthma. ATLAS trial is designed to evaluate the role of dupilumab in preventing/slowing LFD over a period of 3 years versus standard-of-care therapy.

METHODS:ATLAS (NCT05097287) is a randomised, double-blind, placebo-controlled, multicenter study that will include adult patients with uncontrolled moderate-to-severe asthma. Approximately 1828 patients will be randomised (2:1) to dupilumab 300 mg or placebo in combination with maintenance therapy every 2 weeks for 3 years. The primary objective is to assess the effect of dupilumab on preventing or slowing LFD by Year 1 in FeNO population (patients with FeNO ≥35ppb). The effect of dupilumab in slowing the rate of LFD by Year 2 and Year 3 in both FeNO and total populations, exacerbations, asthma control, quality of life, biomarker changes, and utility of FeNO as a biomarker of LFD will also be evaluated.

DISCUSSION:ATLAS is the first trial assessing the effect of a biologic on LFD, designed to establish the role of dupilumab in prevention of long-term loss of lung function and its potential effect on disease modification, which may provide unique insights into asthma pathophysiology, including predictive and prognostic factors of LFD.

Keywords: Asthma, ATLAS, biologics, biomarker, dupilumab, FeNO, lung function decline (LFD)

BACKGROUND

Asthma is a clinically and molecularly heterogeneous chronic inflammatory disease associated with airway inflammation, obstruction, and hyperresponsiveness [1-3]. Patients with asthma may experience lung function decline (LFD) over time [4, 5], which can lead to progressive obstructive patterns in certain patients despite the use of the standard of care (SoC) therapy, especially in patients with moderate-to-severe asthma [4, 6]. LFD may stem from structural airway changes that accompany the underlying airway wall inflammation in asthma [7, 8] and it is known to be associated with increased morbidity and mortality [6, 9]. Therefore, the prevention of LFD should be a core component of asthma management.

Although progressive LFD in patients with asthma has been well recognised, there is limited data to identify patients with asthma who are at increased risk of LFD [10]. In healthy individuals, forced expiratory volume in 1 second (FEV_1) reaches its maximal level in late adolescence or early adulthood and remains stable for several years, a period is known as the plateau of lung function, before gradually declining thereafter [11]. While FEV_1 declines continuously and smoothly over an individual's life [12], evidence suggests that patients with asthma experience a more accelerated decline of up to 51.8 mL/year loss, including moderate-to-severe asthma patients treated with SoC therapies[13-15]. Some potential factors contributing to LFD may include smoking [16], recurrent exacerbations [14], and low baseline FEV_1 [17]. In the Severe Asthma Research Program (SARP) cohort, airway remodeling and hyperinflation identified by computed tomography (CT) imaging were associated with accelerated LFD [3].

Exhaled nitric oxide has demonstrated some potential utility to identify patients at greater risk of LFD. Nitric oxide, a gaseous signaling molecule generated by nitric oxide synthase (NOS), is enhanced by inflammatory stimuli. IL-4 and IL-13 stimulate the production of NO through upregulation of NOS_2 in airway epithelium, which can be measured as fractional exhaled nitric oxide fraction (FeNO) [18, 19]. Increased production of NOS_2 is associated with pro-inflammatory effects, including excess

mucus production, airway remodeling, and increased bronchoconstriction [20, 21]. High FeNO is an established marker of airway inflammation, and recent evidence suggests that airway inflammation may play an important role in the progression of airflow limitation in asthma [6, 22, 23], highlighting the potential role of FeNO as a predictor of progressive LFD [23-25]. Thus, the role of FeNO in identifying patients at risk of loss of lung function over time warrants further investigation. While there are likely environmental and innate influences on patterns of LFD, there is limited evidence from randomised controlled trials (RCTs) to support the use of biomarkers or risk factors to identify individuals at a greater risk of rapid decline.

Dupilumab may have the potential to prevent or slow the rate of LFD over time in patients with uncontrolled moderate-to-severe asthma. In the pivotal phase III 'LIBERTY ASTHMA QUEST' study, patients with asthma exposed to dupilumab sustained lung function over 52 weeks, while placebo patients exhibited 40 mL loss of post-bronchodilator (BD) FEV_1 between Week 4 and Week 52 [26]. These data suggest that dupilumab may have a long-term impact on slowing the rate of loss of lung function over time in patients with asthma. However, there remains a need for long-term studies to understand patterns of LFD, prognostic biomarkers, and potential interventional therapies for patients with moderate-to-severe asthma [10, 11].

The ATLAS (NCT05097287) is a phase III/IV randomised controlled trial designed to establish the role of dupilumab in preventing or slowing the rate of LFD over a period of 3 years versus standard-of-care in patients with moderate-to-severe type 2 asthma, as well as the potential identification of prognostic and predictive markers of LFD. Here, we describe the trial design of the ATLAS study.

METHODS

Study design and setting

ATLAS is a multinational, phase III/IV, multicenter, randomised, double-blind, placebo-controlled, and parallel-group study (Figure 1). The study will include a screening and run-in period of 4 weeks (±1 week), a treatment period of 156 weeks, and a follow-up period of up to 12 weeks.

Patients will be randomised (2:1) to receive a loading dose of dupilumab (two injections of 300 mg) subcutaneously (SC) on Day 1, followed by 300 mg every 2 weeks (q2w) or matching placebo (two injections of 2 mL) SC on Day 1, followed by one placebo injection q2w. Randomisation will be stratified by inhaled corticosteroids (ICS) dose (medium- versus high-dose), FeNO (<35 parts per billion [ppb] versus ≥35ppb), baseline blood eosinophil count (<300 cells/µL versus ≥300 cells/µL), and region.

Post treatment period, the patients will be followed up for 12 weeks or until the patients switch to commercialised dupilumab or any other biologic products, whichever comes first.

All patients will be on stable maintenance therapy with medium-to-high dose ICS with a second controller medication (for example long-acting β_2-adrenergic receptor agonists [LABA], and leukotriene receptor antagonists [LTRA]) for ≥1 month before the screening visit and during the run-in period. A third controller is also allowed but not mandatory. Background asthma therapy would be maintained at a stable dose during the study screening and treatment period unless the patient experiences 2 exacerbations within 9 months, where the background ICS dose may be increased, or additional controllers may be added (Figure 2).

Patients will be allowed to use rescue therapy (Short-acting β-agonists [SABA]) or (single maintenance and reliever therapy [SMART]) throughout the study, as needed. Patients who experience frequent exacerbations will have the opportunity to receive additional therapy based on the rescue algorithm (Figure 2).

Ethical Concerns

This study will be conducted in accordance with Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable laws and regulations (General Data Protection Regulation [GDPR]).

Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the institutional review board/independent ethics committees or study center.

Patient population

The study will include approximately 1828 adult patients (1219 in dupilumab 300mg q2w group, and 609 in placebo group) with moderate-to-severe asthma to characterize lung function decline patterns throughout adulthood. Two study populations have been defined in this trial: the primary population for evaluation will be patients with moderate-to-severe asthma with FeNO ≥35 ppb (defined as FeNO population), as there is evidence suggesting elevated FeNO levels may be associated with greater LFD [23-25], and preliminary data from QUEST suggest that 35 ppb may be an appropriate threshold to identify patients at greater risk of loss of lung function and those who may benefit the most from dupilumab treatment in terms of lung function preservation [27]. However, this threshold has not been evaluated in large-scale long-term studies. Therefore, to determine an appropriate risk threshold, this study will also recruit up to 550 patients with any FeNO levels to include a population with a wide spectrum of FeNO values to assess the role of FeNO as a predictive and prognostic marker of LFD and potentially determine a threshold to optimally identify

patients at high risk of decline. The total population will include all randomised patients, regardless of biomarker levels.

The overall study recruitment will continue until approximately 1278 patients with baseline FeNO ≥35 ppb and up to 550 patients with baseline FeNO <35 ppb at entry are randomised. The study will recruit the patients globally from over 20 countries including approximately 270 sites.

Key eligibility criteria

Patients aged ≥18 years with the diagnosis of uncontrolled moderate-to-severe asthma, pre-BD FEV_1 ≤80% of predicted normal, FeNO ≥35 ppb and asthma control questionnaire (ACQ)-5 score ≥1.5 and undergoing existing treatment with medium-to-high dose ICS in combination with a second controller will be included in the study. Patients with a history or clinical evidence of chronic obstructive pulmonary disease (COPD) and are/were current or previous smokers (>10 pack-years) will be excluded from the study. Detailed inclusion and exclusion criteria are shown in Table 1.

Study objectives

The primary objective of the study is to evaluate the efficacy of dupilumab in preventing or slowing the rate of LFD at Year 1 in the FeNO population compared with placebo (assessed by the rate of change in post-BD FEV_1). Key secondary objectives include evaluation of the effect of dupilumab in preventing LFD in Year 2 and 3, as well as long-term effects on exacerbations, asthma control, or biomarker levels. An exploratory substudy study will be conducted in up to 200 patients to assess the long-term effect of dupilumab on pathophysiological outcomes, small airways, and gene expression profiling. Detailed objectives and endpoints are shown in table 2.

Efficacy assessments

Lung function

Lung function is an important assessment in patients with respiratory diseases and aids in the diagnosis and prognosis of airway pathology. Post-bronchodilator FEV_1 is the gold standard to

evaluate LFD. This method has been used to evaluate the loss of lung function in patients with both asthma and COPD (37, 38), as obtaining FEV_1 after standardised application of a bronchodilator reduces variability compared to pre-BD measurements. This value represents maximally achieved FEV_1 at a given time. The assessment will be performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations [28, 29]. Spirometry will be performed before dupilumab administration and after withholding the standard of care asthma treatment according to their action duration. The units for spirometry outcomes will be expressed in litres (L), mililitres (ml) or percent (%) predicted.

Fractional exhaled nitric oxide (FeNO) levels

FeNO is a biomarker of type 2 inflammation used in the phenotyping of patients with asthma. This assessment should be conducted before spirometry and the patient should refrain from eating and drinking for at least 1 hour before the procedure. FeNO will be assessed through centralised monitoring.

Asthma Control Questionnaire 7 items (ACQ-7)

The ACQ measures both the adequacy of asthma control and change in asthma control which occurs either spontaneously or because of treatment, and an improvement of –0.5 is considered clinically meaningful. ACQ-7 has seven questions [30]. The participants will be asked to recall how their asthma has been during the previous week and respond to the first six questions on a 7-point scale (0 = no impairment, 6 = maximum impairment). The seventh item will be derived from FEV_1 measures evaluated on the same day as the administration of ACQ-6 (FEV_1 pre-bronchodilator, FEV_1 predicted and FEV_1 pre-BD % predicted) [31].

Asthma Quality of Life Questionnaire AQLQ(S)

The AQLQ(S) will measure the functional impairments that are most troublesome to patients as a result of their asthma. The AQLQ(S) has four domains – symptoms (12 items), activity limitation (11 items), emotional function (5 items), and environmental stimuli (4 items). A global score is calculated

ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life. The minimal clinically important difference (MCID) for AQLQ(S) is 0.5.

Severe asthma exacerbation

A severe exacerbation event during the study is defined as a deterioration of asthma requiring the use of systemic corticosteroids (SCS) for ≥3 days; or hospitalisation or emergency room visit because of asthma, requiring SCS.

Statistical analysis

A hierarchical testing procedure will be applied at a 2-sided 5% significant level, and each hypothesis will be formally tested only if the preceding one is significant at a 5% level. All efficacy analyses will be performed on the intent-to-treat (ITT -FeNO and/or ITT population) unless otherwise noted. ITT total population will include all randomised participants; the ITT-FeNO population will include all randomised participants with baseline FeNO ≥35 ppb. Participants will be analysed according to the intervention allocated by randomisation. All safety analyses will be performed on the safety population, which will include all randomised participants who take at least 1 dose of the study intervention. Participants will be analysed according to the intervention they actually received before switching to the open-label rescue group, if applicable.

Statistical inference on treatment comparisons will be derived from the mixed-effect model with repeated measurements (MMRM model). Descriptive analyses will be performed on the data collected after the participants switch to the open-label rescue group. The study is powered to detect significant differences between treatment groups in the primary endpoint for both FeNO population and total populations at >90%.

DISCUSSION

To the best of our knowledge, there is currently no evidence demonstrating the prevention of long-term loss of lung function by any asthma medication beyond one year of treatment. With the advent of multiple biologics in asthma, there is a need for long-term studies examining treatments and

outcomes in asthma that are important from a disease prognostic perspective [10, 11], including the determination of loss of pulmonary function over the long-term, which is important for individualised care to define the specific effect of an intervention and for clinical studies [10]. The ATLAS study is designed to determine the impact of dupilumab on airway remodeling and patterns of LFD in patients with moderate-to-severe type-2 asthma. This is the first trial to prospectively assess the impact of a monoclonal antibody on long-term lung function trajectories in patients with moderate-to-severe asthma, providing unique insights into disease pathophysiology and the potential role of biologics in modifying this process.

Severe airway remodeling, increased hyperinflation, and certain lung deformation gradation patterns are associated with future LFD in adult patients with asthma [3]. Progressive LFD can lead to obstructive patterns similar to COPD [32]. Structural and functional changes seen in asthma patients lead to airway narrowing, which may be driven by type 2 inflammatory cytokines such as IL-13 which promotes goblet cell hyperplasia, excess mucus production, and mucociliary dysfunction, resulting in mucus plugs and subsequent airflow obstruction [33, 34]. Airway mucus plugging is a predictive indicator of future lung function [35]. This study will explore the effect of dupilumab on airway structural changes, small airways through a wide array of imaging outcomes, as well as the association with biomarkers and transcriptome profiles.

Early identification of patients at risk of the accelerated rate of LFD is important, which could help in identifying the most suitable preventive treatment for patients with uncontrolled moderate-to-severe asthma [24]. Excessive NO synthesis is well documented in severe asthma and the Global Initiative for Asthma (GINA) recommends using FeNO levels to identify the presence of type 2 inflammation in the management of patients with uncontrolled moderate-to-severe asthma [36]. Previous studies have shown that high FeNO levels are associated with airway inflammation leading to airway remodeling, causing accelerated LFD [37-39]. A 5-year prospective study (ADONIS study) identified high levels of FeNO as a risk factor for accelerated LFD in patients with newly diagnosed

asthma [24]. Although there is evidence supporting FeNO as an airway biomarker to identify patients at risk of LFD, this hypothesis has not been tested in large clinical trials of sufficient duration. This study will evaluate the role of FeNO as a prognostic biomarker for LFD over time and also as a predictive biomarker for dupilumab impact on loss of lung function. Similarly eosinophilia is related to clinical symptoms in asthma patients [40]; further, adult-onset asthma associated with persistent eosinophilic airway inflammation may have a more rapid decline in FEV_1 [24, 41]. The ATLAS study will also enroll patients across the spectrum of baseline blood eosinophils to better evaluate the ability of these biomarkers to determine patients at risk for the more rapid decline in lung function. Inhaled corticosteroids (ICS) suppressing airway inflammation, and often normalize lung function. However, a proportion of patients remain resistant to therapy showing persistent symptoms, recurrent exacerbations, and/or persistent airflow limitation, despite using high doses of ICS and long-acting bronchodilators [6]. This can also be attributed to poor adherence to inhaled therapy, which is well known. Poor adherence is characterized by underuse of ICS or other inhaled therapy that may contribute to LFD, persistent type-2 inflammation, and elevated FeNO levels in asthma patients [42-44].

Type 2 inflammation underpins lung pathophysiology in asthma, including local IL-13 induced goblet cell hyperplasia and mucus overproduction and systemic IL-4/IL-13 induced smooth muscle proliferation, contractility, and hyperresponsiveness [45]. Dupilumab is a fully human monoclonal antibody that binds to the interleukin (IL)-4 receptor subunit alpha (IL-4Rα) thereby blocking the actions of IL-4 and IL-13 [46], which are key and central drivers of type 2 inflammation and may potentially affect airway remodeling and prevent or slow the rate of LFD associated with asthma. The slope analysis of the post-BD FEV_1 showed no loss in LFD in asthma patients who received dupilumab in the QUEST study, while lung function declined by 40 mL/year in patients who received placebo [26]. This decline is consistent with other studies including different cohorts of patients with asthma [24]. Matsunaga et al, examined the changes in FEV_1 over 3 years in patients with controlled asthma but experiencing exacerbations, where the patients with 1 exacerbation had a decline of

41.3 mL/year [13]. In a 15-year follow-up study by Lange et al, asthma patients had a decline in post-BD FEV_1 of 38 mL/year [16].

This study also has some limitations. In order to assess patterns of LFD, long-term studies following-up subjects for several years are ideal, however, due to feasibility purposes, the duration of this trial was limited to 3 years. The trial population may not be representative of broader asthma populations, such as non-type 2 patients, or those with mild asthma, therefore limiting the applicability of the findings to those patients with moderate-to-severe type 2 asthma. It is also plausible that a higher background therapy adherence could occur as part of closer monitoring in RCTs, which may potentially impact the results. Overall, this 3-year RCT will generate longitudinal data on lung function in patients with moderate-to-severe asthma, including prognostic and predictive biomarkers, the association with other clinically meaningful endpoints such as exacerbations, patient-reported outcomes, or biomarkers, and potential modification of key biologic drivers.

In summary, ATLAS is a landmark trial designed to establish dupilumab's role in preventing or slowing the long-term loss of lung function over 3 years compared with standard of care therapy, as well as its potential effect on disease modification. This trial will also evaluate patterns of lung function decline, including prognostic and predictive markers, potentially providing unique insights into asthma pathophysiology.

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Authors' contributions

All authors contributed to conception and design of the work, drafting, and revising of the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Competing interests

Lucia De Prado Gomez: Sanofi − employees, may hold stock and/or stock options in the company.

Ian Pavord: Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Sanofi/Regeneron, Teva – speaker fees; AstraZeneca, GSK, Sanofi/Regeneron, Teva – payments for organizing educational events; AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Genentech, GSK, Knopp Biosciences, Merck, Novartis, Sanofi/Regeneron, Teva – consultant fees; AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Teva – international scientific meeting sponsorship; Chiesi – research grant; GSK − payments to support FDA approval meetings; Bayer, Insmed, Merck − payments for use of the Leicester Cough Questionnaire (to which he is a co-patent holder of the rights) in clinical trials; expert witness for a patent dispute involving AstraZeneca and Teva.

William Busse: GlaxoSmithKline, Novartis, Sanofi, Teva – consultant, speaker fees.

Christopher E Brightling: Received grants and consultancy from GSK, AZ, Novartis, Chiesi, BI, Genentech, Roche, Sanofi, Regeneron, Mologic, 4DPharma paid to his Institution.

Michael E Wechsler: Consulting and honoraria from : AstraZeneca, Amgen, Glaxosmithkline, Sanofi, Regeneron, Boehringer Ingelheim, Novartis, genentech, Pulmatrix, Teva, Equillium, cytoreason , Restorbio, Cohero Health, cerecor, incyte, sound biologics, kinaset

Klaus F Rabe: AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi, Teva – consultant, speaker fees.

Mei Zhang: Sanofi – employees, may hold stock and/or stock options in the company.

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Paul J Rowe: Sanofi – employees, may hold stock and/or stock options in the company.

Table 1: Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
✓ ≥18 years of age with a diagnosis of asthma based on GINA 2021 [36] ✓ Existing treatment with medium-to-high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a second controller with a stable dose ≥1 month prior to Visit 1 (screening visit) ✓ Patients requiring a third controller for their asthma will be considered eligible and should be on a stable dose of the third controller for ≥1 month prior to Visit 1 ✓ Pre-BD FEV_1 ≤80% of predicted normal at Visit 1 and Visit 2 (Day 1 of the intervention period) ✓ Uncontrolled moderate-to-severe asthma (ACQ-5 ≥1.5) at Visit 1 and Visit 2 ✓ Exhibit bronchodilator reversibility (≥12% and 200 mL improvement in FEV_1 post-SABA administration) during screening ✓ FeNO ≥35 ppb at Visit 2 before randomisation (Up to 550 patients can be enrolled with FeNO <35 ppb at Visit 2) ✓ History of ≥1 exacerbation(s) in the previous year ✓ Capable of giving signed informed consent	✓ History or clinical evidence of COPD including ACOS or any other significant lung disease ✓ Current smoker (cigarette or e-cigarette) or cessation of smoking within 6 months before Visit 1 ✓ Previous smoker with a smoking history >10 pack-years ✓ Severe asthma exacerbation requiring treatment with SCS in the past month before Visit 1 or during the screening period ✓ Treatment with the live (attenuated) vaccine within 4 weeks before Visit 1 ✓ Any biologic therapy or any other biologic therapy/ immunosuppressant/ immunomodulators within 4 weeks before Visit 1 or five half-lives, whichever is longer ✓ Current participation in any clinical trial of an investigational drug or device or participation within three months before the screening visit or five half-lives of the investigational compound, whichever is longer ✓ Treatment with OCS for more than 2 weeks before Visit 1

ACOS, asthma COPD overlap syndrome; ACQ-5, 5-item asthma control questionnaire; BD, bronchodilators; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory

volume in 1 second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; ppb, part per billion; OCS, oral corticosteroids; SCS, systemic corticosteroids; SABA, short-acting beta-agonists

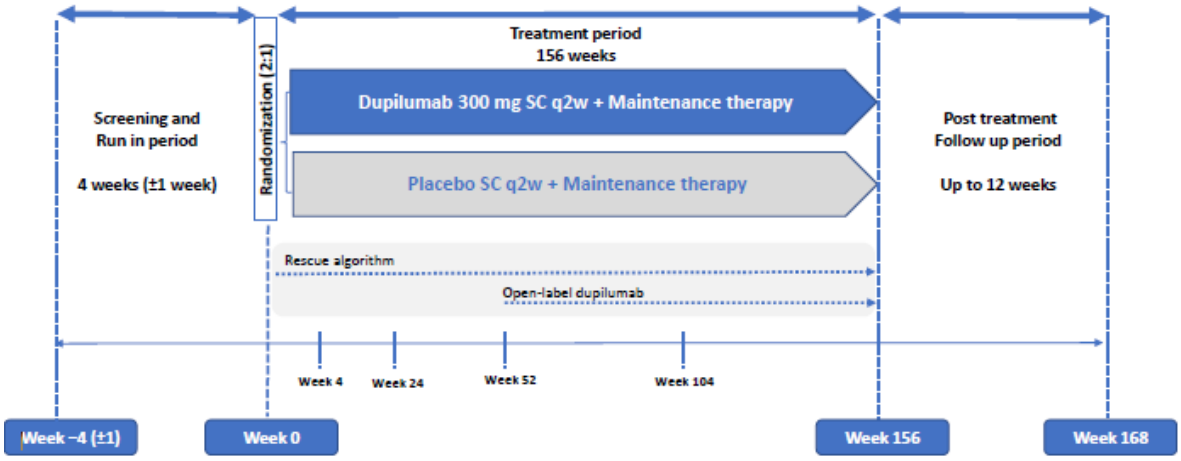
Table 2: Objectives and endpoints of the ATLAS study

Primary objectives	***Primary endpoints***
To assess the effect of dupilumab on preventing or slowing the rate of LFD at Year 1 in the FeNO population compared to placebo	Rate of change from Week 8 to Year 1 in the post-BD FEV_1 (post-BD FEV_1 slope) in the FeNO population
Key secondary objectives	***Key secondary endpoints***
To assess the effect of dupilumab on slowing the rate of LFD at Year 1 in the total population compared with placebo	Rate of change from Week 8 to Year 1 in post-BD FEV_1 (post-BD FEV_1 slope) in the total population
To assess the effect of dupilumab on slowing the rate of LFD at Year 2 in the FeNO population compared with placebo	Rate of change from Week 8 to Year 2 in post-BD FEV_1 (post-BD FEV_1 slope) in the FeNO population
Other secondary objectives	***Other secondary endpoints***
Effect of dupilumab in improving lung function parameters, exacerbations, asthma control, and biomarker levels at Year 1 and Year 2 compared with placebo in the FeNO population and total population	• Change from baseline to Year 1 and Year 2 in pre-BD FEV_1, post-BD FEV_1, FeNO levels, ACQ-7, pre-BD % predicted FEV_1, and FVC • Annualised severe exacerbation rate during 1 year period in the FeNO population and total populations • Rate of change in post-BD FEV_1 from Week 8 to Year 2 (post-BD FEV_1 slope) in the total population
To evaluate the long-term effect of dupilumab in improving quality of life in Year 1 and 2 compared with placebo in the FeNO population and total population	• Change from baseline to Year 1 and Year 2 in AQLQ(S) in the FeNO population and total population
To evaluate the long-term effect of dupilumab on preventing or slowing the rate of LFD by Year 3 compared with placebo in the FeNO population and total population	• Rate of change in post-BD FEV_1 from Week 8 to Year 3 (post-BD FEV_1 slope) in the FeNO population and total population
Exploratory objectives	
To explore the effect of dupilumab on airway structural changes, small airways, and gene expression profiling in the FeNO population (substudy in approximately 200 patients)	• Change from baseline to Year 1, Year 2, and Year 3 in airway resistance from R5 to R20 (resistance at 5 and 20 Hz) measured by FOT and Imaging parameters using high-resolution CT scans and mucus plugs in FeNO population • Nasal brushing and secretion profiling, including transcriptomics and proteomics

	at baseline and Weeks 8, to Year 1, Year 2, and Year 3 in the FeNO population
Safety objectives	***Safety endpoints***
To evaluate the safety of dupilumab	• Incidence of TEAEs and SAEs • Incidence of AESIs

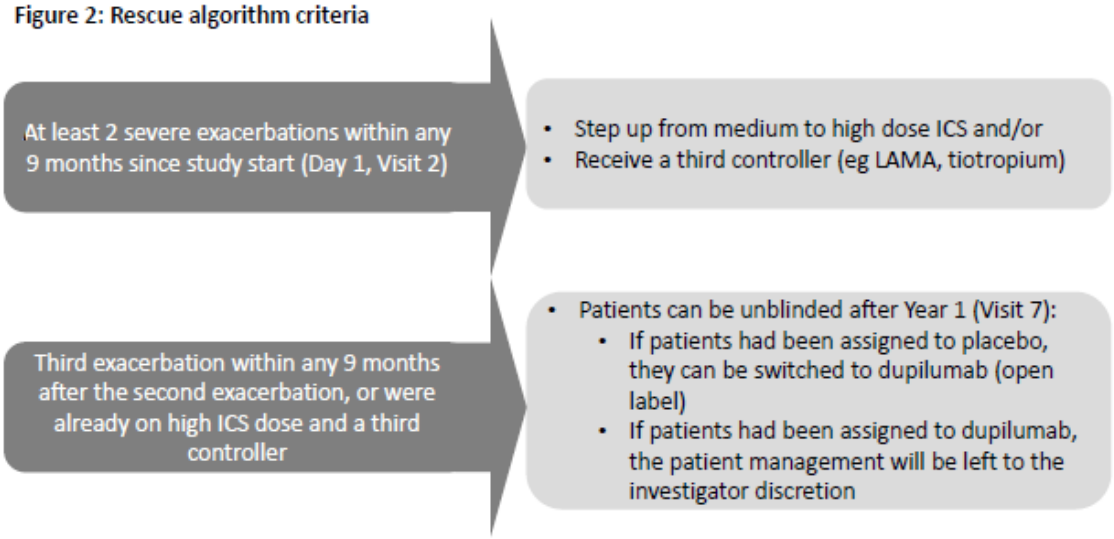
ACQ-7, 7-item Asthma Control Questionnaire; AESIs, adverse events of special interest; AQLQ(S), Asthma Quality of Life Questionnaire with standardised activities; BD, bronchodilators; CT, computerised tomography; FeNO, fractional exhaled nitric oxide; FOT, forced oscillometry technique; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LFD, lung function decline; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events

Figure 1: Study design of the ATLAS trial



q2w, every 2 weeks; SC, subcutaneous

Figure 2: Rescue algorithm criteria



ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonist.

Timeframe of 9 months for the occurrence of exacerbations has been selected to avoid the potential seasonal effect on exacerbations in a broader timeframe.

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