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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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 https://bit.ly/3D5BCFQ

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Abstract

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 COPD. 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 (clinicaltrials.gov identifier NCT05097287) is a randomised, double-blind, placebo-controlled, multicentre study that will include adult patients with uncontrolled moderate-to-severe asthma. ~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 the exhaled nitric oxide fraction (F_{eNO}) population (patients with F_{eNO} ⩾35 ppb). The effect of dupilumab in slowing the rate of LFD by year 2 and year 3 in both F_{eNO} and total populations, exacerbations, asthma control, quality of life, biomarker changes and utility of F_{eNO} 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.

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 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 are limited data to identify patients with asthma who are at increased risk of LFD [10]. In healthy individuals, forced expiratory volume in 1 s (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^{-1} loss, including moderate-to-severe asthma patients treated with standard-of-care 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 cohort, airway remodelling and hyperinflation identified using computed tomography 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 signalling molecule generated by nitric oxide synthase (NOS), is enhanced by inflammatory stimuli. Interleukin (IL)-4 and IL-13 stimulate the production of nitric oxide through upregulation of NOS2 in airway epithelium, which can be measured as fractional exhaled nitric oxide fraction (F_{eNO}) [18, 19]. Increased production of NOS2 is associated with pro-inflammatory effects, including excess mucus production, airway remodelling and increased bronchoconstriction [20, 21]. High F_{eNO} 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 F_{eNO} as a predictor of progressive LFD [23–25]. Thus, the role of F_{eNO} 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 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 (clinicaltrials.gov identifier NCT05097287) is a phase III/IV RCT 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, multicentre, 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 on day 1, followed by 300 mg every 2 weeks or matching placebo (two injections of 2 mL) *s.c.* on day 1, followed by one placebo injection every 2 weeks. Randomisation will be stratified by inhaled corticosteroid (ICS) dose (medium *versus* high dose), F_{eNO} (<35 ppb *versus* ⩾35 ppb), baseline blood eosinophil count (<300 cells·µL^{-1} *versus* ⩾300 cells·µL^{-1}) 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 therapies, whichever comes first.

All patients will be on stable maintenance therapy with medium-to-high dose ICS with a second controller medication (*e.g.* long-acting β_2-adrenergic receptor agonists and leukotriene receptor antagonists) for ⩾1 month before the screening visit and during the run-in period. A third controller is 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 two exacerbations within 9 months, where the background ICS dose may be increased, or additional controllers may be added (figure 2).

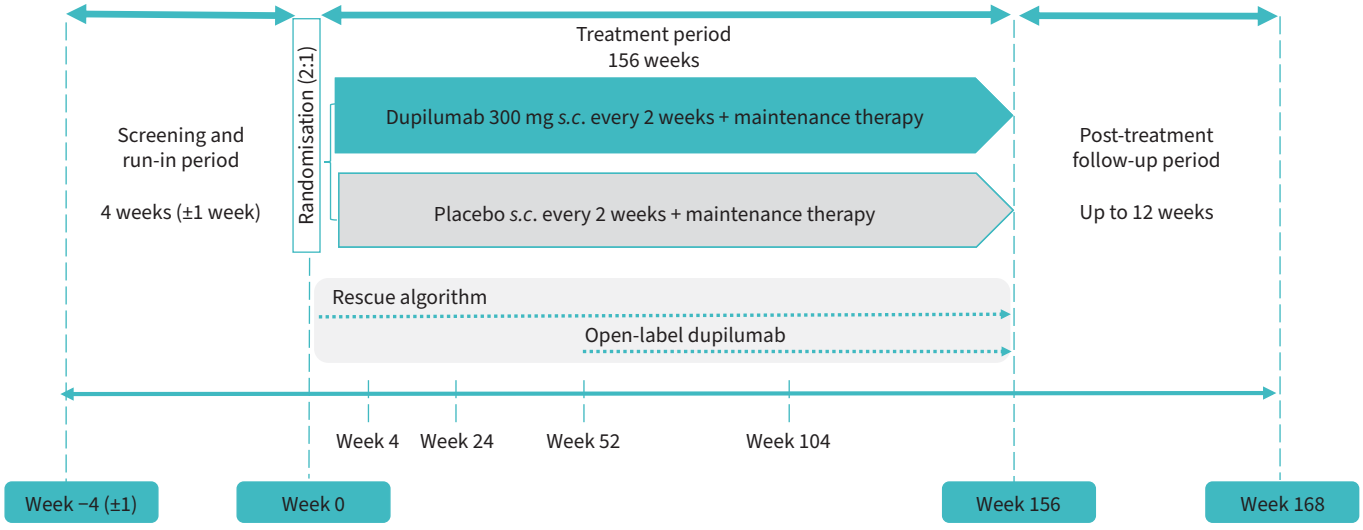

FIGURE 1 Study design of the ATLAS trial.

Patients will be allowed to use rescue therapy (short-acting β-agonists) or single maintenance and reliever therapy 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 Organizations of Medical Sciences international ethical guidelines, applicable International Council for Harmonisation (ICH) good clinical practice 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 Title 21 of the United States Code of Federal Regulations part 50, local regulations, ICH guidelines, privacy and data protection requirements including those of the GDPR and French law, Health Insurance Portability and Accountability Act requirements, where applicable, and the institutional review boards/independent ethics committees of the study centres.

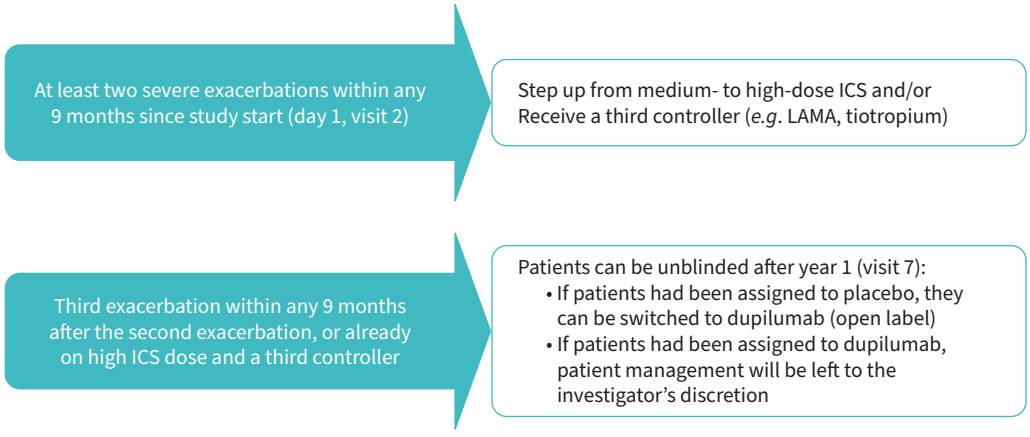

FIGURE 2 Rescue algorithm criteria. The time frame of 9 months for the occurrence of exacerbations has been selected to avoid the potential seasonal effect on exacerbations in a broader time frame. ICS: inhaled corticosteroids; LAMA: long-acting muscarinic antagonist.

Patient population

The study will include ∼1828 adult patients (1219 in the dupilumab 300 mg every 2 weeks group, and 609 in the placebo group) with moderate-to-severe asthma to characterise 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 F_{eNO} ⩾35 ppb (defined as the F_{eNO} population), as there is evidence suggesting elevated F_{eNO} 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 F_{eNO} levels to include a population with a wide spectrum of F_{eNO} values to assess the role of F_{eNO} 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 ∼1278 patients with baseline F_{eNO} ⩾35 ppb and up to 550 patients with baseline F_{eNO} <35 ppb at entry are randomised. The study will recruit the patients globally from >20 countries including ∼270 sites.

Key eligibility criteria

Patients aged ⩾18 years with the diagnosis of uncontrolled moderate-to-severe asthma, pre-bronchodilator FEV_1 ⩽80% predicted, F_{eNO} ⩾35 ppb and five-item 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 COPD and who 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 F_{eNO} population compared with placebo (assessed by the rate of change in post-bronchodilator 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 will be conducted in up to 200 patients to assess the long-term

TABLE 1 Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
Age ⩾18 years with a diagnosis of asthma based on GINA 2021 [28]	History or clinical evidence of COPD including ACOS or any other significant lung disease
Existing treatment with medium- to high-dose ICS (⩾250 μg fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 $\mu g \cdot day^{-1}$ of fluticasone propionate or equivalent) in combination with a second controller with a stable dose ⩾1 month prior to visit 1 (screening visit)	Current smoker (cigarette or e-cigarette) or cessation of smoking within 6 months before visit 1
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	Previous smoker with a smoking history >10 pack-years
Pre-BD FEV_1 ⩽80% predicted at visit 1 and visit 2 (day 1 of the intervention period)	Severe asthma exacerbation requiring treatment with SCS in the past month before visit 1 or during the screening period
Uncontrolled moderate-to-severe asthma (ACQ-5 ⩾1.5) at visit 1 and visit 2	Treatment with a live (attenuated) vaccine within 4 weeks before visit 1
Exhibit BD reversibility (⩾12% and 200 mL improvement in FEV_1 post-SABA administration) during screening	Any biologic therapy or any other biologic therapy/immunosuppressant/ immunomodulators within 4 weeks before visit 1 or five half-lives, whichever is longer
F_{eNO} ⩾35 ppb at visit 2 before randomisation (up to 550 patients can be enrolled with F_{eNO} <35 ppb at visit 2)	Current participation in any clinical trial of an investigational drug or device or participation within 3 months before the screening visit or five half-lives of the investigational compound, whichever is longer
History of ⩾1 exacerbation(s) in the previous year	Treatment with OCS for >2 weeks before visit 1
Capable of giving signed informed consent	

GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; ACQ-5: five-item Asthma Control Questionnaire; SABA: short-acting β-agonist; F_{eNO}: fractional exhaled nitric oxide; ACOS: asthma–COPD overlap syndrome; SCS: systemic corticosteroids; OCS: oral corticosteroids.

effect of dupilumab on pathophysiological outcomes, small airways and gene expression profiling. Detailed objectives and end-points 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 [29, 30], as obtaining FEV_1 after standardised application of a bronchodilator reduces variability compared to pre-bronchodilator measurements. This value represents maximally achieved FEV_1 at a given time. The assessment will be performed in accordance with the European Respiratory Society/American Thoracic Society recommendations [31, 32]. Spirometry will be performed before dupilumab administration and after withholding the standard-of-care asthma treatment according to their duration of action. The units for spirometry outcomes will be expressed in litres, millilitres or % predicted.

F_{eNO} levels

F_{eNO} 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 $\geqslant$1 h before the procedure. F_{eNO} will be assessed through centralised monitoring.

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 [33]. The participants will be asked to recall how their asthma has been during

TABLE 2 Objectives and end-points of the ATLAS study

	Objectives	End-points
Primary	To assess the effect of dupilumab on preventing or slowing the rate of LFD at year 1 in the F_{eNO} 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 F_{eNO} population
Key secondary	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 F_{eNO} 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 F_{eNO} population
Other secondary	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 F_{eNO} population and total population	Change from baseline to year 1 and year 2 in pre-BD FEV_1, post-BD FEV_1, F_{eNO} levels, ACQ-7, pre-BD FEV_1 % predicted and FVC
		Annualised severe exacerbation rate during 1-year period in the F_{eNO} 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 F_{eNO} population and total population	Change from baseline to year 1 and year 2 in AQLQ(S) in the F_{eNO} 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 F_{eNO} 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 F_{eNO} population and total population
Exploratory	To explore the effect of dupilumab on airway structural changes, small airways and gene expression profiling in the F_{eNO} population (substudy in ~200 patients)	Change from baseline to year 1, year 2 and year 3 in airway resistance at 5 Hz to airway resistance at 20 Hz measured by FOT and imaging parameters using high-resolution CT scans and mucus plugs in F_{eNO} 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 F_{eNO} population
Safety	To evaluate the safety of dupilumab	Incidence of TEAEs and SAEs
		Incidence of AESIs

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

the previous week and respond to the first six questions on a seven-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-7 (FEV_1 pre-bronchodilator, FEV_1 % predicted and FEV_1 pre-bronchodilator % predicted) [34].

Asthma Quality-of-Life Questionnaire with standardised activities

The Asthma Quality-of-Life Questionnaire with standardised activities (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 (five items) and environmental stimuli (four items). A global score is calculated ranging from 1 to 7 and scored by domain. Higher scores indicate better quality of life. The minimal clinically important difference 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 two-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 intention-to-treat (ITT-F_{eNO} and/or ITT population) unless otherwise noted. The ITT total population will include all randomised participants; the ITT-F_{eNO} population will include all randomised participants with baseline F_{eNO} ⩾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 one 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. 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 end-point for both the F_{eNO} 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 1 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 remodelling 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 remodelling, 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 [35]. 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 [36, 37]. Airway mucus plugging is a predictive indicator of future lung function [38]. 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 nitric oxide synthesis is well documented in severe asthma and the Global Initiative for Asthma recommends using F_{eNO} levels to identify the presence of type-2 inflammation in the management of patients with uncontrolled moderate-to-severe asthma [28]. Previous studies have shown that high F_{eNO} levels are associated with airway inflammation leading to airway remodelling, causing accelerated LFD [39–41]. A 5-year prospective study (ADONIS study) identified high levels of F_{eNO} as a risk factor for

accelerated LFD in patients with newly diagnosed asthma [24]. Although there is evidence supporting F_{eNO} 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 F_{eNO} 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 [42]; furthermore, adult-onset asthma associated with persistent eosinophilic airway inflammation may have a more rapid decline in FEV_1 [24, 43]. The ATLAS study will also enrol 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.

ICS suppress airway inflammation and often normalise 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 characterised by underuse of ICS or other inhaled therapy that may contribute to LFD, persistent type-2 inflammation and elevated F_{eNO} levels in asthma patients [44–46].

Type-2 inflammation underpins lung pathophysiology in asthma, including local IL-13-induced goblet cell hyperplasia and mucus overproduction and systemic IL-4/-13-induced smooth muscle proliferation, contractility and hyperresponsiveness [47]. Dupilumab is a fully human monoclonal antibody that binds to the IL-4 receptor subunit α, thereby blocking the actions of IL-4 and IL-13 [48], which are key and central drivers of type-2 inflammation and may potentially affect airway remodelling and prevent or slow the rate of LFD associated with asthma. The slope analysis of the post-bronchodilator FEV_1 showed no loss in LFD in asthma patients who received dupilumab in the QUEST study, while lung function declined by 40 $mL \cdot year^{-1}$ in patients who received placebo [26]. This decline is consistent with other studies including different cohorts of patients with asthma [24]. Matsunaga *et al.* [13] examined the changes in FEV_1 over 3 years in patients with controlled asthma but experiencing exacerbations, where the patients with one exacerbation had a decline of 41.3 $mL \cdot year^{-1}$. In a 15-year follow-up study by Lange *et al.* [16], asthma patients had a decline in post-bronchodilator FEV_1 of 38 $mL \cdot year^{-1}$.

This study 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 issues, 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. In addition, it is 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 end-points 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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This study is registered at www.clinicaltrials.gov with identifier number NCT05097287. Qualified researchers may request access to patient-level data and related documents (such as the study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications). Patient-level data will be anonymised and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org/.

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Conflict of interest: L. De Prado Gomez, M. Zhang, J. Xing, J.A. Jacob-Nara and P.J. Rowe are employees of Sanofi, and may hold stock and/or stock options in the company. I. Pavord has received speaker fees from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Sanofi/Regeneron and Teva; payments for organising educational events from AstraZeneca, GSK, Sanofi/Regeneron and Teva; consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Genentech, GSK, Knopp Biosciences, Merck, Novartis, Sanofi/Regeneron and Teva; international scientific meeting sponsorship from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK and Teva; a research grant from Chiesi; and payments to support Food and Drug Administration approval meetings from GSK; payments for use of the Leicester Cough Questionnaire (of which he is a co-patent holder of the rights) in clinical trials from Bayer, Insmed and Merck. He served as an expert witness for a patent dispute involving AstraZeneca and Teva. W. Busse has received consultancy and speaker fees from GlaxoSmithKline, Novartis, Sanofi and Teva. C.E. Brightling has received grants and consultancy fees from GSK, AstraZeneca, Novartis, Chiesi, BI, Genentech, Roche, Sanofi, Regeneron, Mologic and 4DPharma, paid to his institution. M.E. Wechsler has received consulting fees and honoraria from AstraZeneca, Amgen, GlaxoSmithKline, Sanofi, Regeneron, Boehringer Ingelheim, Novartis, Genentech, Pulmatrix, Teva, Equillium, Cytoreason, Restorbio, Cohero Health, Cerecor, Incyte, Sound Biologics and Kinaset. K.F. Rabe has received consultancy and speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi and Teva.

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