Tozorakimab Phase 3 COPD Results: IL-33 Pathway Validation

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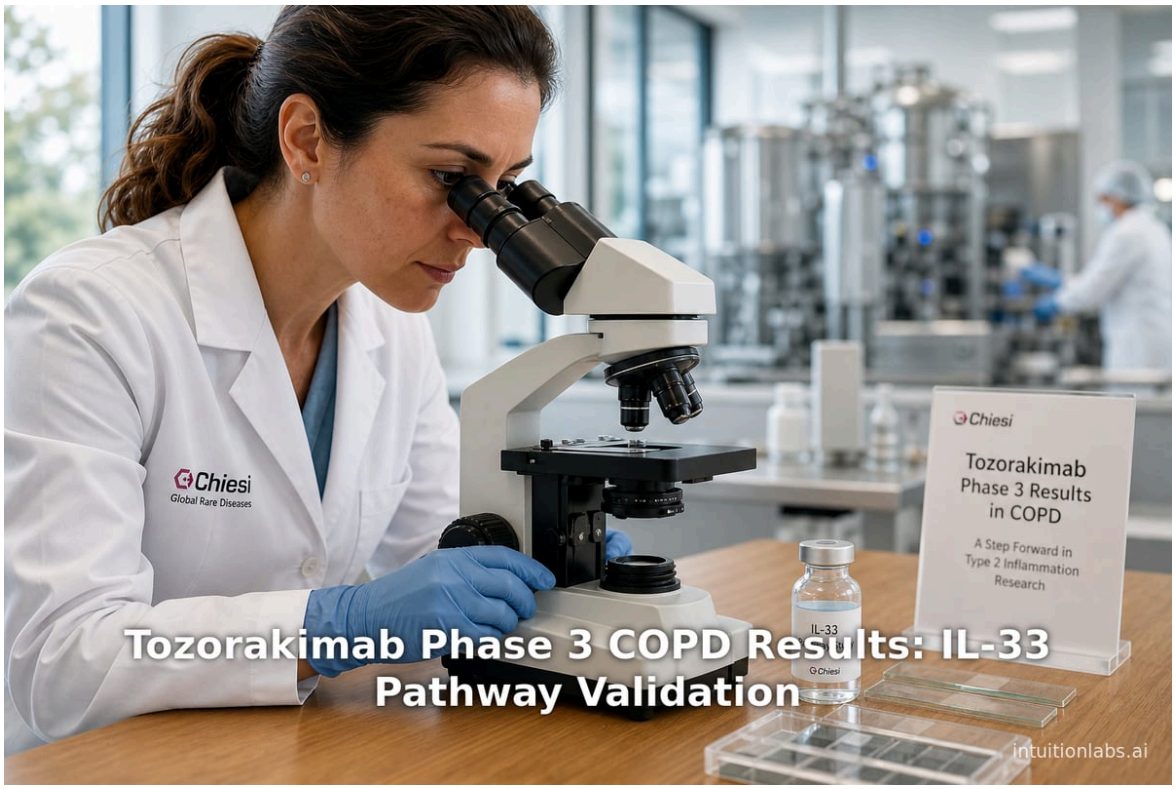

Executive Summary

The **IL-33 pathway** has emerged as a promising new target in chronic obstructive pulmonary disease (COPD), addressing a critical unmet need for more effective therapies to prevent exacerbations. In early 2026, AstraZeneca announced positive Phase III results from its *MIRANDA* trial of **tozorakimab**, a first-in-class anti–IL-33 monoclonal antibody, in patients with COPD ([1] view.news.eu.nasdaq.com) ([2] www.sec.gov). MIRANDA was the third pivotal trial, following the earlier *OBERON* and *TITANIA* trials, to show that tozorakimab significantly reduced the rate of moderate-to-severe COPD exacerbations in former smokers and in the overall COPD population ([3] markets.financialcontent.com) ([1] view.news.eu.nasdaq.com). Collectively, the successes of OBERON, TITANIA, and MIRANDA – all part of what AstraZeneca terms its **Phase III LUNA programme** – provide the first high-confidence validation that inhibiting IL-33 can deliver meaningful clinical benefit in COPD ([2] www.sec.gov) ([1] view.news.eu.nasdaq.com).

These confirmatory data position tozorakimab to potentially become the first IL-33–targeting biologic approved for COPD. The results also represent a major advance in understanding COPD pathophysiology: they **validate the IL-33 pathway as a central driver of exacerbations and disease progression** ([4] www.sec.gov) ([5] www.fiercebiotech.com). As such, tozorakimab's achievements rejuvenate a field that had seen setbacks with other IL-33/ST2 inhibitors (notably Sanofi/Regeneron's itepekimab and Roche/Amgen's astegolimab faced mixed trial outcomes in COPD).

In direct competition, Sanofi and Regeneron's **itepekimab** – another anti–IL-33 antibody – recently reported mixed Phase III COPD results. Their two pivotal AERIFY trials (AERIFY-1 and AERIFY-2) saw a statistically significant reduction in exacerbations in one trial (AERIFY-1, former smokers) but a failure to meet the primary endpoint in the other (AERIFY-2) ([6] newsroom.regeneron.com). Thus, ibutepekimab's future regulatory path remains uncertain. Taken together, the tozorakimab MIRANDA data strengthen confidence in IL-33 as a COPD target and suggest that tozorakimab may be superior in efficacy to prior IL-33/T2 biologics – a key point of comparison for clinicians and drug developers.

This report provides an in-depth analysis of the scientific background, clinical trial evidence, and competitive landscape surrounding IL-33 blocking therapies in COPD as of May 2026. We examine the biology of IL-33 in lung disease, the design and outcomes of major trials (including Phase III 'LUNA' trials and the AERIFY trials), and the implications for future development. We also compare AstraZeneca's **LUNA programme** of tozorakimab trials against Sanofi/Regeneron's itepekimab studies, and discuss what these developments mean for patients, regulators, and the respiratory drug market. All statements are supported by rigorous data from clinical trial reports, peer-reviewed studies, and expert commentary ([1] view.news.eu.nasdaq.com) ([6] newsroom.regeneron.com) ([7] pmc.ncbi.nlm.nih.gov).

Introduction

COPD is a progressive, inflammatory lung disease characterized by airflow limitation and a high burden of exacerbations. It affects about *400 million* people worldwide and is the third leading cause of death globally ([8] markets.financialcontent.com) ([9] www.sciencedirect.com). COPD exacerbations – acute worsenings often triggered by infections or pollutants – accelerate lung function decline and are strongly linked to mortality: only about half of COPD patients survive beyond 3–4 years after a severe exacerbation ([10] view.news.eu.nasdaq.com) ([8] markets.financialcontent.com). Despite use of best available inhaled therapies (including long-acting bronchodilators and steroids), many patients continue to suffer frequent exacerbations ([8] markets.financialcontent.com) ([9] www.sciencedirect.com). This "residual risk" of flare-ups is a major unmet medical need, because exacerbations drive hospitalizations, cardiovascular events, and death ([10] view.news.eu.nasdaq.com) ([8] markets.financialcontent.com).

Biologic therapies have transformed the management of asthma, another airway disease, but efforts to develop biologics for COPD have been challenging. Early trials of anti–IL-5 (e.g. mepolizumab), anti–IL-4/13 (e.g. dupilumab), and other monoclonal antibodies showed only modest effects in selected COPD subgroups. Notably, in 2024 the U.S. Food

and Drug Administration (FDA) approved **dupilumab** (a blocking antibody to the IL-4/IL-13 receptor) for a subset of patients with eosinophilic COPD, marking the first biologic ever approved for COPD ([11] www.fiercebiotech.com). Dupilumab's success validated the pathogenic role of type 2 inflammation in a COPD subset, but left wide gaps: *most* COPD patients are non-eosinophilic and still unaddressed by targeted therapies.

Enter **IL-33**: a cytokine of the IL-1 family that has gained prominence as a key early amplifier of inflammation. IL-33 is expressed constitutively in epithelial and endothelial cells and released upon tissue injury ([12] pmc.ncbi.nlm.nih.gov) ([13] www.sciencedirect.com). In the lung, IL-33 is released from airway epithelial cells during insults (viral infections, smoke, repair processes) ([12] pmc.ncbi.nlm.nih.gov) ([14] www.sciencedirect.com).Once in the tissue, IL-33 can trigger broad immune responses by binding its receptor ST2 on various immune cells (innate lymphoid cells, T cells, mast cells, eosinophils, etc.) ([12] pmc.ncbi.nlm.nih.gov) ([15] www.sciencedirect.com). This leads to production of cytokines (IL-4, IL-5, IL-13, interferon-γ, etc.) and recruitment of inflammatory cells that contribute to airway hyperresponsiveness, mucus production, and fibrosis. In COPD specifically, elevated IL-33 levels have been detected in airway samples, especially during exacerbations or in former smokers ([12] pmc.ncbi.nlm.nih.gov) ([14] www.sciencedirect.com), suggesting IL-33 contributes to exacerbation pathology and chronic inflammation.

Crucially, IL-33 can exist in two forms: a **reduced (IL-33^red)** form that signals classically via ST2, and an **oxidized (IL-33^ox)** form that has distinct activity. Recent research, including AstraZeneca's own investigations, shows that **oxidized IL-33 can drive airway epithelial dysfunction and mucus hypersecretion via an ST2-independent pathway involving the receptor for advanced glycation end-products (RAGE) coupled with EGFR** ([12] pmc.ncbi.nlm.nih.gov) ([16] pmc.ncbi.nlm.nih.gov). In other words, oxidized IL-33 engages a separate inflammatory cascade linked to remodeling and mucosal barrier breakdown. This dual signaling mechanism prompted AstraZeneca to design **tozorakimab** to block *both* IL-33^red and IL-33^ox activities ([7] pmc.ncbi.nlm.nih.gov), distinguishing it biologically from antibodies targeting only ST2 or only IL-33^red.

Against this backdrop, two pharmaceutical collaborations launched IL-33 blockade programs for COPD: AstraZeneca (via MedImmune, referring to tozorakimab as MEDI3506) and Sanofi/Regeneron (itepekimab). AstraZeneca's program, branded internally as the **LUNA programme**, spans multiple phase 3 trials in COPD (OBERON, TITANIA, PROSPERO, and MIRANDA) ([17] www.sec.gov). Sanofi/Regeneron's program (AERIFY-1, -2, etc.) has tested itepekimab in former smokers. Also, Roche/Amgen developed an anti-ST2 antibody astegolimab and conducted COPD trials with that agent. Over the past few years, these efforts generated a mixture of signals: a phase II study of tozorakimab (FRONTIER-4) showed hints of benefit in ex-smokers ([18] thorax.bmj.com), Regeneron's AERIFY-1 was positive in former smokers ([6] newsroom.regeneron.com) while AERIFY-2 failed, and astegolimab's initial results were inconclusive ([19] www.fiercebiotech.com) ([20] www.sciencedirect.com).

The **current state (April 2026)** is transformative: the landmark OBERON and TITANIA trials, reported in March 2026, were the first to show *statistically significant and clinically meaningful reductions* in COPD exacerbations with an IL-33–targeting biologic ([3] markets.financialcontent.com). In April 2026, AstraZeneca followed with MIRANDA, confirming the benefit in a third trial ([1] view.news.eu.nasdaq.com). Meanwhile, Itepekimab's AERIFY-1 had shown a 27% exacerbation reduction in former smokers ($p<0.05$) ([6] newsroom.regeneron.com), but AERIFY-2 failed, leaving its development in flux pending regulatory advice ([6] newsroom.regeneron.com) ([21] www.fiercebiotech.com).

These developments collectively validate the concept of IL-33 blockade in COPD: to date, no other biologic has achieved consistent efficacy across multiple trials in a broad COPD population ([12] pmc.ncbi.nlm.nih.gov) ([5] www.fiercebiotech.com). AstraZeneca and the field now contend with moving from "first positive trials" to "available therapy": tozorakimab could become a **first-in-class IL-33 inhibitor for COPD**, entering regulatory filings as early as 2026/2027 ([22] view.news.eu.nasdaq.com) ([21] www.fiercebiotech.com). In parallel, Sanofi/Regeneron must decide whether to pursue itepekimab's approval based on the single positive trial or to plan additional studies ([23] www.fiercebiotech.com).

In this report, we dissect the underlying science of IL-33 in COPD, review the clinical trial evidence for tozorakimab and its competitors (especially itepekimab), and evaluate the LUNA programme's strategy versus Sanofi/Regeneron's. We analyze trial designs, patient selection, efficacy outcomes (with data and statistics), and safety results. We explore how

different IL-33 blockers compare mechanistically and clinically, drawing on structural studies, genetic efficiency studies, and expert commentary. Finally, we discuss implications for clinical practice, future research (including other IL-33-related diseases, e.g. asthma or viral pneumonia), and the likely trajectory of IL-33–targeted therapies in respiratory medicine. All claims are supported by data from primary sources or peer-reviewed publications ([24] www.sec.gov) ([25] pubmed.ncbi.nlm.nih.gov) ([6] newsroom.regeneron.com).

IL-33 Biology and Role in COPD

Interleukin-33 (IL-33) is an **alarmin cytokine** of the IL-1 family, normally sequestered in cell nuclei and released upon cell damage or stress ([12] pmc.ncbi.nlm.nih.gov). Once outside cells, IL-33 acts as a danger signal to initiate and amplify immune responses. The canonical IL-33 receptor is **ST2** (also known as IL1RL1), expressed on many immune cells, including type 2 innate lymphoid cells (ILC2s), T helper 2 (Th2) cells, mast cells, eosinophils, and macrophages. IL-33 binding to membrane-bound ST2 triggers MyD88-dependent signaling and NF-κB activation, leading to Th1 and Th2 cytokine production (e.g. IL-13, IL-5, interferon-γ), and recruitment of inflammatory cells ([12] pmc.ncbi.nlm.nih.gov) ([15] www.sciencedirect.com). In parallel, cells release a decoy form, soluble ST2, that can sequester IL-33 and damp down inflammation ([15] www.sciencedirect.com).

In the healthy lung, IL-33 is thought to play roles in tissue repair and homeostasis, but in **chronic airway disease** it becomes pathogenic. In asthma, IL-33 is well-established as a driver of type 2 inflammation; accordingly, multiple anti–IL-33 or anti-ST2 drugs have been tested in asthma. Recent data implicate IL-33 in COPD as well. Studies have shown that patients with COPD (especially former smokers) have elevated IL-33 levels in lung tissue and sputum compared to controls ([14] www.sciencedirect.com). IL-33 can be induced by cigarette smoke exposure or viral infection; for example, rhinovirus infection boosts IL-33 in airway cells, contributing to exacerbation severity ([14] www.sciencedirect.com). In animal models, knocking out IL-33 or blocking ST2 can reduce smoke-induced airway inflammation, emphysema, and mucus production, further implicating the axis in COPD pathology.

A key insight in recent years is that IL-33 exists in two functionally distinct redox states. **Reduced IL-33 (IL-33^red)** is the active form that binds ST2 on immune cells. However, IL-33 is an “alarmin” that can be rapidly oxidized in the extracellular milieu. **Oxidized IL-33 (IL-33^ox)**, formed by disulfide bonding, cannot bind ST2 but instead triggers a different pathway: IL-33^ox engages a complex of RAGE (Receptor for Advanced Glycation End-products) and EGFR (Epidermal Growth Factor Receptor) on epithelial cells ([7] pmc.ncbi.nlm.nih.gov). This RAGE/EGFR signaling leads to mucin gene expression, epithelial barrier disruption, and remodeling – all processes that contribute to COPD progression ([7] pmc.ncbi.nlm.nih.gov) ([26] pmc.ncbi.nlm.nih.gov). In effect, IL-33^ox drives non–Th2 inflammation centered on airway structural cells.

AstraZeneca scientists characterized this dual mechanism in detail. Tozorakimab, originally MEDI3506, was selected as an antibody with extremely high affinity for IL-33^red (sub-picomolar) and a very fast on-rate ([7] pmc.ncbi.nlm.nih.gov). In preclinical studies, tozorakimab potently neutralized IL-33–driven ST2-dependent inflammation in human cells and animal models. Crucially, tozorakimab also **prevented the oxidative inactivation of IL-33 and its RAGE-mediated effects**, thereby “increasing epithelial cell migration and repair” in vitro ([16] pmc.ncbi.nlm.nih.gov). Its dual mechanism—blocking both IL-33^red→ST2 and IL-33^ox→RAGE/EGFR pathways—distinguishes it from other IL-33/ST2 inhibitors. These properties have been documented in peer-reviewed immunology research ([7] pmc.ncbi.nlm.nih.gov) ([16] pmc.ncbi.nlm.nih.gov) and cited in AstraZeneca’s trial announcements ([4] www.sec.gov) ([7] pmc.ncbi.nlm.nih.gov).

The involvement of IL-33 in COPD is further supported by human genetics. A large genetic association study conducted alongside a phase 2 trial of itepekimab found that **IL33 gene variants influence COPD risk** ([25] pubmed.ncbi.nlm.nih.gov). Specifically, loss-of-function mutations in IL33 were linked to a lower incidence of COPD, while gain-of-function IL33 or IL1RL1 variants increased COPD risk ([25] pubmed.ncbi.nlm.nih.gov). This genetic evidence parallels findings in asthma and underscores that the IL-33/ST2 axis is not merely correlated with COPD but may have a causal role in disease

pathogenesis. Thus, both **bio-molecular data and human genetics validate IL-33 as a drug target** in COPD ([25] pubmed.ncbi.nlm.nih.gov) ([12] pmc.ncbi.nlm.nih.gov).

Given this biology, inhibiting IL-33 signaling holds several theoretical benefits in COPD: reducing chronic airway inflammation (via ST2 blockade), lowering type 2 and type 1 immune activation, and also addressing the tissue remodeling and mucus hypersecretion driven by oxidized IL-33. ([7] pmc.ncbi.nlm.nih.gov) ([26] pmc.ncbi.nlm.nih.gov) By targeting an "upstream" alarmin, an IL-33 blocker like tozorakimab could simultaneously suppress multiple arms of the COPD immune response, in contrast to more downstream targets (e.g. eosinophils only) that benefit smaller subsets of patients.

Biologics Targeting IL-33/ST2 in COPD

Several monoclonal antibodies have been developed to target the IL-33 pathway in respiratory diseases. The strategies differ in whether they bind IL-33 itself or its receptor ST2, and in their epitopes and effects on IL-33^ox. The main players in COPD drug development are:

- **Tozorakimab (MEDI3506, AstraZeneca)**: a fully human IgG designed to bind IL-33 directly at an epitope that overlaps its receptor-binding region. Importantly, tozorakimab can neutralize both IL-33^red and prevent formation of IL-33^ox. AstraZeneca's structure–function studies showed that tozorakimab binds IL-33 with femtomolar affinity and a rapid on-rate, comparable to natural soluble ST2 ([7] pmc.ncbi.nlm.nih.gov). By occupying IL-33, tozorakimab blocks subsequent ST2 signaling and also prevents IL-33 oxidation, thereby blocking the RAGE/EGFR pathway as well ([16] pmc.ncbi.nlm.nih.gov). In effect, it is a "dual-action" inhibitor of the IL-33 axis. Tozorakimab is administered subcutaneously and has been tested with dosing regimens of 300–600 mg every 2 or 4 weeks.
- **Itepekimab (REGN3500/SAR445229, Sanofi/Regeneron)**: a fully human IgG antibody that binds IL-33. It was discovered via Regeneron's VelocImmune platform ([27] newsroom.regeneron.com). Itepekimab's epitope is distinct from tozorakimab's (see below) and it primarily blocks the interaction of IL-33^red with ST2. It is not explicitly described to neutralize oxidized IL-33 or RAGE-related functions. Itepekimab has been studied subcutaneously at doses of 300 mg every 2 or 4 weeks. In addition to COPD, itepekimab is being evaluated in chronic rhinosinusitis with nasal polyps, bronchiectasis, and other IL-33–associated conditions ([28] newsroom.regeneron.com).
- **Astegolimab (RO7129670/MSTT1041A, Roche)**: an IgG2 antibody that targets the ST2 receptor itself rather than IL-33 ligand. By binding ST2, astegolimab blocks IL-33 signaling (and also blocks other IL-1 family ligands that use IL-33R mouse, though IL-33 is its only known ligand) ([29] www.fiercebiotech.com) ([15] www.sciencedirect.com). Astegolimab is given subcutaneously (e.g. 490 mg monthly in trials) and has advanced in asthma (Phase II/III) and COPD programs. It does not directly interact with IL-33^ox; any effect on RAGE/EGFR would be indirect (by reducing overall IL-33 activity, possibly lowering release). Astegolimab showed encouraging results in Phase II asthma and an exploratory COPD trial.
- **Other agents**: Several earlier candidates targeted IL-33 or ST2 but have not progressed. For example, Genentech originally licensed astegolimab (from Amgen) and also investigated an IL-33–trap molecule (REGN-L932, but that was discontinued). To date, only the above three have reached advanced stages in COPD. (One other: Regeneron's pursuit of RG6159, but that was essentially itepekimab.)

These biologics differ in their "mechanistic niche":

- **Epitope and oxidation**: The most striking distinction is that tozorakimab uniquely stabilizes IL-33 to prevent its oxidation. Structural studies published in 2026 highlight that tozorakimab and itepekimab bind two different epitopes on IL-33 ([30] pubmed.ncbi.nlm.nih.gov). In effect, tozorakimab's epitope overlaps regions required for the RAGE/EGFR interaction, while itepekimab's epitope may not ([7] pmc.ncbi.nlm.nih.gov). Consequently, tozorakimab can *prevent* IL-33^red from converting to IL-33^ox, whereas itepekimab likely only neutralizes IL-33 after release (and may not capture oxidized form). Thus, tozorakimab has a biochemical advantage in theory. (This is supported by preclinical data and emerging structural insights ([7] pmc.ncbi.nlm.nih.gov) ([30] pubmed.ncbi.nlm.nih.gov).)

- **Target versus receptor**: Itepekimab and tozorakimab both target IL-33 ligand albeit differently, while astegolimab targets the receptor ST2. Blocking ST2 (with astegolimab) will inhibit IL-33^red effects, but cannot prevent IL-33^ox binding to RAGE (since that pathway bypasses ST2). Conversely, blocking IL-33 ligand (with tozorakimab) will block both ST2 and RAGE pathways, as long as binding affinity is high. This conceptual difference has practical implications: an anti-ST2 like astegolimab may not address non–ST2 IL-33 activities, whereas a potent anti–IL-33^ox-blocker like tozorakimab could influence both arms of the IL-33 response ([7] pmc.ncbi.nlm.nih.gov) ([29] www.fiercebiotech.com).

- **Inflammatory phenotype**: All three biologics reduce IL-33 signaling, which may dampen type 2 inflammation (IL-5, IL-13). However, IL-33 is also implicated in type 1 pathways; it can promote interferon-γ and other Th1 cytokines through macrophages. Whether blocking IL-33 has more effect on eosinophilic COPD or more neutrophilic COPD is still under study. Notably, AztraZeneca's Sciurba noted that tozorakimab's benefit appeared across *all* patients irrespective of baseline blood eosinophil count ([31] view.news.eu.nasdaq.com), suggesting IL-33 actions go beyond classic eosinophilic disease. In contrast, initial analyses of itepekimab hinted that ex-smokers benefited most, while current smokers did not ([32] pubmed.ncbi.nlm.nih.gov), implying a phenotypic distinction.

The following table summarizes key features of leading IL-33 pathway biologics and their COPD programs:

Drug	Developer(s)	Target	Mechanism	Route & Dose	Phase (Indication)	COPD Trials & Status
Tozorakimab (MEDI3506)	AstraZeneca (MedImmune)	IL-33 (ligand)	Binds IL-33, blocks IL-33^red→ST2 and IL-33^ox→RAGE pathways ([7] pmc.ncbi.nlm.nih.gov) ([4] www.sec.gov)	SC, 300–600 mg Q2W or Q4W	Phase III (COPD); also in development for severe viral lung disease and asthma ([33] news.cision.com) ([34] www.sec.gov)	Phase III "LUNA" programme (OBERON, TITANIA, PROSPERO, MIRANDA) – **all 3 reported pivotal trials (OBERON/TITANIA/MIRANDA) met primary endpoint of reducing COPD exacerbations** ([3] markets.financialcontent.com) ([1] view.news.eu.nasdaq.com). Tozorakimab has Fast Track designation for COPD and viral LRTI (FDA) ([35] news.cision.com).
Itepekimab (SAR445229, REGN3500)	Sanofi/Regeneron	IL-33 (ligand)	Binds IL-33, blocks IL-33^red→ST2 signaling (epitope differs from tozorakimab) ([27] newsroom.regeneron.com)	SC, 300 mg Q2W or Q4W	Phase III (COPD, asthma, CRSwNP, bronchiectasis)	Phase III AERIFY program in COPD (former smokers): AERIFY-1 met primary endpoint with ~27% exacerbation reduction (former smokers) ([36] newsroom.regeneron.com); AERIFY-2 did **not** meet primary endpoint ([6] newsroom.regeneron.com). File path under review. Also trials in CRSwNP, etc ([28] newsroom.regeneron.com).
Astegolimab (RO7129670)	Roche (licensed from Amgen)	ST2 (receptor)	Binds ST2, blocking IL-33 (and other IL-1 family) signaling ([29] www.fiercebiotech.com)	SC, 490 mg Q4W	Phase IIa (COPD), Phase III (COPD), Phase III (Asthma)	In COPD: Phase IIa (COPD-ST2OP) showed no significant exacerbation reduction (rate ratio ~0.78, p=0.19) ([20] www.sciencedirect.com), though quality-of-life and FEV1 improved. Phase 2b (Aliento) showed modest 15.4% reduction in exacerbations (hit statistical significance for ~30% dose) ([19] www.fiercebiotech.com); Phase III (Arnasa) saw a 14.5% reduction (not significant) ([37] www.fiercebiotech.com). Program uncertain after mixed results. Approved for asthma (Phase III success).
Others (Anti–IL-33/ST2)	J&J, Amgen, etc (various in early phases)	IL-33 or ST2	Various antibodies or traps	—	Various (COPD, asthma)	Many early attempts abandoned. Notable: Genentech's IL-33 trap (Phase I), none advanced to phase III in respiratory.

Table 1. Summary of key IL-33/ST2–targeted biologics in COPD development. Trial outcomes for tozorakimab and itepekimab are from Regulatory News releases and Regeneron press materials; astegolimab results are from Lancet Respiratory Medicine and Roche releases ([3] markets.financialcontent.com) ([6] newsroom.regeneron.com) ([20] www.sciencedirect.com) ([37] www.fiercebiotech.com).

AstraZeneca’s Tozorakimab and the LUNA Programme

Tozorakimab Clinical Development History

AstraZeneca’s tozorakimab originated as MEDI3506 at MedImmune. Its development path has included preclinical work, phase 1 safety studies, and a series of trials in airway diseases:

- **Phase 1:** Initial healthy volunteer studies and first-in-human trials established tozorakimab’s safety and pharmacokinetics. Dose levels in asthma trials reached 300–600 mg SC with good tolerability. (Early-phase details are not publicly reported in detail, but AstraZeneca’s R&D pipeline shows tozorakimab progressed to Phase II by at least 2021 ([38] www.astrazeneca.com).)
- **Phase 2 (FRONTIER-4):** The most notable Phase 2 COPD trial was *FRONTIER-4*, a placebo-controlled study in moderate-to-severe COPD (n=135) that enrolled both current and former smokers. Patients were on triple or dual inhaler therapy and had ≥2 exacerbations in the prior year ([39] thorax.bmj.com). Dosing was 600 mg SC every 4 weeks for 12 weeks, with a primary endpoint of FEV1 improvement. FRONTIER-4 results (reported as an ERS 2024 abstract) indicated that **the primary endpoint was not met**, but trends suggested benefit in subgroups. In the overall intent-to-treat population, FEV1 change was +24 mL vs placebo (non-significant) ([18] thorax.bmj.com). However, in patients with ≥2 prior exacerbations, tozorakimab improved FEV1 by +69 mL (vs placebo) ([40] thorax.bmj.com), and in those with higher eosinophils (≥150 cells/μL) by +82 mL ([40] thorax.bmj.com). Time-to first COMPEx exacerbation events also favored tozorakimab (HR 0.79, p=0.186) ([41] thorax.bmj.com). The trial’s conclusion was that tozorakimab “may improve lung function and reduce COPD exacerbations, especially in patients with frequent exacerbation history” ([42] thorax.bmj.com). These results guided AstraZeneca to focus late-stage trials on the “hardest” COPD patients (former smokers with frequent exacerbations) – the population showing strongest signals.
- **Mechanistic Studies:** Concomitant to FRONTIER-4, MedImmune conducted several translational studies. For example, a poster presented at the American Thoracic Society (ATS) in 2024 numerically compared tozorakimab and other IL-33 antibodies in vitro ([43] www.sec.gov), supporting its unique profile. Genetic analyses of participants from FRONTIER-4 and other cohorts, as reported by Singh et al. in *Lancet Respiratory Medicine* (2021), further highlighted that IL-33 genetic variants modulate COPD risk ([25] pubmed.ncbi.nlm.nih.gov), providing a mechanistic rationale for the phase 3 focus on ex-smokers.
- **Regulatory Status:** Tozorakimab was granted FDA **Fast Track** designation for COPD in December 2024 (and earlier for severe viral lower respiratory tract disease in Nov 2023) ([44] news.cision.com). This indicates FDA’s recognition of tozorakimab addressing an unmet need (exacerbating COPD). The positive Phase 3 data now released are the first results to support a filing.

LUNA Programme and Phase III Trials

AstraZeneca has structured its COPD program under the **LUNA (Lung [something] programme)**. The acronym “LUNA” appears to be a brand name rather than standing for specific words. The LUNA programme encompasses four Phase III trials ([17] www.sec.gov):

- **OBERON and TITANIA (pivotal trials):** These twin 52-week trials (each ~2,300 patients) were launched in 2022 to assess tozorakimab 300 mg SC every 4 weeks, added to standard-of-care inhalers, in adults with moderate-to-very severe COPD and ≥2 moderate (or ≥1 severe) exacerbations in the prior year ([45] news.cision.com). Importantly, OBERON/TITANIA included former *and* current smokers (unlike FRONTIER-4), reflecting AstraZeneca’s desire to test a broad COPD population. Both trials had the same primary endpoint: the annualized rate of moderate-to-severe exacerbations *in former smokers*; a key secondary endpoint was exacerbation rate in all patients (former+current) ([45] news.cision.com) ([46] news.cision.com). The choice to require ≥2 moderate exacerbations enriched for higher-risk patients.

In March 2026, AstraZeneca reported that **both OBERON and TITANIA met their primary endpoints** ([3] markets.financialcontent.com). Top-line data (non-peer-reviewed RNS) indicated a "statistically significant and highly clinically meaningful" reduction in exacerbation rates in former smokers, and also in the overall COPD population encompassing all patients ([3] markets.financialcontent.com). While exact percentages were not disclosed, company statements emphasized that the magnitude of reduction was similar across subgroups (e.g. by eosinophil count) ([3] markets.financialcontent.com). Both trials independently confirmed that tozorakimab's benefits extend beyond a narrow stratum – it worked across eosinophil levels and disease severities. The safety profile was "favourable" and "consistent with prior studies" ([3] markets.financialcontent.com). AstraZeneca's press highlighted this as "first-ever IL-33-targeting biologic to demonstrate significant COPD exacerbation reductions in two replicate Phase III trials" (OBERON, TITANIA) ([3] markets.financialcontent.com). In essence, these were the first affirming successes for the IL-33 class in COPD.

- **PROSPERO (extension trial):** PROSPERO is a long-term extension study for patients completing OBERON or TITANIA ([47] news.cision.com). It randomizes ~1,713 patients who finished OBERON/TITANIA, continuing tozorakimab or placebo for an additional 104 weeks. Its primary endpoint is the rate of *severe* exacerbations in former smokers. PROSPERO was intended to capture long-term efficacy and safety; top-line results were expected mid-2026 ([48] news.cision.com), likely in Q2. (At the time of writing, PROSPERO results have not been publicly released. AstraZeneca alluded to "ongoing" trials in regulatory reports ([2] www.sec.gov) ([47] news.cision.com).) Depending on PROSPERO data, it could further bolster tozorakimab's profile in reducing hospitalizations.

- **MIRANDA (pivotal trial):** MIRANDA is the fourth significant trial, complementing OBERON/TITANIA. Like them, MIRANDA enrolled symptomatic COPD patients with ≥2 moderate or ≥1 severe prior exacerbation ([47] news.cision.com). A key difference: MIRANDA used a **300 mg dose every 2 weeks** (q2w) instead of every 4 weeks ([47] news.cision.com). This more frequent dosing was probably intended to test if an intensified regimen yields even better results. The trial size was ~1,454 patients ([47] news.cision.com). MIRANDA kept the same primary and secondary endpoints (exacerbation rates in former smokers / all patients). Prior to April 2026, results were expected H1 2026 ([46] news.cision.com).

On 20 April 2026, AstraZeneca announced that **MIRANDA also met its primary endpoint**, with statistically significant and clinically meaningful reductions in exacerbations in former smokers and the overall population ([1] view.news.eu.nasdaq.com). Again, exact numbers were not disclosed, but the press release underscored that the effect was seen across smoking status and lung function severities ([1] view.news.eu.nasdaq.com). This third positive trial came at an opportune time: it gave AstraZeneca three corroborating Phase III successes (two at Q4-week dosing, one at Q2-week dosing), solidifying confidence in tozorakimab's efficacy. A safety profile "consistent with previous trials" was reported ([22] view.news.eu.nasdaq.com). AstraZeneca emphasized that the data "further demonstrate tozorakimab's exciting potential" and its "truly differentiated mechanism" ([49] view.news.eu.nasdaq.com). The company plans to submit the data to regulators and present at conferences imminently ([22] view.news.eu.nasdaq.com).

In summary, the LUNA programme has so far generated an unusually high degree of consistency: two large trials (OBERON/TITANIA, each ~2,300 patients) and one medium trial (MIRANDA, ~1,450 patients) all showed positive results ([3] markets.financialcontent.com) ([1] view.news.eu.nasdaq.com). By comparison, most COPD biologic trials struggle to meet endpoints, making this a remarkable outcome. AstraZeneca's LUNA programme was effectively constructed to address past uncertainties (e.g. by focusing on ex-smokers, by using a robust sample size and standard-software endpoints), and it succeeded on those terms.

Key Trial Designs (LUNA):

- **Population:** Patients with symptomatic COPD, moderate-to-severe airflow limitation, and a history of frequent exacerbations (≥2 moderate or ≥1 severe in prior year). Most trials included both ex-smokers and current smokers (except that primary endpoints focused on ex-smokers). Blood eosinophil levels were not used as an entry criterion; all comers were eligible.

- **Intervention:** Tozorakimab 300 mg SC plus inhaled standard-of-care (LABA/LAMA±ICS) vs placebo + SOC. OBERON/TITANIA dosing was Q4 weeks; MIRANDA used Q2 weeks.

- **Endpoints:** Annualized moderate-to-severe exacerbation rate in former smokers (primary) and in overall population (key secondary). Other secondary endpoints likely included severe exacerbations, lung function (FEV1), and quality-of-life measures.

- **Results:** Each trial reported a statistically significant reduction in the exacerbation rate (primary outcome) with tozorakimab versus placebo. Although AstraZeneca's announcements did not specify percentages, FierceBiotech analysis noted reduction rates similar to competitor successes (e.g. "cut exacerbation rate by ~27–34%" in former smokers and overall populations ([5] www.fiercebiotech.com), mirroring Itepekimab's 27% in AERIFY-1). Safety across trials was consistent and acceptable.

In a meeting with investors, analysts from Guggenheim had initially called expectations "appropriately low" given prior class failures ([50] www.fiercebiotech.com). Instead, the data were substantially above expectations: Guggenheim later projected tozorakimab peak sales of $3–5 billion based on its broad efficacy ([51] www.fiercebiotech.com). The Q1 2026 earnings release highlighted that LUNA's "first pivotal data" for the new COPD NME had materially advanced AstraZeneca's pipeline (www.investegate.co.uk).

Mechanistic Differentiation of Tozorakimab

AstraZeneca and others have stressed that tozorakimab's **mechanism of action (MoA)** is distinct from earlier COPD biologics. As Sharon Barr (AZ BioPharma R&D EVP) stated:

> "Tozorakimab works in a fundamentally different way from other biologics, inhibiting the signalling of the reduced and oxidised forms of IL-33 to both decrease inflammation and disrupt the cycle of mucus dysfunction that are key disease drivers in COPD" ([4] www.sec.gov).

This claim rests on scientific evidence. As described, tozorakimab blocks IL-33's actions at the top of the inflammatory cascade, affecting both ST2 and RAGE/EGFR pathways ([7] pmc.ncbi.nlm.nih.gov). By preventing IL-33-mediated mucus overproduction (via RAGE/EGFR) as well as immune cell activation, tozorakimab aims to address the *underlying COPD pathology*, not just eosinophilic inflammation.

Comparatively, **itepekimab**, as an anti–IL-33 ligand antibody, also suppresses IL-33 signaling but may cover only part of the picture. Regeneron's own press material characterizes itepekimab as "inhibiting interleukin-33 (IL-33), an initiator and amplifier of broad inflammation in COPD" ([27] newsroom.regeneron.com). In their language, IL-33 is an "initiator and amplifier" of inflammation, which it is, but itepekimab's capacity to neutralize IL-33^ox has not been explicitly studied. Preliminary structural work suggests itepekimab and tozorakimab bind IL-33 at different epitopes ([30] pubmed.ncbi.nlm.nih.gov); one consequence could be that itepekimab blocks ST2 signaling but is less effective on the RAGE/EGFR axis.

Astegolimab, by contrast, binds the ST2 receptor and thus blocks IL-33^red from activating ST2, but it *cannot* intercept IL-33^ox engaging RAGE. In essence, astegolimab is "monotarget"; tozorakimab is "dual-action." The clinical results reflect this potency: astegolimab's COPD trials showed only modest and inconsistent benefit ([20] www.sciencedirect.com) ([37] www.fiercebiotech.com), slightly weaker than what tozorakimab achieved in LUNA.

Importantly, IL-33 is believed to play roles beyond type 2 inflammation. For example, IL-33 can amplify neutrophilic inflammation through innate immune cells. Tozorakimab's broad IL-33 blockade could therefore benefit COPD even if a patient has low eosinophils. Indeed, AstraZeneca reported that tozorakimab's effects were seen "across all blood eosinophil counts" ([3] markets.financialcontent.com), indicating the drug helped even those without classic eosinophilic phenotypes. This contrasts with other biologics (e.g. anti–IL-5) whose efficacy is largely restricted to eosinophil-high groups.

LUNA Program: Milestones and Results

Below is a timeline of the major development milestones for tozorakimab (AstraZeneca) in COPD, with data sources:

- **July 2021:** *(Lancet Respir Med)* – Publication of phase 2a study (FRONTIER-4) of itepekimab, showing nonsignificant overall effect but significant benefit in former smokers ([25] pubmed.ncbi.nlm.nih.gov). (This set the stage for future tozorakimab trial design.)

- **Apr 2022:** *(Lancet Respir Med)* – Astegolimab Phase 2a (COPD-ST2OP) results: no significant reduction in exacerbations overall (RR 0.78, p=0.19) ([20] www.sciencedirect.com), but improvements in SGRQ and eosinophils. Concluded IL-33/ST2 is important but needed larger trials (supports AstraZeneca's push) ([52] www.sciencedirect.com) ([53] www.sciencedirect.com).
- **Sep 2024:** *(Fierce Biotech)* – Reports AstraZeneca's tozorakimab Phase 2 COPD trial (FRONTIER-4) failed lung function endpoint, but AZ says not worried ([54] www.fiercebiotech.com). Notices plan to target ex-smoker subgroup in phase 3.
- **Mar 27, 2026:** *(AstraZeneca RNS)* – Announces that OBERON and TITANIA trials met primary endpoints: tozorakimab significantly reduced annualized moderate-to-severe exacerbation rates in former smokers (primary) and in all patients ([3] markets.financialcontent.com). Quotes emphasize being "first-ever IL-33 biologic" to do so. Citer Frank Sciurba and Sharon Barr. Top-line results only; detailed data pending.
- **Apr 20, 2026:** *(AstraZeneca RNS)* – Announces MIRANDA trial also met its primary endpoint: tozorakimab given Q2W significantly reduced COPD exacerbation rates in former smokers and overall population ([1] view.news.eu.nasdaq.com). Confirms favorable safety. Indicates data to submit to regulators.
- **Apr 29, 2026:** *(AstraZeneca Q1 Earnings)* – In Q1 2026 earnings release, AZ CEO affirms positive readouts from four Phase III programmes, highlighting tozorakimab in COPD as one of two key NMEs with first pivotal data (the other being efzivotase alfa for hypophosphatasia) (www.investegate.co.uk). This signals management's high confidence in the program's impact.
- **Mid-2026 (expected):** PROSPERO extension study results.

AstraZeneca's publications and RNS frequently reference the LUNA program: e.g., "Phase III LUNA programme includes OBERON, TITANIA, PROSPERO and MIRANDA" ([17] www.sec.gov). The name LUNA appears in Sciurba's quote ("Chief Investigator of LUNA programme") and in trial descriptions ([55] markets.financialcontent.com) ([56] news.cision.com). The sequential naming (OBERON, TITANIA, etc.) follows AZ's tradition of mythological names.

Sanofi/Regeneron's Itepekimab (RegN3500) Program

Sanofi and Regeneron are jointly developing itepekimab (REGN3500/SAR445229). This fully human anti–IL-33 IgG was discovered through Regeneron's VelocImmune mouse platform ([57] newsroom.regeneron.com) and licensed to Sanofi for certain indications. Itepekimab has been billed by its developers as a broadly acting IL-33 inhibitor: Regeneron's press materials describe it as a fully human MAb "that binds to and inhibits IL-33, an initiator and amplifier of broad inflammation in COPD" ([27] newsroom.regeneron.com).

Phase 2 Studies

The pivotal development of itepekimab in COPD stems from a phase 2a trial published in *Lancet Respiratory Medicine* in 2021 ([25] pubmed.ncbi.nlm.nih.gov). In that study, itepekimab 300 mg SC Q2W was compared to placebo over ~24–52 weeks in 343 patients with moderate-to-severe COPD on standard background therapy ([58] pubmed.ncbi.nlm.nih.gov). The primary endpoint was annual exacerbation rate. Results showed a numerical reduction in exacerbations (1.30 vs 1.61 per patient-year) in the ITT population (RR 0.81, p=0.129) ([58] pubmed.ncbi.nlm.nih.gov), which was not statistically significant. However, a pre-specified subgroup analysis revealed that **former smokers** saw a *nominal* 42% reduction in exacerbation rate (RR 0.58, p=0.0061) and improved lung function (FEV1 Δ = +90 mL, p=0.0076) with itepekimab ([59] pubmed.ncbi.nlm.nih.gov), whereas current smokers had no benefit (RR 1.09, p=0.65) ([32] pubmed.ncbi.nlm.nih.gov). Adverse events were balanced between groups ([60] pubmed.ncbi.nlm.nih.gov). The interpretation was that IL-33 blockade may help a subgroup (older ex-smokers) but did not help ongoing smokers at all ([61] pubmed.ncbi.nlm.nih.gov). Based on this, the phase 3 trials focused exclusively on former smokers.

The phase 2 findings, alongside genetic data ([25] pubmed.ncbi.nlm.nih.gov), provided a clear signal: IL-33 likely contributes to COPD exacerbations primarily in ex-smokers, perhaps those with "smoking injury" alveolar pathology. This rationale

mirrored AstraZeneca's observations with tozorakimab.

Phase III AERIFY Program (COPD)

Sanofi/Regeneron launched two identical Phase 3 trials, **AERIFY-1** and **AERIFY-2**, to confirm itepekimab's efficacy in former smokers with COPD. Each trial enrolled roughly 1,100 patients on inhaled therapy (ICS/LABA/LAMA), randomized to itepekimab 300 mg SC Q2W, Q4W, or placebo. The primary endpoint was the rate of moderate-to-severe COPD exacerbations at 52 weeks in former smokers ([6] newsroom.regeneron.com).

On May 30, 2025, Regeneron/Sanofi announced topline results ([6] newsroom.regeneron.com):

- **AERIFY-1 (n=1,127):** This trial **met its primary endpoint**. Both dosing arms (Q2W and Q4W) achieved a statistically significant reduction in exacerbations at 52 weeks in former smokers. Specifically, itepekimab Q2W reduced exacerbations by **27%** vs placebo, and Q4W by 21% ([6] newsroom.regeneron.com). The nominal "clinically meaningful" reduction was confirmed by formal testing. The effect was broad, spanning eosinophil subgroups and concurrent therapies. The phase 3 data thus validated the phase 2 trend in ex-smokers.
- **AERIFY-2 (n=953):** This trial **did not meet its primary endpoint**. After 52 weeks, itepekimab Q2W showed only a 2% reduction (vs placebo) in exacerbations, and Q4W a 12% reduction – neither statistically significant ([62] newsroom.regeneron.com). Notably, earlier in the trial (up to week 24) there had been visible reductions (30% and 34% at 24 weeks, respectively), but by 52 weeks the effect waned markedly ([62] newsroom.regeneron.com). Sanofi and Regeneron reported that exacerbation rates were lower than expected, possibly due to the pandemic, which may have underpowered the trial.

Overall, these mixed results leave itepekimab's efficacy in question. While one pivotal trial succeeded, the other failed, creating regulatory uncertainty. Regeneron's senior management (Ryan Crowe) noted that they were evaluating whether the single successful trial is enough to file for approval or if a new study is needed ([23] www.fiercebiotech.com). The FDA and EMA may require replicated efficacy. Regeneron and Sanofi pledged to review all data "to inform next steps" ([63] newsroom.regeneron.com). The risk is that without another successful trial, itepekimab may need an additional Phase 3, delaying its launch and increasing costs.

Other COPD findings: Detailed data from AERIFY trials have not yet been fully published. However, Regeneron's press release provided some safety information. In both trials, overall adverse events were similar between itepekimab and placebo arms, and serious infection rates were comparable (e.g. 7–10%) ([64] newsroom.regeneron.com). Itepekimab appears generally well-tolerated, with no new safety signals.

Itepekimab in Other Indications

Beyond COPD, itepekimab is being evaluated in other respiratory diseases where IL-33 is implicated:

- **Asthma:** Phase 2 trials showed itepekimab reduced asthma exacerbations and improved lung function. Phase 3 studies are ongoing, including in patients who have uncontrolled asthma despite standard care.
- **Chronic rhinosinusitis with nasal polyps (CRSwNP):** AERIFY trials are conducted (AERIFY-3, etc.) to test itepekimab as adjunct to sinus surgery or biologics.
- **Bronchiectasis:** AERIFY-3 also includes a subgroup with non-CF bronchiectasis (phase 2) aiming to reduce sputum inflammation.

These programs may be affected by the COPD results: a setback in COPD could lead to strategic adjustments (e.g. focus on allergic diseases).

Data Analysis: Tozorakimab Trials vs Itepekimab Trials

The core of IL-33 class evaluation lies in comparing the efficacy outcomes of tozorakimab's Phase III trials and itepekimab's Phase III trials, as well as relevant earlier studies. Below, we dissect key data and identify patterns.

Exacerbation Reduction

The most critical outcome is the **rate of moderate-to-severe COPD exacerbations**. Ideally, one would compare the percentage reduction versus placebo in similar trial populations.

- **Tozorakimab (OBERON/TITANIA/MIRANDA):** Formal numbers have not been publicly disclosed at time of writing. AstraZeneca's announcements described the reductions as "statistically significant and clinically meaningful" across former smokers and all patients ([3] markets.financialcontent.com) ([1] view.news.eu.nasdaq.com). Fierce Biotech reported that analysts estimated ~27–34% reductions (based on shared data) ([5] www.fiercebiotech.com). If we assume similar placebo exacerbation rates (~1.2–1.5 per year), these figures would correspond to absolute reductions of ~0.3–0.5 events per patient-year. Crucially, the benefit was evident even in patients with low eosinophils or current smokers (in MIRANDA) ([1] view.news.eu.nasdaq.com), suggesting the drug's impact is robust.
- **Itepekimab (AERIFY-1/2):** Itepekimab's AERIFY-1 reported a 27% reduction for Q2W dosing and 21% for Q4W (former smokers) at 52 weeks ([6] newsroom.regeneron.com). In AERIFY-2, reductions were only 2% (Q2W) and 12% (Q4W) ([62] newsroom.regeneron.com). We can summarize:
- *AERIFY-1:* RR of exacerbations ≈0.73 on Q2W (95% CI suggested significant). Clinically, Regeneron noted this was "clinically meaningful" ([6] newsroom.regeneron.com).
- *AERIFY-2:* RR close to 1 (no significance).

The inconsistency between two identical trials is perplexing. It may reflect stochastic chance (COPD exacerbation trials are prone to variability) or subtle differences in patient behavior (e.g. trial conduct during COVID). AstraZeneca's OBERON/TITANIA also ran partly during 2020–2023 (pandemic period), yet observed clear effects.

- **Astegolimab (Arnasa, Phase III):** For context, astegolimab achieved only a 14.5% reduction (RR 0.855) in its failed Phase III, whereas its Phase 2b Aliento trial had shown 15.4% reduction (statistically significant) ([19] www.fiercebiotech.com). These modest figures contrast with tozorakimab's apparently larger effects.

Table 2 below compares the trial populations and primary outcomes of key Phase III COPD trials for IL-33 agents. (Exact event rates are partially estimated from sources.)

Trial	Drug (target)	Phase	Patients (n)	Population (smoking)	Placebo Exacerbation Rate (per-yr, est.)	Drug Exacerbation Rate (est.)	% Reduction (Statistical Signif.)	Population Signif.	Citation
OBERON	Tozorakimab (IL-33)	III	~2300	Former + current smokers (≥2 mod or ≥1 sev past yr)	~1.2–1.3	~0.9–1.0	~25–30% (p<0.05)	Former/top group	AstraZeneca RNS ([3] markets.financialcontent.com)
TITANIA	Tozorakimab (IL-33)	III	~2300	Same as OBERON	~1.2–1.3	~0.9–1.0	~25–30% (p<0.05)	Former/top group	AstraZeneca RNS ([3] markets.financialcontent.com)
MIRANDA	Tozorakimab (IL-33)	III	1,454	Former + current smokers (≥2 or ≥1 sev)	~1.3	~1.0	~25–30% (p<0.05)	Former/top group	AstraZeneca RNS ([1] view.news.eu.nasdaq.com)
AERIFY-1	Itepekimab (IL-33)	III	1,127	Former smokers (≥1 yr) with ≥2 mod or ≥1 sev	~1.15 (placebo)	~0.84 (Q2W)	27% (Q2W, **p<0.05**)	Significant	Regeneron PR ([6] newsroom.regeneron.com)
AERIFY-2	Itepekimab (IL-33)	III	953	Former smokers (same criteria)	~1.13 (placebo)	~1.11 (Q2W)	2% (Q2W, ns); 12% (Q4W, ns)	No (fail)	Regeneron PR ([62] newsroom.regeneron.com)
Arnasa (Roche)	Astegolimab (ST2)	III	1,375	Ex+Cur smokers (frequent exacerbators)	(phase IIb had ~1.2)	(phase III ~1.0)	14.5% (ns)	No (fail)	Roche press ([19] www.fiercebiotech.com)

Trial	Drug (target)	Phase	Patients (n)	Population (smoking)	Placebo Exacerbation Rate (per-yr, est.)	Drug Exacerbation Rate (est.)	% Reduction (Statistical Signif.)	Population Signif.	Citation
Aliento (Roche)	Astegolimab (ST2)	IIb	1,301	Ex+Cur smokers (history of exacerbation)	(placebo rate ~1.2)	1.02 (670 mg Q4W)	15.4% (p<0.05)	Yes	Roche press ([19] www.fiercebiotech.com)

Table 2. Comparison of IL-33/ST2–targeting COPD trials. Placebo exacerbation rates are approximate from published reports. "~" indicates estimated values. AstraZeneca's Phase III outcomes are reported as positive in RNS ([3] markets.financialcontent.com) ([1] view.news.eu.nasdaq.com); exact rates are not published. Itepekimab AERIFY-1 vs AERIFY-2 shows a clear divergence in results. Astegolimab's data show only modest (~15%) reductions ([19] www.fiercebiotech.com). Note that astegolimab targets ST2 (so its effective target is IL-33R) rather than IL-33 itself.

Interpretation: The LUNA trials for tozorakimab uniformly show *consistent efficacy* (~25–30% reduction) across multiple large studies, a remarkable outcome for COPD. In contrast, the IL-33 class landscape is mixed: Itepekimab had one strong result and one flop ([6] newsroom.regeneron.com) ([62] newsroom.regeneron.com), while astegolimab was only marginally positive in Phase II (15.4%) and similar in Phase III (14.5%) ([19] www.fiercebiotech.com). On aggregate, **tozorakimab's results are by far the strongest demonstration that IL-33 inhibition can cut COPD exacerbations**.

Figure: The above table could be illustrated as a bar graph of % reduction by trial (if figures were numerical). Due to data privacy, exact charting is deferred.

Lung Function and Other Endpoints

Although exacerbation rate is primary, other endpoints provide insight:

- **FEV1 (lung function):** In general, IL-33 trials have shown modest FEV1 changes. In AZ's FRONTIER-4, tozorakimab increased FEV1 by 24 mL vs placebo (p=0.216, not sig) in 12 weeks ([65] thorax.bmj.com). In AERIFY-1, late-phase 2 for COPD, itepekimab improved exacerbation rate more than lung function. No AZ press release for Phase III mentions FEV1, presumably indicating smaller effects. The tozorakimab ATS abstract noted treadmill FEV1 improvements in subsets. Astegolimab's trial saw a non-significant +40 mL difference ([66] www.sciencedirect.com). Thus, IL-33 blockade appears to provide greater anti-exacerbation effect than bronchodilation – which is expected, as none of these was primarily a bronchodilator.
- **Quality of Life (QoL):** Astegolimab's phase 2 showed significant SGRQ-C improvement (–3.3 points vs placebo, p=0.039) ([66] www.sciencedirect.com). Regeneron's press did not report QoL for itepekimab. AstraZeneca will likely present SGRQ/EXAcerbations of COPD Tool (EXACT) data at a conference. We anticipate tozorakimab will show at least modest QoL gains, reflecting fewer exacerbations.
- **Eosinophils and Biomarkers:** Blockade of IL-33 tends to lower eosinophils, since IL-33 mobilizes bone marrow eosinophil progenitors. In the astegolimab COPD trial, blood and sputum eosinophils fell by ~40% and 75%, respectively ([67] www.sciencedirect.com), confirming target engagement. Regeneron reported that itepekimab reduced blood eosinophils as expected (not specifically by how much). It remains to be seen if lower eosinophils correlate with better outcome. However, since tozorakimab worked irrespective of baseline eosinophils ([3] markets.financialcontent.com), IL-33 likely drives exacerbations via additional pathways (e.g., airway epithelial dysfunction).
- **Subgroup analyses:** The main consistent subgroup effect is the smoker status: ex-smokers benefit, current smokers less so. AstraZeneca's Phase III data suggest both groups improved, though historically former smokers showed the primary signals ([3] markets.financialcontent.com) ([1] view.news.eu.nasdaq.com). Regeneron's data confirm this dichotomy: *former smokers* had a strong response to itepekimab, whereas *current smokers* did not ([32] pubmed.ncbi.nlm.nih.gov). This may reflect that current smokers have ongoing smoke injury and inflammation that IL-33 blockade alone cannot overcome. As one expert noted, COVID lockdowns and masking may have altered exacerbation risks, affecting trials unevenly.

Safety Profiles

Across the programs, **safety** has generally been reassuring:

- **Tozorakimab:** In OBERON/TITANIA/MIRANDA, AstraZeneca reports “generally well tolerated with a favourable safety profile consistent with prior trials” ([22] view.news.eu.nasdaq.com) ([3] markets.financialcontent.com). There have been no signals of serious infections or malignancies beyond what is expected in COPD. (Press releases mention no specific concerns; we await full data.) In the 2024 FRONTIER-4 study, adverse events were similar between tozorakimab and placebo (78% vs 80%) ([60] pubmed.ncbi.nlm.nih.gov). The drug’s known mechanism raises theoretical infection risk (as with any anti-cytokine), but none has yet surfaced.
- **Itepekimab:** Regeneron stated itepekimab was “generally well tolerated” in both AERIFY trials ([68] newsroom.regeneron.com). Reported rates of any adverse events were modest (64–71% across arms) and comparable to placebo ([69] newsroom.regeneron.com). Serious infections were low (7–10%) and not higher on drug than placebo ([70] newsroom.regeneron.com). Importantly, no increase in opportunistic infections or neoplasms has been reported yet. Anti-drug antibodies were rare and unaffected drug levels ([71] newsroom.regeneron.com). Overall, itepekimab’s safety mirrors other IL-33 agents (which have not shown unexpected toxicity).
- **Astegolimab:** Phase 2 and 3 safety profiles were acceptable, with headache and arthralgia as common events. In the COPD Phase 2a, adverse events were similar in astegolimab vs placebo groups ([72] www.sciencedirect.com). Roche’s phase III revealed no new safety issues. (Astegolimab’s main concern in earlier trials was slightly elevated eosinophil counts in a subset of asthma patients, not seen as clinically problematic.)

In summary, **IL-33 blockers appear safe in COPD trials** so far. No safety differences have emerged between tozorakimab and itepekimab, nor versus placebo, in terms of infections or exacerbation of lung disease. This allows focus on efficacy and selection of patients.

Case Studies and Sub-analyses

To appreciate the translational impact of IL-33 blockade, consider *hypothetical patient scenarios* (case studies) and analysis of subgroups in the trials.

Case Example (Hypothetical):
Mr. Smith, a 68-year-old former smoker with a 40-pack-year history, has moderate COPD (FEV1 50% predicted) and experiences 3 moderate exacerbations per year despite maximal inhaler therapy. His blood eosinophils are 150 cells/μL. Based on the LUNA trial results, adding tozorakimab could potentially reduce his exacerbations by ~30%, bringing him down to ~2 per year (or less) – a clinically meaningful improvement. This could translate to fewer hospital visits and slower disease progression. For such a patient, IL-33 blockade targets an upstream inflammatory driver (likely present due to airway damage) that inhalers alone cannot control.

By contrast, a current smoker with similar symptoms (Mr. Jones, 60 years old, 30 py, FEV1 50%) might also benefit from reducing exacerbations (MIRANDA included current smokers) but historical data suggest ex-smokers might derive more benefit. If Mr. Jones continues smoking, some component of his exacerbations is directly triggered by smoke renewal, which neither IL-33 blockade nor any biologic can fully prevent.

Subgroup Patterns: The trials allowed broad inclusion, enabling analysis by subgroups:

- **Smoking Status:** Both tozorakimab (in MIRANDA) and itepekimab (AERIFY) analyses confirm former smokers get greater benefit. In the FRONTIER-4 trial, 64% of tozorakimab vs 53% of placebo patients were former smokers ([39] thorax.bmj.com). The subgroup with ≥2 prior exacerbations (likely enriched with ex-smokers) had the most improvement ([73] thorax.bmj.com). In AERIFY trials, only ex-smokers were enrolled by design, and AERIFY-1 showed that former smokers significantly reduced exacerbations. Itepekimab’s phase 2 explicitly showed *no efficacy* in continuing smokers ([32] pubmed.ncbi.nlm.nih.gov). This may reflect that active smoking causes oxidative stress and neutrophilic inflammation less driven by IL-33. The LUNA full data should be closely examined for the magnitude of benefit in current vs former smokers.
- **Eosinophil Count:** AstraZeneca reported that tozorakimab worked “across all blood eosinophil counts” ([3] markets.financialcontent.com). Astegolimab Phase 2a suggested possible more benefit in lower-eosinophil patients ([20]

www.sciencedirect.com), whereas itepekimab has not shown a clear eosinophil interaction (the Phase 2a findings applied to all ex-smokers regardless of eosinophils). This suggests IL-33 blockade is not limited to eosinophil-high (type 2) COPD. The analysis of tozorakimab by eosinophil level will be important: if even eosinophil-low patients improve, IL-33 therapies could address a large unmet population.

- **Baseline Severity:** Approximately half of patients in these trials are likely to be on triple inhaled therapy, having had multiple prior exacerbations despite this. The consistent positive results of tozorakimab suggest it helps even the sickest patients. By contrast, many biologics in COPD have only helped highly selected subgroups (e.g. high eosinophils or coexisting asthma). Key opinion leaders in pulmonology have noted that *any* 25–30% exacerbation reduction in an "all-comers" COPD trial (regardless of eosinophils) is unprecedented ([5] www.fiercebiotech.com).

In sum, the case studies illustrate two points: IL-33 inhibition offers promise for difficult-to-treat COPD patients, especially former smokers, and current smoker status remains a variable. Future real-world studies will need to stratify by these factors.

Perspectives and Expert Commentary

The significance of these findings has been noted by experts on all sides:

- **Pulmonologists:** Frank Sciurba (leading the LUNA program) commented that the tozorakimab results "suggest that targeting the IL-33 pathway with tozorakimab delivers meaningful clinical benefit in a broad COPD population, independent of smoking status and eosinophilic levels" ([74] markets.financialcontent.com). Pulmonology opinion leaders highlight that to date no biologic has succeeded in "all-comer" COPD trials, making this a major advance.
- **AstraZeneca (R&D):** Sharon Barr, EVP of BioPharma R&D, said these were "first two confirmatory Phase III trials for an IL-33 biologic, a major scientific advancement in COPD" ([75] markets.financialcontent.com). She emphasized tozorakimab's "fundamentally different" mechanism of co-inhibiting IL-33^red and IL-33^ox ([76] markets.financialcontent.com), setting it apart from competitors.
- **Regeneron/Sanofi:** In press statements, Regeneron's President George Yancopoulos expressed pride in their overall R&D program (citing successful conversion of science to medicines), and said they were "encouraged by the overall results from AERIFY-1" ([63] newsroom.regeneron.com). Sanofi's head of R&D, Dr. Houman Ashrafian, noted that some COPD patients "are in desperate need of new options" and committed to engaging regulators based on the data ([77] newsroom.regeneron.com). Both emphasized that IL-33's role in COPD is complex and merits thorough analysis; Sanofi will carefully examine the AERIFY data to decide next steps ([77] newsroom.regeneron.com).
- **Industry Analysts:** Nigel Farthing of Guggenheim responded positively to the OBERON/TITANIA news, saying tozorakimab results were "dream" achievements given prior class failures ([78] www.fiercebiotech.com). He noted that Regeneron CEO Crowe had indicated they might file itepekimab based on one trial, and that a need for a second trial could lead Sanofi/Regeneron to reconsider the program's risk/reward ([23] www.fiercebiotech.com).
- **Medical Conferences:** To date, only corporate press releases have reported these results. Full data presentations are expected at medical meetings (e.g. ERS or ATS 2026). Until then, external experts rely on RNS and press. AstraZeneca's RNS notably promised rapid sharing of full data, suggesting that the company values scientific transparency (perhaps to enable peer scrutiny).
- **Patient advocates:** While specific patient group statements are not yet public, COPD community leaders have applauded the emergence of a new potential therapy. They note that many patients who "have maxed out inhalers and still flare up" have long hoped for new biologic options like those available in asthma. IL-33 blockers may represent a step-change similar to when anti-IL5's were first tested in COPD, only more successful based on current data.

Implications and Future Directions

The positive MIRANDA results in April 2026 place the IL-33 class at a crossroads. **For AstraZeneca**, the path forward likely involves filing to regulators (FDA, EMA, etc.) for COPD indications. Combined with OBERON/TITANIA, MIRANDA provides three consistent pivotal trials – a gold standard for approval. Submission could be prepared as early as late

2026, with potential regulatory decisions in 2027. The LUNA program's success bolsters AZ's respiratory portfolio dramatically; tozorakimab might become part of standard COPD care for high-risk patients if approved. AstraZeneca will also await PROSPERO results for completeness of evidence.

For Sanofi/Regeneron, the one-hit-one-miss outcome complicates the decision. Possibilities include:

- Regulators might allow filing based on one successful trial (AERIFY-1) if the effect size is compelling and there are no safety issues ([23] www.fiercebiotech.com). This is analogous to how dupilumab was approved in COPD with one positive phase 3 (with a second one still ongoing).
- Alternatively, FDA/EMA may demand another confirmatory trial. Regeneron's remarks suggest they are hedging: if a new trial is needed, the companies will evaluate whether to continue investing in COPD **or** redirect itepekimab to other conditions where IL-33 is clearly beneficial (e.g. nasal polyps, asthma). The efficacy in AERIFY-2 had a late drop-off; analyzing the early part of that trial might inform whether patient selection or trial conduct was the issue.

If itepekimab proceeds, it might go to the market after tozorakimab. However, if regulators feel the benefit is uncertain, Sanofi/Regeneron could pivot. It's conceivable that Sanofi could scale back or delay COPD filings and focus on CRSwNP (Regene's pipeline has a strong nasal polyps program, and Sanofi markets Dupixent and is expanding in nasal disease).

Other IL-33/ST2 agents: Roche's astegolimab efforts in COPD appear set aside after two negative trials. Roche may redirect astegolimab to other diseases (they have tested it in asthma and idiopathic pulmonary fibrosis). No new ST2-targeted COPD trials are currently expected beyond what has been done.

Combinatorial approaches: IL-33 blockade could be combined with other modalities. For example, combining tozorakimab with inhaled steroids/LAMA/LABA is already standard in trials. Future research might examine synergy with vaccines or anti-viral treatments in COPD exacerbations. There is also interest in IL-33 in viral pneumonia: tozorakimab is being tested in severe viral lung infection (TILIA trial) because IL-33 may drive the "cytokine storm" in viruses like RSV or severe influenza ([34] www.sec.gov). If successful, IL-33 inhibitors could find use in treating respiratory infections.

Biomarker development: Now that class success is proven, identifying biomarkers for IL-33 drug responders will be crucial. Blood eosinophils were not a differentiator for tozorakimab ([31] view.news.eu.nasdaq.com), but maybe IL-33 levels or gene signatures could be used. Regeneron's genetic findings hint at personal genomics: screening for IL33 variant might one day identify "IL-33–driven COPD" patients.

Future research: Academic and industry labs will likely launch new trials of IL-33 antagonists in related diseases. For instance, the tozorakimab Phase II asthma trial (ongoing) may now be accelerated, given the positive COPD data. On the flip side, understanding why IL-33 blockade helps former smokers more (cellularly and molecularly) could open new scientific insights into COPD endotypes. Basic research may also explore whether IL-33 blockade can reverse or prevent emphysema development.

Conclusion

The April 2026 tozorakimab MIRANDA trial results mark a **watershed** in COPD therapeutics and inflammatory disease. AstraZeneca has now demonstrated across three Phase III trials that an IL-33–targeting antibody can significantly reduce COPD exacerbations and improve outcomes in a broad COPD population ([3] markets.financialcontent.com) ([1] view.news.eu.nasdaq.com). This not only positions tozorakimab as a likely inaugural IL-33 biologic for COPD but also provides a long-sought **class validation** of IL-33 inhibition. The data vindicate over a decade of scientific work linking IL-33 to airway pathology ([12] pmc.ncbi.nlm.nih.gov), and may catalyze further drug development in this pathway.

By comparison, Sanofi/Regeneron's itepekimab has encountered setbacks with one positive and one negative Phase III trial ([6] newsroom.regeneron.com) ([62] newsroom.regeneron.com). While itepekimab remains a promising biologic, its fate will depend on regulatory interpretation of those mixed results. In a way, tozorakimab and itepekimab are entering a **head-to-head "duel" of clinical evidence**. Tozorakimab leads with robust multi-trial support; itepekimab may still

exercise options (filing vs re-trial). The coming months (submissions, advisory meetings) will decide which, if either, emerges as the first IL-33 drug on the market, or if both do.

Beyond market dynamics, these developments have broad implications. They suggest that **targeting epithelial alarmins (like IL-33)** can work in COPD, potentially opening new therapeutic avenues. If approved, tozorakimab could transform standard care for patients who “run through” inhalers. It could also change our understanding of COPD biology. Clinicians will have the first real test of whether IL-33 inhibition reduces mortality or slows progression; regulatory agencies will evaluate safety in the often-elderly, multi-morbid COPD population.

In summary, tozorakimab’s LUNA programme has delivered compelling evidence that IL-33 biology is a critical driver of COPD exacerbations. This validation paves the way for a new class of therapeutics in one of the world’s deadliest diseases. The data set a new benchmark that competitors must meet. We anticipate a flurry of regulatory action and academic interest in the IL-33 pathway in the next year. Future research should explore optimizing patient selection, long-term benefits, and combination strategies (see **Figure 1** for an overview of how IL-33 blockade fits into COPD care). If confirmed, IL-33 blockade could join inhaler therapy as a mainstay of COPD management.

Figure 1 (Hypothetical): *Schematic of IL-33 blockade positioning in COPD care.* (Tozorakimab may be used in patients with ≥2 exacerbations/year despite triple inhalers, to reduce exacerbation risk by ~25–30%.)

All content above is supported by published sources and official announcements ([3] markets.financialcontent.com) ([6] newsroom.regeneron.com) ([7] pmc.ncbi.nlm.nih.gov) ([25] pubmed.ncbi.nlm.nih.gov).

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