

Asthma Update 2023

Part 2: Asthma Drug Pipeline 2023

Asthma is a major serious global health problem, affecting both children and adults. The [Global Burden of Disease Study 2019](#) estimated that about 262 million people worldwide were affected by asthma in 2019. Asthma is a chronic inflammatory disease of the airways associated with mucosal inflammation, airway remodelling and airway hyperresponsiveness. Exposure to certain triggers may cause a constriction of the bronchial tubes, which causes the typical asthma symptoms such as wheezing, chest tightness, coughing and shortness of breath. The intensity of symptoms varies over time along with variable (later possibly persistent) expiratory airflow limitation. Modern diagnostics includes spirometric testing of variable expiratory airflow limitation, bronchial provocation tests and/or allergy testing. In addition, the assessment of so called “*type-2 biomarkers*” (eosinophil count in blood/sputum, fractionated exhaled nitric oxide, serum IgE-levels) permits to differentiate “*Type-2 asthma*” (T helper cell 2 driven; mostly eosinophilic asthma) from “*Non-type 2 asthma*” (T helper cell 1/17 driven: mostly neutrophilic, mixed granulocytic or paucigranulocytic asthma). The aim of modern asthma therapy is the prevention of symptoms and exacerbations and stabilization of lung function using “*Disease Modifying Anti-Asthmatic Drugs*” such as inhaled corticosteroids with or without long-acting-beta₂ agonist or long-acting-muscarinic antagonists; and the addition of a biologic as a more target-selective treatment in cases of severe uncontrolled asthma.



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The **Charité Research Organisation GmbH** has longstanding experience in the conduction of early phase projects for new asthma medicines. We want to share our asthma expertise in this special Whitepaper that comes in two parts.

In **PART 1**, the **MODERN ASTHMA MANAGEMENT** will be presented and the progress in asthma diagnostics and therapy discussed based on current applicable Guidelines including the Global Initiative for Asthma 2023. A special focus is laid on recent research to novel biomarkers for the identification of certain asthma endotypes that can be used in the clinics for modern asthma management.

In **PART 2**, the **ASTHMA DRUG PIPELINE 2023** will be presented and some of the new drug candidates discussed. In addition, the efforts made to provide advanced medical devices to improve drug exposure to the lung will be addressed in some detail. More sustainable medical devices to reduce the Green House Gas effect are already available on the market. We will focus on the different device technologies and their propellants, especially concerning their *Carbon Footprint* and contribution to the *Global Warming Potential*.

Introduction

In the last decade, a tremendous progress in asthma management has been achieved. Nevertheless, a substantial percentage of asthma patients still suffer from “uncontrolled asthma” characterized by poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma) and/or frequent exacerbations (≥ 2 /year) requiring an OCS, or serious exacerbations (≥ 1 /year) requiring hospitalizations. Despite a high intensity treatment, usually consisting of high dose inhaled corticosteroids combined with long-acting beta₂-agonists (ICS-LABA), a significant part of them are categorized as “difficult to treat asthma” mostly due to an incorrect inhaler technique, poor adherence, smoking or comorbidities, or because of a wrong diagnosis [[GINA 2023](#), [Chung et al. 2014](#)]. About 4 to 5% of asthma patients are evaluated as “*severe uncontrolled asthma*”, i.e. those patients with “difficult to treat asthma” despite good adherence and inhaler technique [[Hekking et al., 2015](#); [Backman et al., 2019](#)].

Spontaneous remissions may occur in the transient asthma phenotype in children, remissions in adults (no symptoms/ exacerbations, no asthma medication for at least 1 year) may occur after a therapeutic intervention (off treatment) or during therapy (on treatment). So far, there is only one longitudinal study reporting that about 16% of adults with recently diagnosed asthma may experience clinical remission within 5 years [[Westerhof et al., 2018](#)]. Further research is on demand to identify significant new targets and treatment approaches to increase the number of remissions in asthma patients.

Many new drug candidates for asthma therapy are on the horizon, which will be discussed according to their development phase in this Whitepaper. In particular, we will give some insights into a “*First in human*” trial including a “*Proof of Mechanism*” asthma cohort to investigate SAR443765 (a bifunctional NANOBODY® molecule blocking TSLP and IL-13), which was recently conducted at the [Charité Research Organisation GmbH](#). The positive results thereof were already presented as *Breaking News* at the American Thoracic Society 2023 International Conference held in Washington DC (USA) in May 2023.

Since a safe and effective drug delivery to the lung is key for a successful asthma management, the recent innovations on the medical device market with respect to different device technologies and propellants, especially concerning the *Carbon Footprint* and contribution to the *Global Warming Potential*, will also be discussed in this article.

Asthma Drug Pipeline

Many new drug candidates have entered the asthma drug pipeline in 2023, which will be presented and discussed according to their development phase in the following. The review of phase 1 new drug candidates has been limited to projects with at least one asthma cohort in a completed/ongoing clinical trial. Biomarker research has become an integrate part in asthma drug development. For a more thorough overview related to asthma biomarkers, please refer to Part 1 of this Whitepaper “Modern asthma Management”. A thorough tabular overview of the current asthma drug pipeline 2023 is given in [Table 1](#) at the end of this chapter.

Phase 1 asthma drug candidates

ARO-MUC5AC (Arrowhead Pharmaceuticals) is a small interference RNA (siRNA) which acts by targeting MUC5AC in bronchial epithelium. It is developed based on Targeted RNAi Molecule (TRiM) platform. A Phase 1/2a study (NCT05292950) is currently evaluating the effects of ARO-MUC5AC in healthy subjects and patients with muco-obstructive lung disease (asthma and COPD).

ARO-RAGE (Arrowhead Pharmaceuticals) is an RNA interference therapeutic intended to reduce production of the Receptor for Advanced Glycation End products (RAGE) as a potential treatment for various muco-obstructive and inflammatory pulmonary diseases. A phase 1/2 study (NCT05276570) is now evaluating the effects of multiple ascending doses of ARO-RAGE inhalation solution in healthy subjects and in patients with mild to moderate asthma. *Interim results* demonstrated a reduction in soluble RAGE in asthma patients as measured in serum (after singular and two dose regime) and bronchoalveolar lavage fluid (after a single dose), which lasted for at least six weeks. ARO-RAGE showed a good safety profile at the doses tested so far. Arrowhead is yet to analyze data from the highest dose level ([HTTPS://WWW.CLINICALTRIALSARENA.COM/NEWS/ARROWHEAD-REPORTS-INTERIM-DATA-FROM-ARO-RAGE-STUDY/?CF-VIEW](https://www.clinicaltrialsarena.com/news/arrowhead-reports-interim-data-from-aro-rage-study/?cf-view) : accessed 29 September 2023).

AZD8630 (AstraZeneca) is a new inhaled antibody fragment against human thymic stromal lymphopietin (anti-TSLP Fab). TSLP is an epithelial-derived cytokine and key upstream regulator driving inflammatory airway responses in asthma. At current, the only approved biologic targeting TSLP is tezepelumab that is effective in type-2 asthma and led to significant reductions in asthma exacerbations, even in patients without evidence of type-2 inflammation [[Theofani et al., 2023](#), [Corren et al., 2021](#)]. AZD8630 was tested in a phase 1 study (NCT05110976) evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of AZD8630 (administered by dry powder inhaler) in healthy adult subjects and adults with asthma on medium to high dose inhaled corticosteroids and long-acting beta₂-agonists. The pharmacodynamic effect of AZD8630 on the *Fraction of exhaled Nitric Oxide* (FeNO) after daily inhaled AZD8630 over 29 days was assessed and compared to placebo. The study was completed in August 2023, the results thereof have not been published yet.

SAR443765 (SANOFI) is a bispecific NANOBODY[®] molecule blocking TSLP and IL-13 that is in development for the treatment of asthma. Epithelial-derived TSLP is a key initiator of the alarmin pathway, while IL-13 is involved in goblet cell metaplasia and bronchial hyperresponsiveness. TSLP and IL-13 are both triggering type-2 inflammatory airway responses including the production of related biomarkers such as *Fractional exhaled Nitric Oxide* (FeNO) (**Figure 1**).

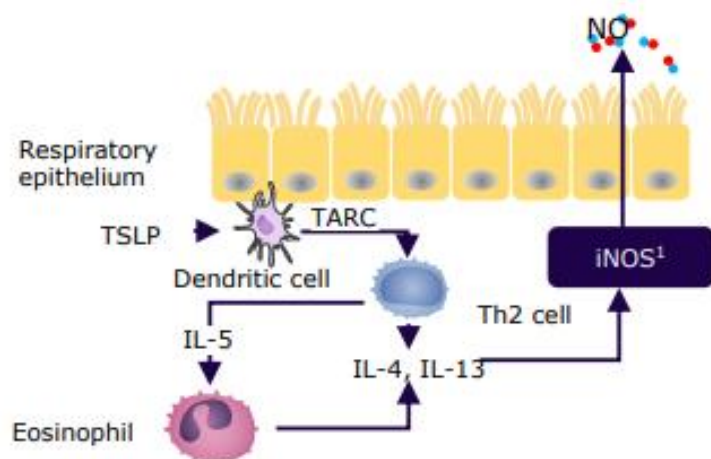


Figure 1: TSLP and IL-13 as key drivers of type-2 inflammatory airway responses in asthma.

¹ IL-13 was shown to activate inducible nitric oxide synthase, and as a result, increase the production of FeNO in the airways [[Santus et al. 2019](#), [Alving et al. 2010](#)].

Background: Elevated FeNO is associated with an increased exacerbation risk, worse FEV1 (Forced Expiratory Volume in 1 second), and an accelerated loss of lung function. FeNO often remains elevated in severe asthma despite use of inhaled and even oral corticosteroids. Monovalent biologics such as Tezepelumab (an anti-TSLP mAb) or Lebrikizumab (an anti-IL-13 mAb) have been shown to lower FeNO in asthma [[Corren et al. 2011](#), [Corren et al. 2021](#)]. Tezepelumab (Tezspire[®], Astra-Zeneca) has already been approved by the U.S. Food and Drug Administration (FDA, 2021) and the European Medicines Agency (EMA, 2022) as add-on maintenance treatment because it was effective in reducing the number of severe asthma flare-ups in two main studies including over 1,500 adults and adolescents with inadequately controlled asthma. Lebrikizumab (Roche) was in the asthma pipeline as an anti-IL-13 therapy, but one of two identical phase 3 studies failed to meet its primary endpoint of reducing exacerbations in patients with severe asthma. Tralokinumab (MedImmune), another anti-IL-13 mAb, improved FEV1 but failed to reduce exacerbation rates in a phase 2b study of patients with severe uncontrolled asthma [[Brightling et al. 2016](#)]. Combining anti-TSLP and anti-IL-13 therapies could potentially result in an additive effect, which may yield superior reduction of exacerbations and improvement in lung function than with either agent alone.

The *First-Time-in-Human* Study with SAR443765 including an additional *Proof of Mechanism* asthma cohort was conducted at the Charité-Research Organisation GmbH and delivered

positive results, which were presented as *Breaking News* at the American Thoracic Society 2023 International Conference held in Washington DC (USA) in May 2023.

The *Proof of Mechanism* part (NCT05366764) was a single dose, randomized (2:1), placebo-controlled, double-blind study to evaluate the safety, tolerability and pharmacokinetics of subcutaneously administered SAR443765 in 36 mild to moderate asthma patients with elevated FeNO (≥ 25 ppb). Potential participants were pre-screened for eligibility using a pre-study approach. **Figure 2** shows the Recruitment panel for this trial.

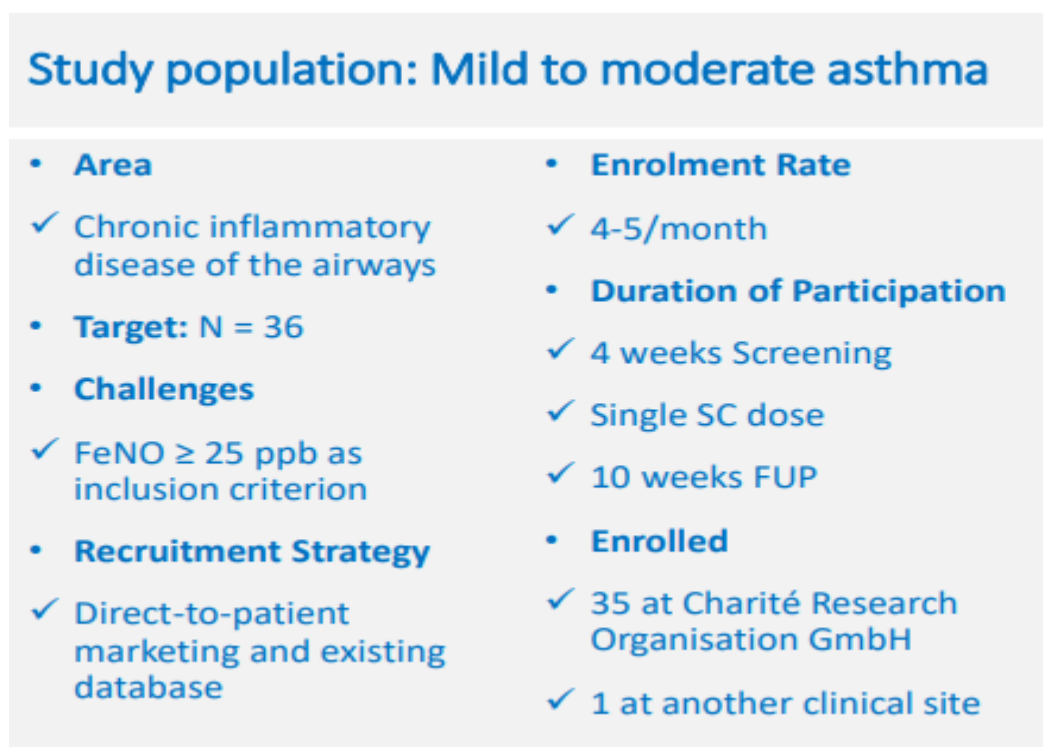


Figure 2: Recruitment panel of the *Proof of Mechanism* cohort in the FTIH-study with SAR443765

Source: Charité Research Organisation GmbH

Outcome Measures: Single doses of SAR443765 were administered by subcutaneous injection. The primary outcome was safety, and the change in FeNO from baseline compared to placebo at 4 weeks post-dose was a secondary endpoint. Blood-based type 2 biomarkers included IL-5, eotaxin-3, TARC (thymus and activation-regulated chemokine), IgE, and eosinophils. Lung function change was assessed as an exploratory outcome.

Results: Overall, SAR443765 was safe and well tolerated. A single dose of SAR443765 decreased FeNO concentrations as early as week 1, with significant reductions vs. placebo at week 4 (point estimate, -40.9 ppb; 90% CI, -55.43 to -26.39). Notwithstanding that lung function was normal to near-normal at baseline, rapid numerical improvement was seen for pre-bronchodilator FEV1 in the SAR443765 group as of week 1 that was largely maintained

through Day 29. Blood-based type-2 biomarkers such as eosinophils and IgE, and other biomarkers including eotaxin-3, IL-5, and TARC were reduced.

Taken together, blocking TSLP and IL-13 by the bispecific NANOBODY® SAR443765 was safe and well tolerated, and reduced FeNO concentrations and other biomarkers of type-2 airway inflammation and improved lung function in adult patients with mild to moderate asthma. A phase 2b study AIRCULES (NCT06102005) is now investigating the efficacy, safety, and tolerability of repeated subcutaneous injections of SAR443765 as add-on therapy in patients with moderate to severe asthma.

TAKC-02 (TAK Circulator Co.) is an antisense oligonucleotide inhibiting the synthesis of the RNA-binding protein MEX3B that is involved in the expression of various cytokines associated with the onset and exacerbation of several inflammatory diseases including asthma. The research team of Professor Akiyama demonstrated that Mex3B enhances the expression of IL-33 by inhibiting miR-487b-3p function and that TAKC-02 was able to suppress eosinophilic airway inflammation in a mouse model of allergic asthma [Yamazumi et al., 2016]. In addition they showed that Mex3B-mediated induction of CXCL2 (a potent chemotactic factor for neutrophils) is required for the development of steroid resistant neutrophilic airway inflammation. Intranasal administration of an anti-CXCL2 antibody or TAKC-02 suppressed neutrophil infiltration into the lungs [Yamazumi et al., 2019]. As treatment with aerosolized TAKC-02 reduced both eosinophilic (allergic) and neutrophilic type of inflammation in these asthma mouse models, it is expected to reduce both eosinophilic *and* neutrophilic inflammation in patients with severe asthma. (Figure 4). The *first-time-in-human* trial [NCT05018533] investigating the safety, tolerability and PK of single and multiple ascending doses of a TAKC-02 inhalation solution in healthy volunteers was completed by end of 2021. According to TAK-Circulator Corporation, the results thereof support the further development of TAKC-02 as a new inhalative medicine for patients with severe asthma.

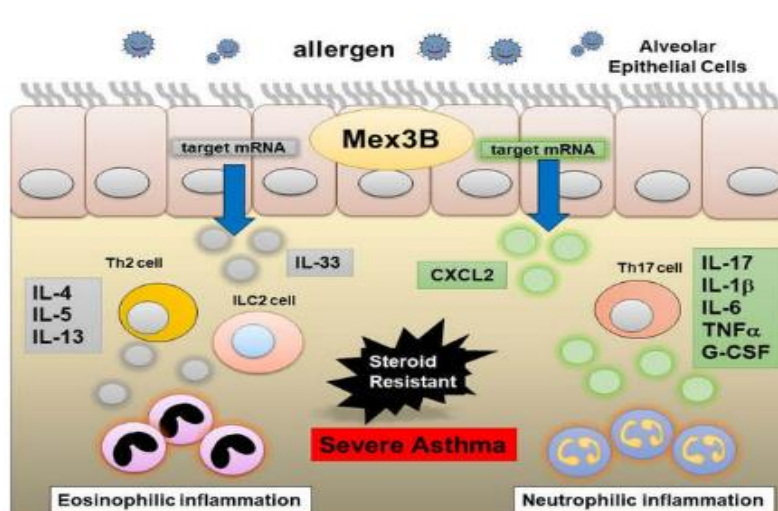


Figure 4: TAKC-02 suppresses both eosinophilic and neutrophilic type of inflammation

Source: TAK-Circulator Corporation Website (public domain)

Zavegepant (Pfizer) is an *oral* calcitonin gene-related peptide (CGRP) receptor antagonist which is currently in development for the treatment of allergic asthma. A pathogenic role of CGRP has been proposed in asthma, chronic obstructive pulmonary disease and cystic fibrosis [Atanasova et al., 2018; Pavón-Romero et al., 2021]: CGRP is expressed in nerve fibres that innervate the airways as well as in pulmonary neuroendocrine cells throughout the airway tree and in the alveoli. CGRP can induce mucus secretion in the airways, from both glands and goblet cells and amplifies the pro-contractile effects of capsaicin and electrical field stimulation.

A Phase 1b trial [NCT04987944] with a double-blind, placebo-controlled, parallel-group design evaluating the safety and efficacy of *oral* Zavegepant in subjects with mild allergic asthma has been completed in April 2023. The efficacy was measured as allergen induced late asthmatic response (LAR) assessed as FEV1 after 3-7 hours of an allergen inhalation challenge. So far no results are available in the public domain.

Zavegepant nasal spray (ZAVZPRET™) has been already approved by the FDA for the acute treatment of migraine with or without aura in adults.

Phase 2 asthma drug candidates

ADX-629 (Acloproxalap, Aldeyra Therapeutics Inc.) is a *first-in-class* orally administered reactive aldehyde species (RASP) inhibitor. In a placebo-controlled crossover trial (NCT04728711) of eight mild asthma patients treated for 7 days, asthma symptom scores and sputum eosinophil cell counts were numerically reduced following treatment with ADX-629 relative to treatment with placebo. Compared to placebo, ADX-629 led to statistically significant reductions in plasma levels of the pro-inflammatory cytokines IL-5 (p=0.02) and TNFα (p<0.0001), and numerical reductions in plasma levels of malondialdehyde (unpublished top-line data announced by Aldeyra Therapeutics in March 2022).

Amlitelimab (formerly KY1005, SANOFI) is a human mAb that binds to OX40-ligand (OX40L) thereby blocking the alarmin pathway involved in inflammatory and remodeling changes in the airway mucosa that predispose to asthma exacerbations. Release of epithelial alarmins

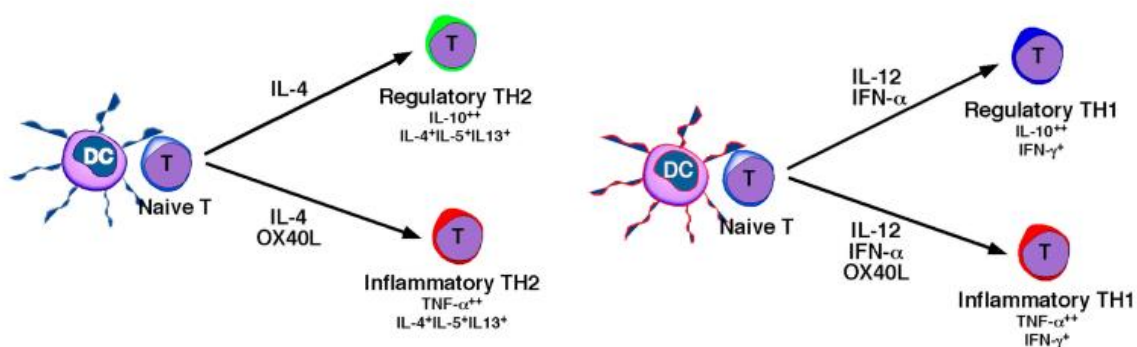


Figure 5: Th1 and Th2 cell responses evoked by OX40L

DC = dendritic cell, OX40L = OX40 ligand, TH1 = T helper 1 cell, TH2 = T helper 2 cell

Source: Figure adopted from Ito et al., 2005

such as thymic stromal lymphopoietin (TSLP) induces the expression of OX40 ligand on dendritic cells (DCs) to promote their mobilization to locally draining lymph nodes where they activate naive CD4+ T cells to differentiate into a proinflammatory TH2 phenotype expressing IL-4, IL-5, IL-13, and TNF-alpha. T regulatory cells interacting with TSLP-activated DCs (through OX40L) switch from an IL-10 producing regulatory subtype into a proinflammatory TNF-a producing subtype [Ito et al., 2005] (Figure 5). Amletemimab is tested in a phase 2 trial (NCT05421598) to reduce the rate of severe exacerbations in patients with moderate-to-severe asthma.

AVTX-002 (Avalo Therapeutics) AVTX-002 is a *potential first in class mAb* directed against human LIGHT protein (= Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator (HVEM), a receptor expressed by T lymphocytes). Blocking LIGHT protein signaling will potentially inhibit proinflammatory and profibrotic pathways directly relevant to asthma pathogenesis (Figure 6).

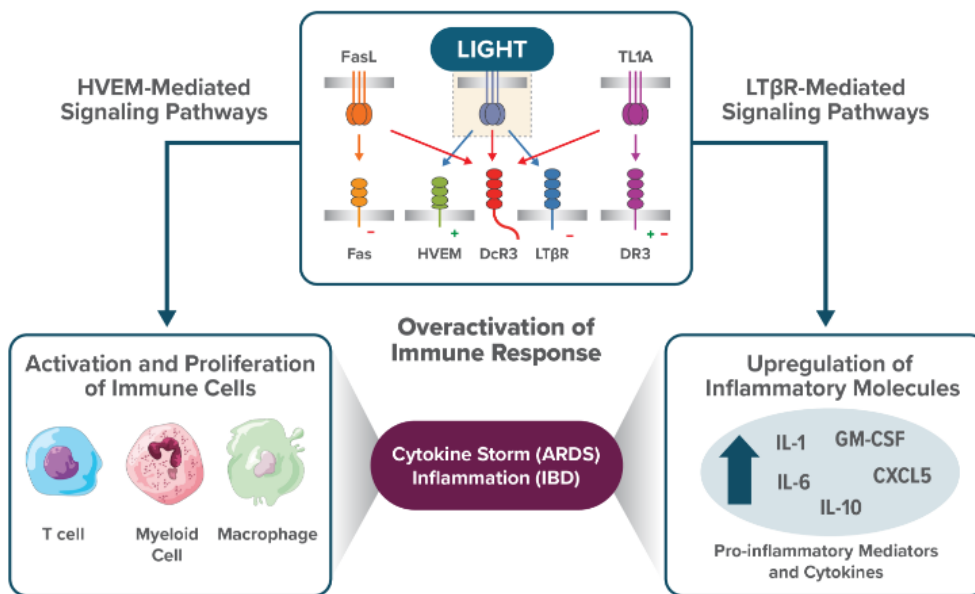


Figure 6: Targeting LIGHT (inflammatory cytokine)

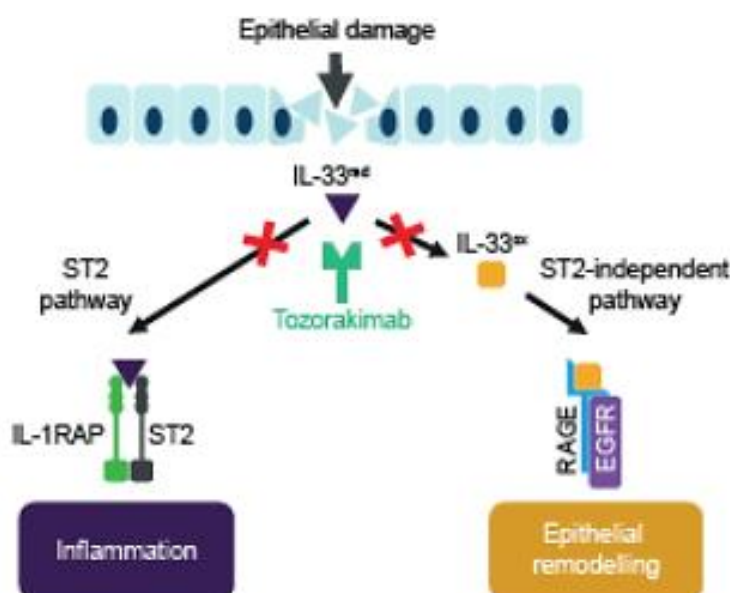
CXCL5, C-X-C motif chemokine 5; DcR3, decoy receptor 3; DR3, death receptor 3; FasL, Fas ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; HVEM, herpesvirus entry mediator; IL, interleukin; LTβR, lymphotoxin-β receptor; TL1A, TNF-like ligand 1A; TNF, tumor necrosis factor.

Source: Avalo Therapeutics Website: [HTTPS://WWW.AVALOTX.COM/PIPELINE/IMMUNOLOGY/AVTX-002](https://www.avalotx.com/pipeline/immunology/avtx-002)

AVTX-002 is currently tested in a phase 2 trial (NCT05288504) in patients with non-eosinophilic asthma (PEAK Trial). LIGHT plays an important role in regulating immune responses in the lung, gut, and skin and is “upstream” (or proximal) in the inflammatory cascade to many well recognized cytokines like IL-1, IL-6, IL-10, IL-13, tumor necrosis factor (TNF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). LIGHT has been implicated as a key driver of asthmatic airway remodelling in preclinical animal models and relevant cell culture systems, despite having little effect on airway eosinophilia [Doherty et al. 2011]. Human data has demonstrated elevated levels of TNF-LIGHT in the airways of asthmatic subjects with persistent airflow limitation [Hirano et al., 2021].

AZD1402 (Astra Zeneca) is an IL-4R α antagonist (Anticalin[®] protein, Pieris Pharmaceuticals) for inhalation. A phase 2 trial [NCT04643158] evaluating the efficacy and safety of inhaled AZD1402 administered for 4 weeks in adults with asthma on medium-to-high dose inhaled corticosteroids has been *prematurely terminated* in July 2023. The decision was based on lung findings from a non-clinical 13-week Good Laboratory Practice (GLP) toxicology study.

Tozorakimab (MEDI 3506 from MedImmune, clinical development by AstraZeneca) is an anti-IL-33 mAb with dual action inhibiting *reduced* IL-33 (IL-33red) and *oxidized* IL-33 (IL-33ox) activities through distinct serum-stimulated 2 (ST2) and receptor for advanced glycation end products/epidermal growth factor receptor (RAGE/EGFR complex) signaling pathways. Tozorakimab potently inhibited ST2-dependent inflammatory responses driven by IL-33 in primary human cells and in a murine model of lung epithelial injury. [England et al., 2023] (Figure). Tozorakimab has recently investigated in a phase 2 trial (NCT04570657) to assess the efficacy and safety of Tozorakimab in adults with uncontrolled moderate-to-severe asthma, which has been completed in February 2023.



Reduced IL-33 (IL-33red) that is released following epithelial damage, binds tozorakimab with a high affinity and a fast association rate. Tozorakimab directly neutralizes IL-33red inflammatory activities at the ST2 receptor. The IL-33red–tozorakimab complex prevents the oxidation of IL-33, IL-33ox–RAGE/EGFR signaling and epithelial dysfunction.

Figure 7: Tozorakimab – Dual Mode of Action

EGFR, epidermal growth factor receptor; IL-1RAP, interleukin-1 receptor accessory protein; ox, oxidized; RAGE, receptor for advanced glycation end products; red, reduced
 Source: Figure adopted from England et al., 2023

Sunshine 610 (Sunshine Guojian Pharmaceutical (Shanghai) Co., Ltd.) is a humanized anti-IL-5 mAb for subcutaneous injection. A multicenter phase 2 trial [NCT05528679] with a randomized, double-blind, placebo-controlled design is currently testing the efficacy and safety of Sunshine 610 treatment in patients with severe eosinophilic asthma. The primary outcome measure is the change in pre-bronchodilator FEV1 from baseline at week 16 after repeated doses of Sunshine 610 every 4 weeks.

Phase 3 asthma drug candidates

Depemokimab (GSK3511294, GSK) is a *long-acting* monoclonal antibody against interleukin 5 (IL5). A phase 3 trial (NCT04718103) for asthma is currently investigating the efficacy and safety of Depemokimab as an adjunctive therapy in patients with severe uncontrolled asthma with an eosinophilic phenotype (biomarker: blood eosinophil count >150/ μ l). Monoclonal antibodies against the IL5-receptor have already been approved (mepolizumab, reslizumab or benralizumab), as effective treatments for patients with type-2 asthma.

Masitinib (AB Science) is an *oral* tyrosine kinase inhibitor (small molecule), targeting stem cell factor receptor (c-kit) and platelet-derived growth factor (PDGF) receptor, which are expressed on several cell types including mast cells and bronchial cells, respectively. The primary endpoint was met in a phase 3 trial (NCT03771040) evaluating oral masitinib (titration up to 6 mg/kg/day) in severe asthma uncontrolled by high-dose inhaled corticosteroids (ICS) and with blood eosinophil counts >150 cells/ μ L. Results showed a statistically significant 29% reduction in severe exacerbations relative to placebo; the frequency was 0.43 in the masitinib arm, compared with 0.62 in the placebo arm. Another phase 3 study (NCT01449162), evaluating masitinib (6mg/kg/day) for the treatment of severe uncontrolled asthma either with oral corticosteroids (OCS) or high-dose inhaled corticosteroids/long-acting beta₂ agonists (high dose ICS/LABA), found that the drug reduced severe asthma exacerbations by 35% compared with placebo [[Davidescu et al., 2022](#)].

MM09-MG01 (Immunotek S.L.) is a *modified* natural grass allergen extract for subcutaneous injection. Glutaraldehyde-modified natural allergen extracts show significant reduction in the IgE-binding capacity and proteolytic activity. This allows the administration of higher doses in a shorter period of time, and to mix different allergen extracts.

An observational multicenter cohort study reported that specific immunotherapy using natural modified allergen vaccines is safe to treat allergic patients, even at higher doses and in mixtures of unrelated allergen extracts [[Guzmán-Fulgencio et al. 2016](#)]. Based on these results, a multicenter phase 3 trial [NCT04874714] with a randomized, placebo-controlled design is now investigating the efficacy and safety of MM09-MG01 for the treatment of asthma and allergic rhinitis/rhinoconjunctivitis. The outcome measures include a Combined Symptoms and Medication Score (CSMS), number of symptom-free days, number of days without need of medication, and changes in FEV1 and immunological parameters (total and specific IgE, specific IgE index / total IgE and specific IgG4).

Table 1: Asthma: Potential Pharmacological Treatments

Product Class/Product	Biomarker	Mechanism of Action/Target/Route of administration	Outcome Measure/Endpoints	NCT and/or Eudra-CT
Phase 1				
ARO-MUC5AC (Arrowhead Pharmaceuticals)	Unknown	ARO-MUC5AC for inhalation is a siRNA that acts by targeting mucin 5AC in bronchial epithelium. ARO-MUC5AC is developed based on Targeted RNAi Molecule (TRiM) platform.	Outcome Measures in asthma/COPD cohort: safety, tolerability and PK profile after 3 inhaled doses of ARO-MUC5AC	NCT05292950 : Study of ARO-MUC5AC in Healthy Subjects and Patients With Muco-Obstructive Lung Disease (Asthma and COPD). <i>Completion expected in February 2024.</i>
ARO-RAGE (Arrowhead Pharmaceuticals)	Unknown	ARO-RAGE inhalation solution is a RNA interference therapeutic designed to reduce production of the Receptor for Advanced Glycation End products (RAGE) as a potential treatment for various muco-obstructive and inflammatory pulmonary diseases.	Outcome Measures in asthma patients: Safety, tolerability, PK-profile, and changes in lung function (FEV1, FVC, and DLCO) after multiple ascending doses of ARO-RAGE.	NCT05276570 : A Phase 1/2a Study Evaluating the Effects ARO-RAGE Inhalation Solution in Healthy Subjects and Patients With Inflammatory Lung Disease. <i>Completion expected in February 2024.</i>
AZD8630 (AstraZeneca)	FeNO of ≥ 35 ppb at the Screening Visit and ≥ 30 ppb at randomisation as inclusion criterion PD-biomarker: Change in FeNO following daily inhaled AZD8630	TSLP FAb for inhalation (dry powder inhaler)	Primary outcome measure: Safety and tolerability, and PK-profile of AZD8630 PD Endpoint: Effect of daily AZD8630 inhalations on FeNO over 29 days compared to placebo.	NCT05110976 : A Study to Investigate the Safety, Tolerability and Effects of AZD8630 in Healthy Subjects and Subjects With Asthma on Inhaled Corticosteroids and Long-acting Beta-agonists. <i>Completion date: August 2023. Results not published yet.</i>
SAR443765 (SANOFI)	FeNO ≥ 25 ppb as inclusion criterion, PD-biomarker: - Change from baseline in FeNO level at Week 4	Anti-TSLP/IL-13 bifunctional NANOBODY® blocking TSLP and IL-13 for subcutaneous injection	Positive top-line results: - significant reductions in FeNO versus placebo at week 4 (point estimate, – 40.9 ppb; 90% CI, –55.43 to –26.39)	NCT05366764 : A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Doses of SAR443765 in Healthy Adult

Product Class/Product	Biomarker	Mechanism of Action/Target/Route of administration	Outcome Measure/Endpoints	NCT and/or Eudra-CT
	- Plasma CCL26, serum TARC, IL-5 and IgE levels, and eosinophil count in blood		<ul style="list-style-type: none"> - reductions in blood-based type 2 biomarkers including IL-5, eotaxin-3, TARC, IgE and eosinophils - TEAEs were comparable with the placebo group. 	Participants and of a Single Dose of SAR443765 in Participants With Mild-to-moderate Asthma. <i>Completed in February 2023.</i>
TAKC-02 (TAK-Circulator Co.)	Unknown	Antisense oligonucleotide (RNaseH-dependent) that inhibits MEX3B synthesis for inhalation	Outcome Measures: <ul style="list-style-type: none"> - Changes in the rate of adverse events - PK (AUC, Cmax, Tmax, T1/2) 	NCT05018533 : The Safety and Pharmacokinetics Study of TAKC-02 Inhalation Solution in Healthy Adult Males. <i>Completed in 2021.</i>
Zavegepant (Pfizer)	Unknown	Zavegepant, a calcitonin gene-related peptide (CGRP) receptor antagonist will be developed as oral treatment for allergic asthma.	Outcome Measure: Allergen induced late asthmatic response (LAR) assessed as FEV1 after 3-7 hours of an allergen inhalation challenge.	NCT04987944 : A Phase 1b, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate Safety and Efficacy of Oral Zavegepant in Subjects With Mild Allergic Asthma. <i>Completed in April 2023.</i>
Phase 2				
ADX-629 (Acloproxalap, Aldeyra Therapeutics Inc.)	Sputum eosinophilic count	Potential first-in-class orally administered reactive aldehyde species (RASP) inhibitor	Top-line results announced in March 2022: Compared to placebo, ADX-629 reduced pro-inflammatory cytokines IL-5 ($p=0.02$) and TNF α ($p<0.0001$), and numerical reductions in plasma levels of malondialdehyde and sputum eosinophils (<i>unpublished results</i>)	NCT04728711 : A Double Masked, Placebo Controlled, Single Center, Randomized Clinical Trial to Assess the Safety and Efficacy of ADX-629 in Subjects with Mild Asthma Induced by the Bronchial Allergen Challenge (BAC). <i>Completion in 2022: No results posted.</i>
Amlitelimab (SANOFI) (before KY1005)	Unknown	Anti-OX40-Ligand humanized bi-specific mAb for subcutaneous injection	Primary EP: Annualized rate of severe exacerbation events over 48 weeks	NCT05421598 : Dose Ranging Study of Amlitelimab in Adult Participants With Moderate-to-severe Asthma (TIDE-

Product Class/Product	Biomarker	Mechanism of Action/Target/Route of administration	Outcome Measure/Endpoints	NCT and/or Eudra-CT
				asthma). <i>Completion expected March 2025.</i>
AVTX-002 (Avalo Therapeutics Inc.)	Blood eosinophil count $\leq 300/\mu\text{l}$ as inclusion criterion Safety biomarker: change from baseline in FeNO	Potentially first in class fully human anti-LIGHT mAb for subcutaneous injection LIGHT (Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator (HVEM), a receptor expressed by T lymphocytes).	Primary Outcome Measure: Proportion of patients who experience asthma related events through 14 weeks such as ≥ 6 additional reliever puffs of SABA (compared to baseline) in a 24-hour period on 2 consecutive days	NCT05288504 : A Study to Evaluate the Safety and Efficacy of AVTX-002 for the Treatment of Poorly Controlled Non-Eosinophilic Asthma. <i>Completed in May 2023.</i>
AZD1402 (Astra Zeneca)	FeNO and immuno-biomarkers as PD parameter	IL-4Rα antagonist (Anticalin [®] protein class from Pieris Pharmaceuticals Germany) for inhalation (dry powder)	Primary Outcome Measures: To investigate the safety, tolerability and efficacy of inhaled AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA.	NCT04643158 : Efficacy and Safety of Inhaled AZD1402 Administered for Four Weeks in Adults With Asthma on Medium-to-High Dose Inhaled Corticosteroids (APATURA). <i>Prematurely terminated in July 2023.</i>
Tozorakimab (MEDI 3506 from MedImmune/ developed by AstraZeneca)	Unknown	IL-33 mAb for subcutaneous injection with dual action inhibiting reduced IL-33 (IL-33red) and oxidized IL-33 (IL-33ox) activities through distinct serum-stimulated 2 (ST2) and receptor for advanced glycation end products/epidermal growth factor receptor (RAGE/EGFR complex) signaling pathways	Primary Endpoint: To assess the effect of MEDI3506 compared with placebo on lung function (pre-BD FEV1) between baseline and week 16, in adult participants with uncontrolled moderate-to-severe asthma.	NCT04570657 : Study to Assess the Efficacy and Safety of MEDI3506 in Adults With Uncontrolled Moderate-to-severe Asthma (FRONTIER-3). <i>Trial Completion in February 2023.</i>
Sunshine 610 (Sunshine)	Blood eosinophil count $\geq 150/\mu\text{l}$ within 6	Humanized anti-IL-5 mAb for subcutaneous injection	Primary Outcome Measure: Change from baseline in pre-	NCT05528679 : A Multicenter, Randomized, Double-blind, Placebo-

Product Class/Product	Biomarker	Mechanism of Action/Target/Route of administration	Outcome Measure/Endpoints	NCT and/or Eudra-CT
Guojian Pharmaceutical (Shanghai) Co., Ltd.)	months before screening or $\geq 150/\mu\text{l}$ at screening as inclusion criterion		bronchodilator forced expiratory volume in one second (FEV1) at week 16 after repeated doses of 610 every 4 weeks	controlled Phase II, Efficacy and Safety Study of Recombinant Anti-IL-5 Humanized Monoclonal Antibody Therapy in Adult Subjects With Severe Eosinophilic Asthma. <i>Completion expected September 2023.</i>
Phase 3				
Depemokimab (GSK3511294, GSK)	Blood eosinophil count $>150/\mu\text{l}$ as inclusion criterion	Anti-IL-5 mAb for subcutaneous injection	Primary EP: Annualised rate of clinically significant exacerbations over 52 weeks in severe eosinophilic asthma	NCT04718103 : A Study of GSK3511294 (Depemokimab) in Participants With Severe Asthma With an Eosinophilic Phenotype. <i>Completion expected May 2025.</i>
Masitinib (AB Science)	Blood eosinophil count $>150/\mu\text{l}$ as inclusion criterion	Oral selective tyrosine kinase inhibitor, which selectively targets mast cells through inhibition of tyrosine kinases c-Kit (stem cell factor), and platelet-derived growth factor (PDGF) receptor.	Positive Outcomes of two phase 2b/3 trials: Patients with severe uncontrolled asthma treated with high dose ICS <i>or</i> OCS showed significant reductions of severe asthma exacerbations by Masitinib compared to placebo.	NCT03771040 : Masitinib in the Treatment of Patients With Severe Uncontrolled Asthma and Elevated Eosinophil Levels. <i>Completed 2020.</i> NCT01449162 : Masitinib in Treatment of Patients With Severe Persistent Asthma Treated With Oral Corticosteroids. <i>Completed 2019.</i>
MM09-MG01 (Immunotek SL, Spain)	Specific IgE against one of the components of the mixture of grasses as inclusion criterion	Modified grass allergen extract for subcutaneous injection	Outcome Measure: Combined Symptoms and Medication Score Immunological parameters: Analyses of total and specific IgE, specific IgE index / total IgE and specific IgG4	NCT04874714 : Efficacy and Safety Evaluation for the Treatment of Asthma and Allergic Rhinitis/ Rhinconjunctivitis. <i>Completion expected October 2023.</i>

DLCO = Diffusing Capacity for Carbon Monoxide, FeNO = Fraction of exhaled Nitric Oxide, FEV1 = Forced Expiratory Volume in 1 second, FVC = Forced Vital Capacity, SABA = short-acting beta2-agonist, TARC = Thymus and Activation-Regulated Chemokine, TEAEs = Treatment-emerging adverse events, TSLP = Thymic Stromal Lymphopoietin

Application Systems in the Treatment of Asthma

Pulmonary drug delivery is a form of a drug targeting whether to the site of action in the lungs for topically acting drugs or the site of absorption for systemically acting drugs. The topical application allows sufficient dosing avoiding systemic side effects and the possibility of immediate onset of action. Sounding obvious and simple, topical drug delivery is very complex starting from active compound characteristics with the respective propellants, different inhaler technologies, mechanical, chemical and immunological barriers of the lung surface and tissue until behavioral aspects of self-medication including adherence.

We would like to focus on the different device technologies and their propellants, especially concerning the *Carbon Footprint* and contribution to the *Global Warming Potential*.

Medical Devices for Asthma

A safe and effective drug delivery to the bronchial airways is key for a successful asthma management. Medical devices such as inhalers and nebulizers are meanwhile broadly used. The availability of sufficient inspiration, the ability to coordinate the intended use of the device on patient site and the particle size and technology determine the selection of an appropriate application system. The main characteristics of each device type have been thoroughly reviewed by [Lavorini et al. 2019](#).



Metered Dose Inhalers (MDIs) deliver the specific dose of the medication shrouded in a propellant cloud - today mostly hydrofluoroalkanes (HFA) to the lung. There are MDIs which use drug crystals attached to porous particles of phospholipids. It provides a stable homogenous suspension and delivers a drug dose throughout the life of the inhaler. In order to reach the bronchi the particle size has to be less than 6 μm . The small airways are the key targets in the pathophysiology and the site of action of treatments in asthma. Extra fine pressured MDI formulations with particle size of less than 1 μm have enabled delivery into the small airways. Most patients rely on the use of MDIs because they are easy to carry around, can deliver multiple doses and they have lower costs. The majority of MDI sold are reliever therapies. However, a proportion of patients rely on using MDIs reliever and/or maintenance products to manage their condition, being familiar with this kind of device as reliever [[United Nations MCTOC Assessment Report 2018](#)]. Patients also benefit from the use of MDIs because this allows them to use spacers to reduce deposition of medication in the mouth and throat and reduce the amount of swallowed drug.



Dry Powder Inhalers (DPIs) contain a dose of one or more medications in a dry powder form. The drug is delivered in the form of particles in a capsule or blister, which must be punctured before use. A DPI is a breath-actuated device; thus there is no need of propellant in the inhaler. Dose release and distribution of particle size are both depending on the breathing flow. The patient must inhale more forcefully from the start of the inhalation than with MDIs. But a spacer is not needed and patients do not need to hold their breath after each use.

Caution: Powder inhalers should however not be used in severe asthma attacks because of inadequate inspiratory flow. In an emergency, inhalation can be done with a metered dose inhaler with spacer or with a nebulizer [[German S2k-Guideline 2023](#)].



Soft Misted Inhalers (SMIs) release a pre-measured amount of liquid medicine into a mist that can be inhaled as a slow-moving mist. The aerosol generation does not depend on the patient's inspiratory pressure. The liquid drug itself can be packed in customized cartridges. SMIs are ideal for the delivery of both small molecules and biologics, and is specially designed to optimize lung deposition whilst minimizing oropharyngeal deposition.



Nebulizers turn liquid asthma medicine into a mist. The patient is breathing the medicine through a mask or a mouthpiece. Particle size determines the distribution of the mist in the different parts of the bronchi, *the duration of the inhalation determines the dose.*

There are different types of individualized disease oriented solutions:

- Compressed Jet Nebulizers using air or similar pressurized gas to convert liquid into a fine spray or mist and to push medications toward the mouth.
- Breath-Actuated Pneumatic Nebulizers produce aerosol only when the patient inhales. Loss of drug is less and delivery is more efficient
- Ultrasound Nebulizers where the ultrasound technology determines the particle size and influences therefore the place of disposition. They are used for specific indications to deliver bronchodilators or hypertonic saline to stimulate sputum production.
- *Mesh nebulizer* create vibrations (piezo) that move to the liquid formulation through a fine mesh (aperture plate) to develop aerosol medication. The diameter of the aperture determines the size of the particle generated.

New Developments on the Device Market

There is progress in the development of devices on one hand and improvements in the formulations of administered active ingredients on the other hand. Innovative particle processing methods have been introduced to improve lung targeting and dose consistency on the one hand and to reduce off-target effects and flow rate dependencies on the other hand. The new technologies enable greater control of the micromeritic properties of the particles, including their size, density, surface composition, surface morphology, and physical form of the drug substance (reviewed by [Anderson et al., 2022](#)):

- spray drying,
- spray freeze drying,
- various supercritical fluid-processing methods, and
- lithography or “printing” of highly uniform particles with a consistent shape

Because of the new technologies, the total lung dose that can be achieved with pharmaceutical aerosols has been remarkably increased reaching in some products up to

90%. For example, spray-dried powders with reduced interparticle cohesive forces enable improved powder flow and dose delivery to the lungs [Geller et al., 2011].

New advanced nebulizers with mesh technology become more sophisticated including accurate control of droplet size, true breath synchronization, matching delivery to inspiratory profiles helping patients to inhale correctly. With the availability of bronchodilators, anti-inflammatory drugs, PDE inhibitors, mucolytics, vasodilators or antibiotics in nebulized formulations and the development new pipeline agents, one can speculate that nebulizers offer a valuable platform to allow for future therapeutic approaches using compounds alone or in combination [Troy et al., 2023].

High dose delivery has been accomplished by Jet Nebulizers, but those are causing a high treatment burden due to long administration times. The introduction of Vibrating Mesh Nebulizers as well as the development of first high-dose dry powder formulations allow a more rapid delivery of high doses. Mesh Nebulizers have become the first choice for new nebulized pharmaceutical drug developments [Pritchard et al., 2018]: Vibrating Mesh Nebulizers (e.g. PARI e-Flow, Phillips Respironics Innospire) provide improved portability, and more efficient delivery into the lungs with significantly reduced administration times compared to jet nebulizers and less degradation of biologics.

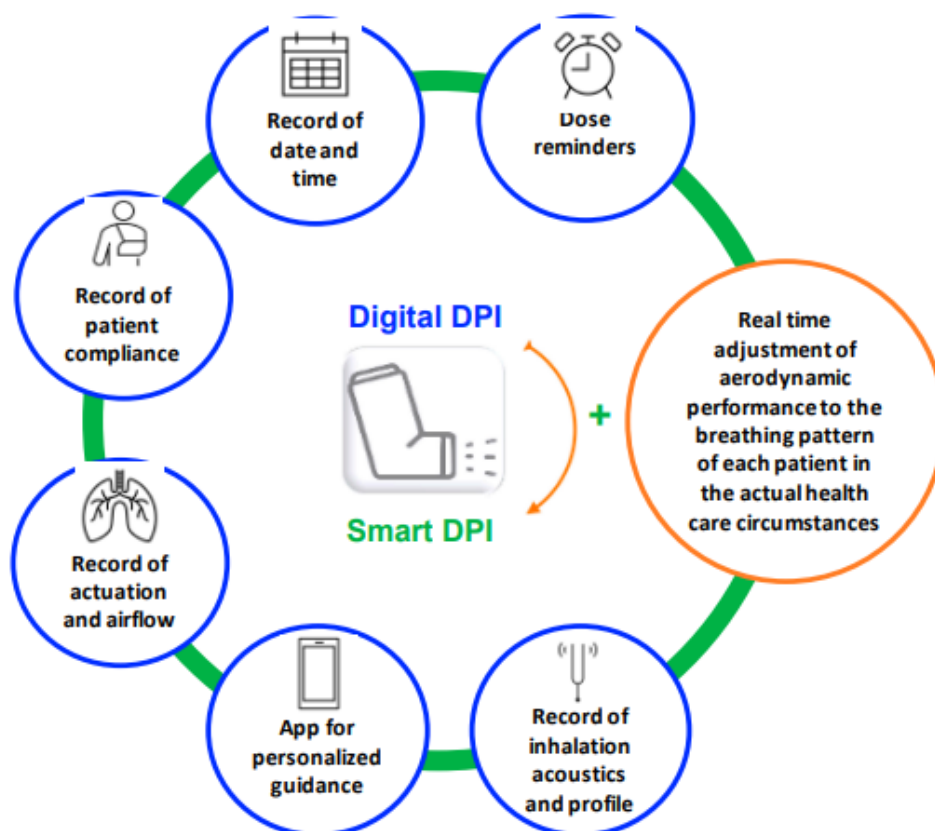


Figure 8: Digital functions of the current available digitalized Dry Powder Inhalers and additional features required for a “Smart” device

Source: Figure adopted from [Xiroudakis et al. 2021](#)

Electronic aids or mobile devices can be used, depending on the patients' preference and capabilities, to improve inhaler technique and patient compliance [[Xiroudaki et al., 2021](#)]. New advanced digital devices to enhance treatment adherence have already reached the market. In addition, so called "smart" devices are able to interact with patients, with other health care providers, and with other devices. Moreover, it should be able to produce reliable data, and their patterns should be available in real time to all stakeholders in the health system. Regulatory authorities approve a device as "smart" only when it is scientifically proved and able to predict and adjust to different clinical parameters such as breathing patterns of patients (**Figure 8**).

Some patient-centric innovations are already available on the market that contribute to improve the patients' compliance to treatment regimen and their quality of life. The integrated-digital-inhaler GoResp®Digihaler® (Teva, UK) allows asthma patients to mainly self-manage their condition and share their data with healthcare professionals. For example, the reusable inhaler system Spiriva®Respimat® (Boehringer-Ingelheim, Germany) features an advanced, patient-centric design and allows easier handling of the device [[Wachtel et al., 2017](#)].

Furthermore, simplifying inhaler regimens by applying the same type of inhaler for concomitant inhaled medications over time minimizes device misuse, leading to improved clinical outcomes and reduced health care use in patients with asthma or COPD [[Usmani et al., 2021](#)]. If possible, one inhalation system (one type of metered dose inhaler or powder inhaler) should be prescribed for all required medications for long-term therapy [[German S2k-Guideline 2023](#)].

Device Propellants with lower Carbon Footprint/Global Warming Potential

The first medication sprays were introduced in 1956 with the propellant chlorofluorocarbon (CFC) which was used in industrial production since 1930. CFCs are characterized by low toxicity, reactivity and flammability – but deplete the ozone layer. The prohibition of CFC propellants required by the *Montreal protocol of 1987* approved by 197 states the legally binding *Kigali-amendment of 2016* meanwhile signed by 152 states as provided by the Depositary, the United Nations Office of Legal Affairs, New York in August 2023 [[HTTPS://OZONE.UNEP.ORG/ALL-RATIFICATIONS](https://ozone.unep.org/all-ratifications)].



The European Union has adopted the regulation and industry is currently developing solutions.

With the decision in Kigali to globally reduce the consumption of climate-damaging hydrofluorocarbons (HFCs), the Montreal Protocol was extended to a new group of substances. The HFCs include hydrofluoroalkanes (HFAs) propellants such as HFC-134a introduced in the mid-1990s for Metered Dose Inhalers (MDIs) to replace for CFCs. Although HFAs account for only 0.032% of the total greenhouse gases

(GHG) emissions, their atmospheric persistence however is about 250 years [Emeryk et al., 2021] (Figure 9).

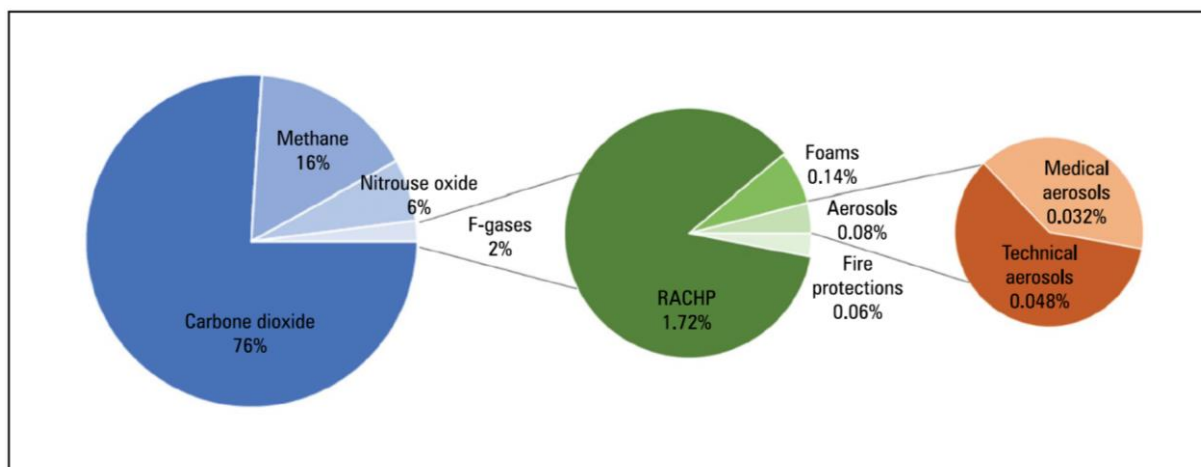


Figure 9: The share of medical aerosols in the total Greenhouse Gas pool (F-gases) in the world in 2016.

RACHP — Refrigeration, Air-Conditioning, Heat Pump

Source: Figure adopted from [Emeryk et al., 2017](#)

The *Global Warming Potential* (GWP) was developed to allow comparisons of the global warming impacts of different gases [U.S. Environmental Protection Agency]: The GWP is a measure of how much energy the emissions of 1 ton of a gas will absorb over a given period of time, relative to the emissions of 1 ton of carbon dioxide (CO₂). The larger the GWP, the more that a given gas warms the Earth compared to CO₂ over that time period. The United Nations Framework Convention on Climate Change (UNFCCC) addresses several groups of fluorinated greenhouse gases (F-gases). Most of these F-gases have very high GWPs in comparison with other greenhouse gases. Among them are hydrofluorocarbons (HFCs), perfluorocarbons (PFCs), sulphur hexafluoride (SF₆) and nitrogen trifluoride (NF₃). They are also covered by the Kyoto Protocol and included in the EU's commitment under the Paris Agreement.

In 2015, the new F-gas Regulation (No 517/2014) (EU, 2014b) was implemented, which aims to reduce F-gas emissions by two thirds of the 2010 level by 2030 [European Environment Agency Report 2022]. The EU regulation No 517/2014 recognizes however an exemption for HFA propellants for pharmaceutical use until alternative low GWP fluorocarbons are identified as safe replacements [Panigone et al., 2020]. Development work is underway to introduce propellants with lowest GWP like HFC-152a or HFO-1234ze in pressured MDIs (pMDI) into the market in 2025 [United Nations MCTOC Assessment Report 2022].

The *Carbon Footprint* is also different for every specific product and proper quantification is needed to assess current impact. It is important to note that just one dose of an average pMDI has a *Carbon Footprint* 25 times greater than that of an equivalent dose given via an average Dry Powder Inhaler (DPI) [NHS DDICB & System Partners Greener Inhaler Prescribing Guidance V4, 2021]. Thus, changing patients from a pMDI to a DPI would be environmentally

beneficial. For every 10% of MDIs changed to DPIs, 58 kt CO₂e could be saved annually in England [[Wilkinson et al., 2019](#)].

For example, the reusable inhaler system Spiriva®Respimat® (Boehringer-Ingelheim, Germany) makes it possible to reduce waste and the *Carbon Footprint* over the course of the product life cycle [[Dhand et al., 2019](#); [Haensel et al., 2019](#)].

Determining the relative costs of MDIs and DPIs depends on several device features, such as device complexity, formulation, and number of doses per device. Switching to DPIs may be achieved alongside reduced drug costs by using less expensive brands. Substantial carbon savings can also be made by using small volume HFA134a MDIs, in preference to large volume HFA134a MDIs, or those containing HFA227ea as a propellant.

In all these considerations the optimal management and quality of care of patients with asthma needs to remain the absolute priority for prescribers, to avoid stigmatization with inappropriate switching inhalers with deterioration in disease outcomes.

According to [Usmani & Levy \(2023\)](#):

“The most appropriate and environmentally friendly inhaler is one
that a patient will adhere to and use correctly,
this minimizes wastage and promotes disease control. “

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