Corporate Presentation

November 2024

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Upstream Bio: Building a leading immunology company

- Developing verekitug, the only known clinical-stage antibody targeting the TSLP receptor, for severe respiratory diseases
- Antibody discovered by Astellas/Regeneron, acquired by Upstream
- Potential for a differentiated profile, with rapid, complete and sustained occupancy of the TSLP receptor
  - Pharmacology profile driven by potency and allowing evaluation of both 12 and 24 week dosing intervals in ongoing Phase 2 trials
  - In patients with asthma, differentiated suppression of disease-associated biomarkers, including F_ENO and eosinophils
- Currently in Phase 2 trials in both severe asthma and CRSwNP
  - Trials are being conducted in a broad range of patients, not limited by biomarker cutoff
- Planning for initiation of Phase 2 trial in COPD in 2H 2025
- Highly experienced team with deep knowledge of the therapeutic and competitive landscape
- $220.7 million in cash, cash equivalents and short-term investments as of September 30, 2024, plus October 2024 IPO proceeds of $268.7 million expected to fund operations through 2027; 53.6 million shares outstanding

TSLP – Thymic Stromal Lymphopoietin; **CRSwNP** – Chronic Rhinosinusitis with Nasal Polyps; **COPD** – Chronic Obstructive Pulmonary Disease; **F_ENO** – Fractional Exhaled Nitric Oxide; **PK** - Pharmacokinetic

Asthma MAD data provide proof of concept, support differentiated profile

Attribute	Verekitug	Tezepelumab	Dupilumab	Mepolizumab
Target	TSLP Receptor	TSLP Ligand	IL-4/-13 Receptor	IL-5 Ligand
Dosing Interval	12, 24 weeks	4 weeks[2]	2 weeks[3]	4 weeks[5]
Injection Volume	0.5 ml (100 mg) 2.0 ml (400 mg)	1.91 mL[2]	2 mL[3]	1 mL[5]
Effect on FeNO	↓54%[1]	↓~25%[2]	↓~27%[4]	No effect[6]
Effect on Eosinophils	↓54%[1]	↓~45%[2]	↑~30%[4]	↓84%[5]
Biomarker – restricted population	Not anticipated	No[2]	Yes; eosinophilic phenotype or CS resistant asthma[3]	Yes; eosinophilic phenotype[5]

FeNO: Fractional Exhaled Nitric Oxide

[1] 100 mg dose data from MAD study; [2]Astrazeneca AB, Tezspire (tezepelumab-ekko) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761224s003lbl.pdf; [3]Regeneron Pharmaceuticals, Dupixent (dupilumab) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761055s059lbl.pdf; [4]Multidisciplinary review of Dupixent in moderate-to-severe eosinophilic asthma. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761055Orig1s007.pdf;[5]Glaxosmithkline LLC, Nucala (mepolizumab) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125526Orig1s021,761122Orig1s011Corrected_lbl.pdf;[6]Ramonelle. Ann Allergy Asthma Immunol. 2021 January ; 126(1): 102–104.

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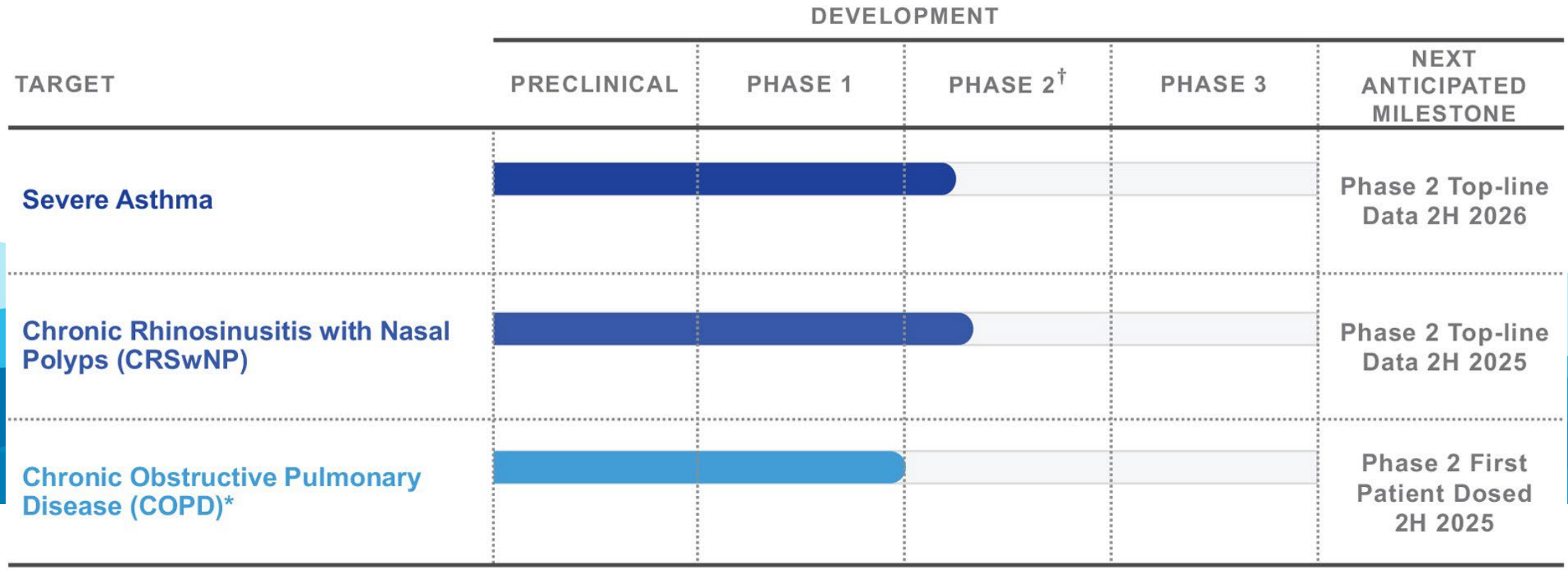
Developing verekitug in multiple indications with unmet need



† Phase 2 clinical trial in CRSwNP and severe asthma were initiated in January 2024 and March 2024, respectively, and enrollment is currently ongoing.

* Planning activities for a Phase 2 clinical trial in COPD have commenced, including development of a clinical trial protocol and regulatory approval strategy.

Leadership team

Deep experience and complementary areas of expertise

Executive Team

Rand Sutherland, MD
Chief Executive Officer
SeekerBio
TranslateBIO sanofi

Aaron Deykin, MD
Chief Medical Officer & Head of R&D
Biogen
Brigham and Women's Hospital
Founding Member, Mass General Brigham

Mike Gray
Chief Operating Officer & Chief Financial Officer
CARMOT THERAPEUTICS imara

Adam Houghton, PhD
Chief Business Officer
abbvie Lilly

Functional Leadership

Maryse Courval, MS
VP, Clinical Operations
Biogen NOVARTIS
Bristol Myers Squibb

Lisa Fiering
SVP, People & Culture
TRILLIUM THERAPEUTICS INC. Ironwood
genzyme A SANOFI COMPANY

Amy Iannelli
Sr Director, Finance
TranslateBIO
Idenix PHARMACEUTICALS

Ashish Kalra, PhD
VP, Translational Research
ScholarRock
merrimack

Mersedeh Miraliakbari, PharmD
SVP, Regulatory & Quality
Nabriva THERAPEUTICS AstraZeneca
Johnson & Johnson

Parika Petaipimol, MS
VP, Technical Operations
PANDION THERAPEUTICS
Biogen

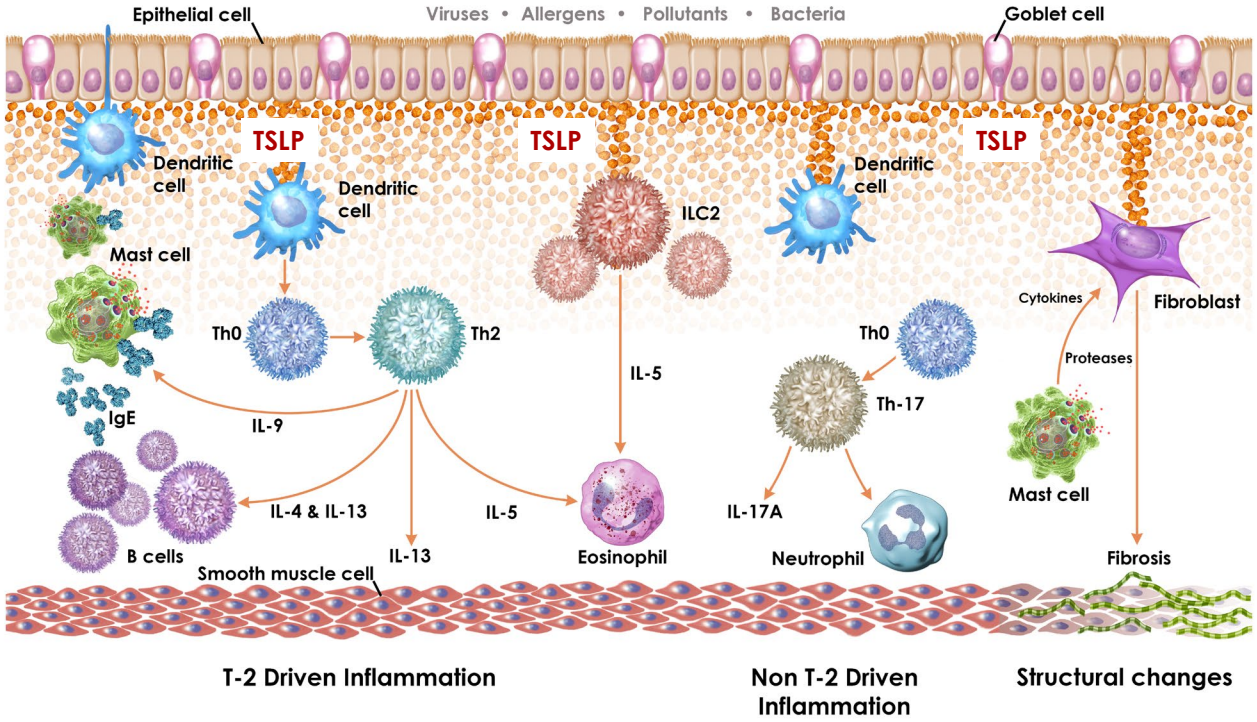
Sumathi Sivapalasingam, MD
VP, Clinical Development
EXCISION BIOTHERAPEUTICS
REGENERON

Fang Xie, PhD
VP, Biometrics
insmed
AMGEN Pfizer

Targeting TSLP receptor with verekitug: Severe Asthma, CRSwNP and COPD

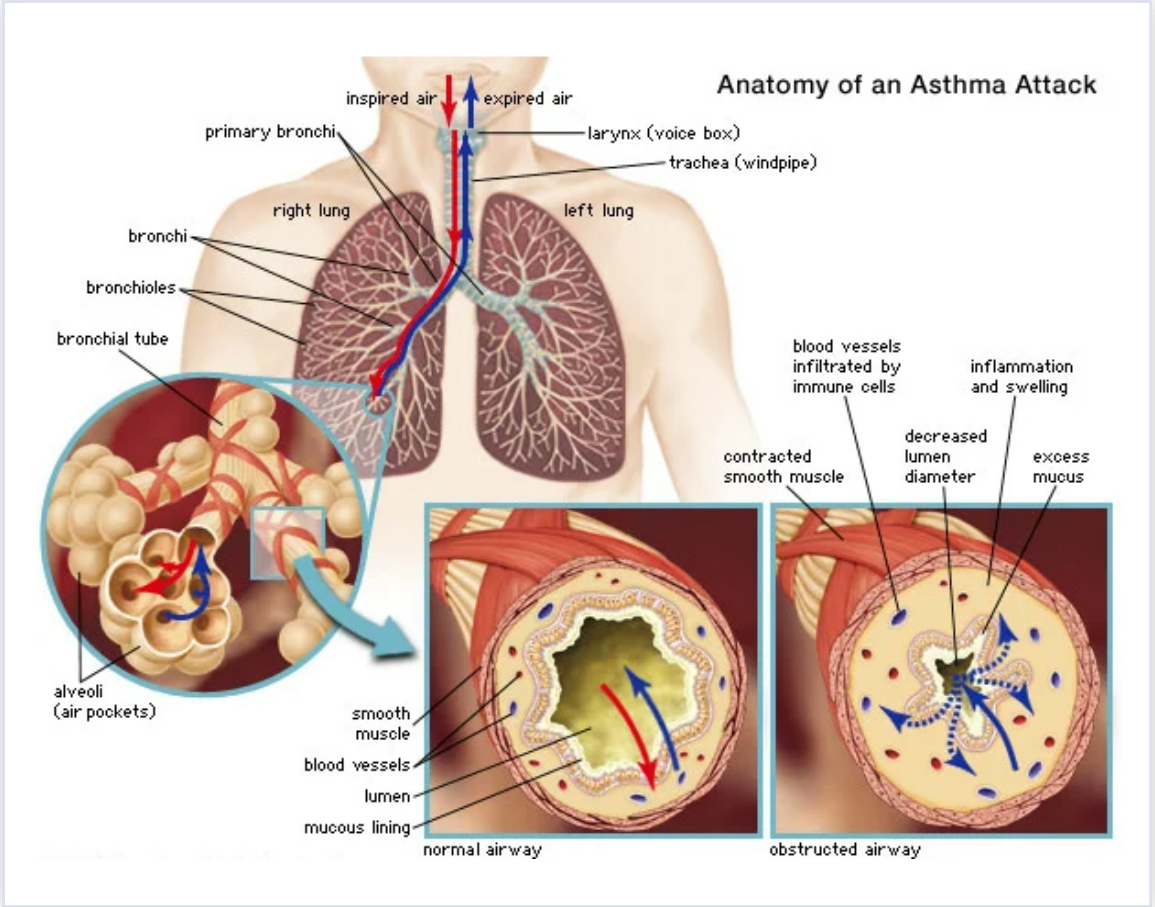
TSLP is an upstream mediator of key inflammatory pathways

- An “alarmin” cytokine at mucosal surfaces
  - Produced by epithelial cells, keratinocytes and fibroblasts response to stress, injury
- Broadly-expressed heterodimeric receptor comprised of the TSLP receptor and IL-7Rα
- Signaling via the TSLP receptor initiates multiple downstream inflammatory cascades leading to type 2 and non-type 2 inflammation, and fibrotic responses
- Validated role in human disease (e.g., asthma, CRSwNP and COPD)
  - Genetic association
  - Animal models
  - Human tissue
  - Clinical efficacy



Asthma is a chronic inflammatory disease of the airways

- Characterized by episodic symptoms
  - Chest tightness
  - Shortness of breath
  - Cough
- Caused by narrowing of the bronchioles
  - Edema
  - Hyperresponsiveness → muscle contraction
  - Mucus production
- >25M Americans affected[1], 350M people globally[2]
  - Between ~5-10% of the population has severe disease[1]
  - High rates of morbidity and mortality:
    - >1M emergency department visits per year in US[3] and $80B in annual costs[4] of care, absenteeism and mortality
    - >3500 deaths per year in US[5]

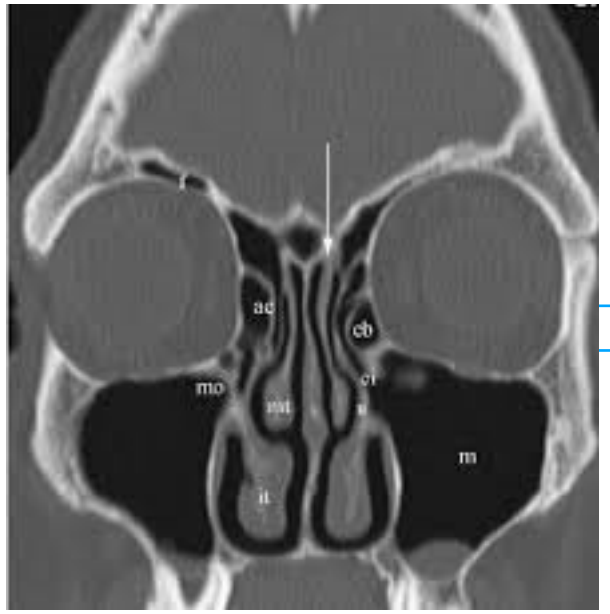


[1] https://www.lung.org/lung-health-diseases/lung-disease-lookup/asthma/learn-about-asthma/types/severe-asthma
[2] Garcia-Marcos et al., Asthma management and control in children, adolescents, and adults in 25 countries: a Global Asthma Network Phase I cross-sectional study. Lancet Glob Health 2023.
[3] Qin et al., Asthma-related emergency department (ED) visits and post-ED visit hospital and critical care admissions, National Hospital Ambulatory Medical Care Survey, 2010-2015. J. Asthma May 2021.
[4] Nurmagambetov et al., The Economic Burden of Asthma in the United States, 2008-2013. Division of Environmental Hazards and Health Effects, CDC.
[5] https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm
Figure: https://www.britannica.com/science/asthma

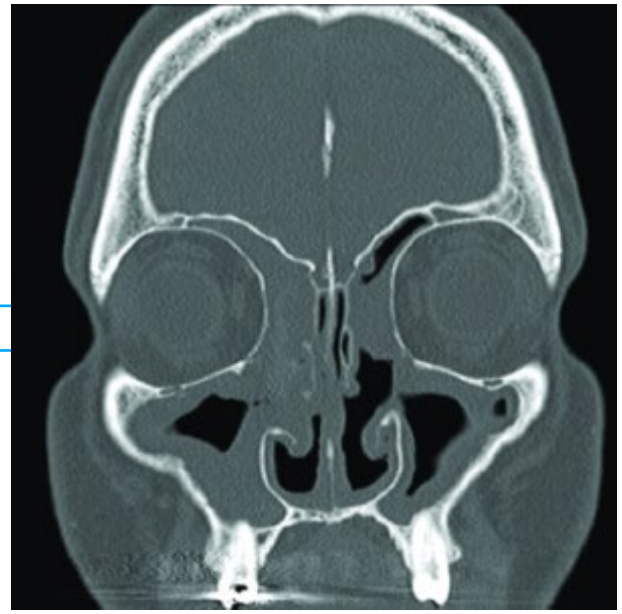
CRSwNP is a chronic upper airway inflammatory disease, with significant unmet need and a strong association with asthma

Coronal CT Scans

Healthy[1]



CRSwNP[2]



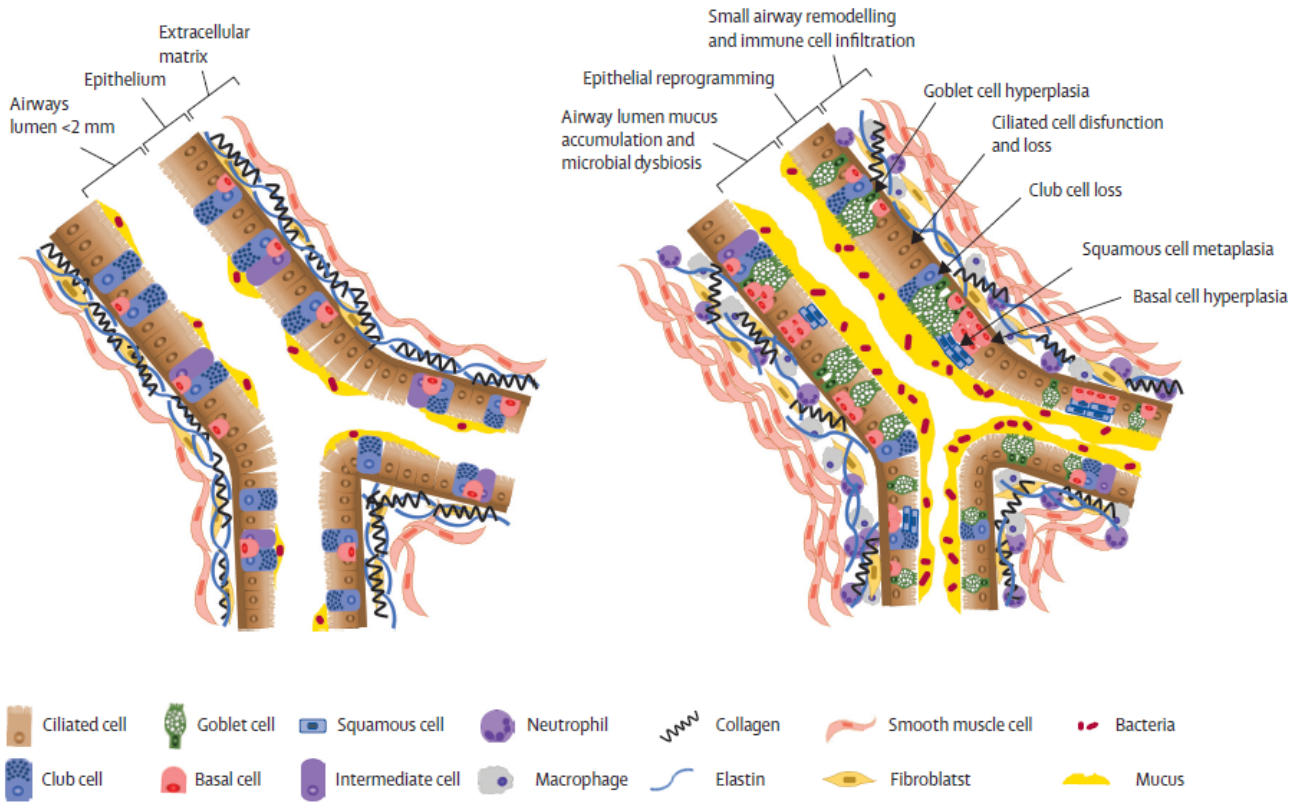
- Loss of smell
- Nasal obstruction and/or congestion
- Nasal secretion, post-nasal drip
- Facial pain, pressure

- CRSwNP is characterized by chronic inflammation of the sinonasal mucosa with the presence of nasal polyps
- Up to 65% of CRSwNP patients also have asthma; patients with comorbid asthma and CRSwNP tend to have more severe disease
- It is estimated that ~900K patients in the US and Europe suffer from CRSwNP

[1] Jaksha *et al* F1000 Research 5 (2016) 2377-2387
[2] Connor *et al* Imaging, 19 (2007), 39-54

COPD is a chronic inflammatory disease of the lung and airways

- COPD is characterized by **structural abnormalities of the airway, lung parenchyma and pulmonary vasculature** due to chronic inflammation caused by recurrent exposure to external irritants (e.g., tobacco smoke, air pollution)
  - **Destruction of alveoli and elastic fibers** in the lung parenchyma, **bronchoconstriction, and excessive mucus** production result are driven by inflammatory mediators produced by granulocytes (neutrophils, eosinophils, mast cells) and macrophages
  - Together, these processes **cause airflow obstruction** and **impaired gas exchange**[2]
- Patients with COPD experience **dyspnea, reduced exercise tolerance and exacerbations** triggered by exposure to irritants or infections (viral or bacterial).
- COPD is the **third leading cause of death** worldwide, causing ~3.2 million deaths in 2019[1]



Christenson et al., *Lancet* 2022; 399: 2227–42

[1]WHO https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
[2]Up to Date https://www.uptodate.com/contents/chronic-obstructive-pulmonary-disease-diagnosis-and-staging?search=copd&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Clinical Data Overview

Verekitug has demonstrated a differentiated profile to date

Phase 1 data from 120 participants (88 healthy volunteers and 32 patients with asthma) indicate:

- Generally well-tolerated
- Showed a predictable and consistent PK profile
- High subcutaneous bioavailability (~70%)
- No clinically-meaningful immunogenicity observed
- Rapid, substantial and sustained effects on disease related biomarkers known to correlate with asthma exacerbations

Attribute	Verekitug	Tezepelumab	Dupilumab	Mepolizumab
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Dosing Interval	12, 24 weeks	4 weeks[2]	2 weeks[3]	4 weeks[5]
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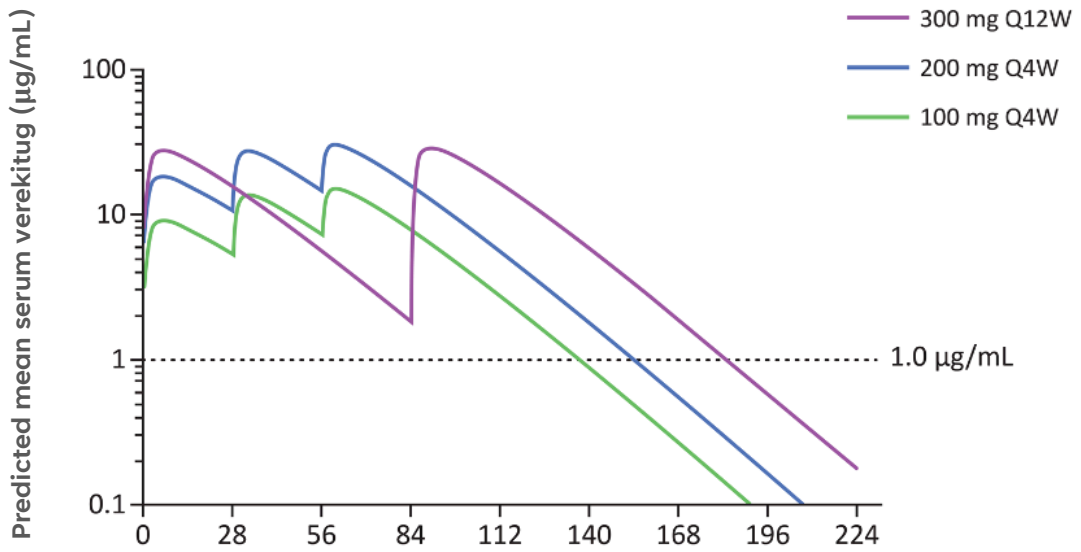
First-in-human study supported tolerability and potential for extended dosing intervals

- Single doses of verekitug ranging from 0.03-10 mg/kg were generally well tolerated in healthy volunteers
  - No treatment-emergent adverse events leading to study withdrawal or treatment discontinuation
  - No clinically relevant increase in the frequency of TEAEs with increasing doses
- Attractive pharmacology profile
  - Dose-proportional PK observed across estimated therapeutic dose range
  - Subcutaneous administration: ~70% bioavailability
  - Post-hoc analysis indicates PD effect (reduced eos) consistent with TSLP antagonism



PK modeling suggested maintenance of effective exposures possible with dosing interval of at least every 12 weeks based on a conservative estimate of the therapeutic threshold

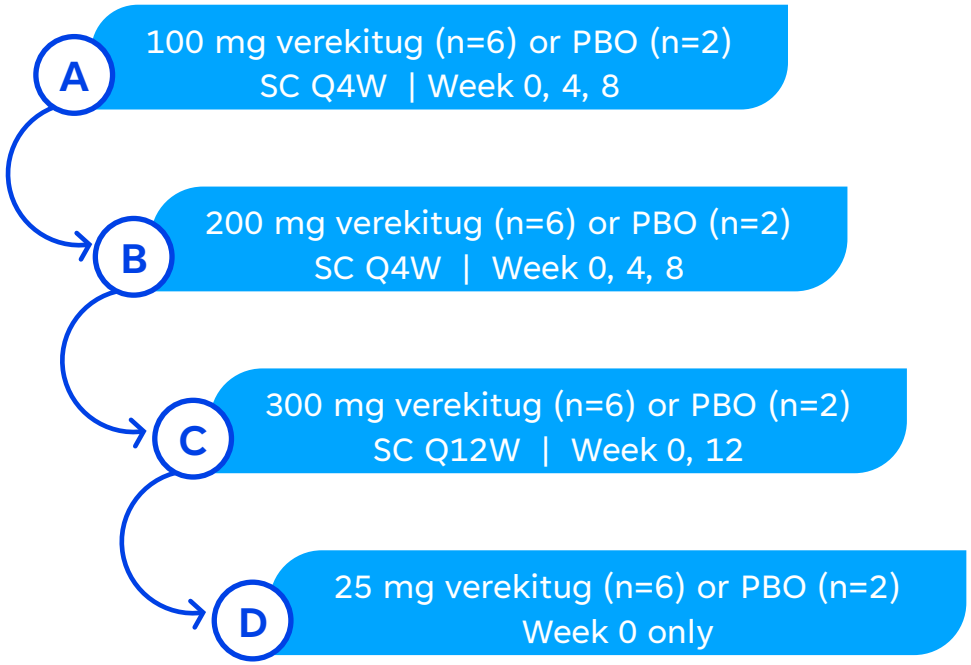
PK – pharmacokinetic; PD - pharmacodynamic

MAD study designed to evaluate PD effects in asthma patients and inform Phase 2 dose selection

Study results presented at American Thoracic Society International Conference in May 2024

Key eligibility criteria

- Adults with asthma, aged 18-60 years
- Blood eosinophils ≥200 cell/µL **or** ≥150 cell/µL with FeNO >25 ppb
- Participants on stable nonbiologic asthma medications with no dose adjustments, who experience no exacerbations, and with no new prescribed drugs within 8 weeks prior to screening



Primary objective:

To assess safety and tolerability of verekitug administered in MAD

Secondary objective:

- To assess PD effect of verekitug on FeNO and blood eosinophils
- To assess the degree and duration of TSLPR occupancy in peripheral monoctyes
- To assess immunogenicity and PK of verekitug

MAD study showed a generally favorable tolerability profile

Treatment emergent adverse events were mild or moderate

>90% of TEAEs were deemed unrelated to study drug

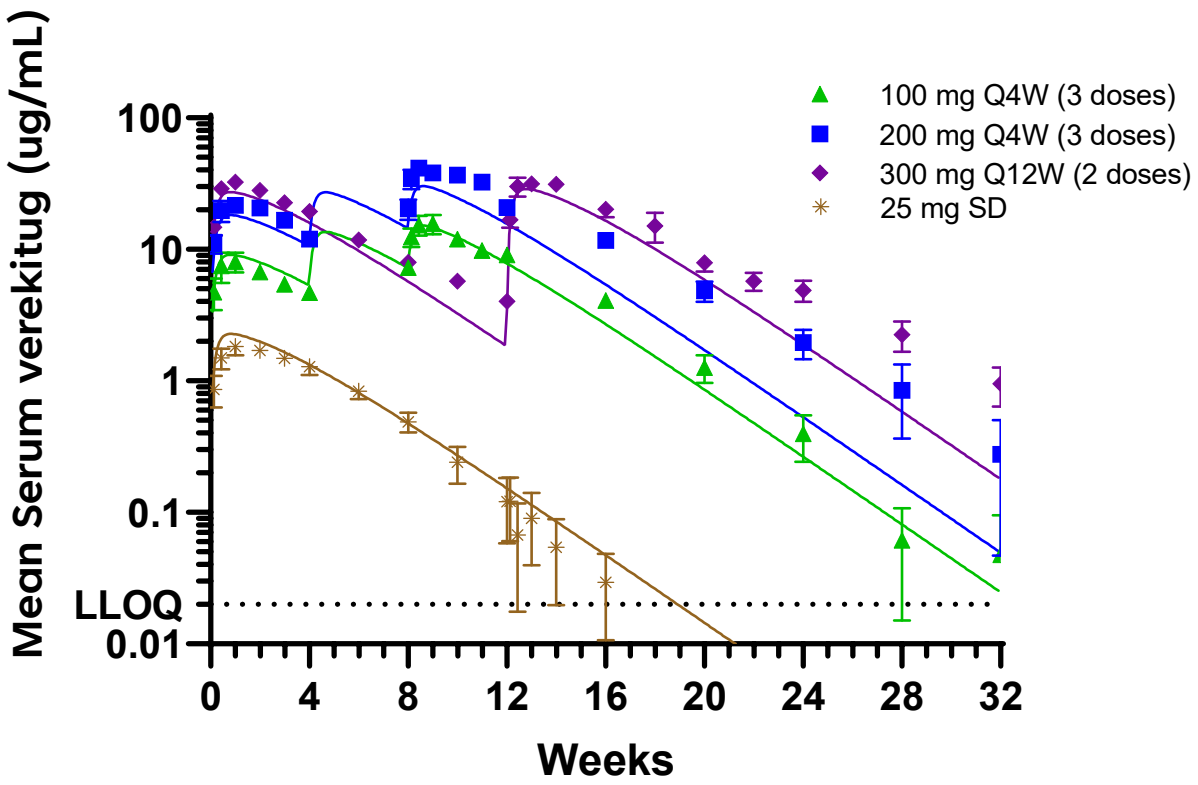
	100 mg Q4W (N=6)	200 mg Q4W (N=6)	300 mg Q12W (N=6)	25 mg X 1 (N=6)	Placebo (N=8)	Overall (N=32)
Number of TEAE	19	17	12	9	25	82
Number of Related TEAE	2	1	3	0	1	7
Subjects with any TEAE, n (%)	5 (83.3)	6 (100)	6 (100)	4 (66.7)	7 (87.5)	28 (87.5)
Mild, n (%)	1 (16.7)	4 (66.7)	5 (83.3)	0	3 (37.5)	13 (40.6)
Moderate, n (%)	4 (66.7)	2 (33.3)	1 (16.7)	4 (66.7)	4 (50.0)	15 (46.9)
Severe, n (%)	0	0	0	0	0	0
Subjects with any Related TEAE, n (%)	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (12.5)	5 (15.6)
Subjects with any Serious TEAE, n	0	0	0	0	0	0
Subjects with any TEAE Leading to Withdrawal, n	0	0	0	0	0	0
Subjects with any TEAE Leading to Discontinuation of IMP, n	0	0	0	0	0	0

Most Common TEAE: Headache
Several participants had mild, short-lived, and self-limited injection site reactions; none were reported as an adverse event
No withdrawals from the trial or treatment discontinuation due to TEAEs

TEAE = treatment emergent adverse event; **Q4W** = every 4 weeks; **Q12W** = every 12 weeks

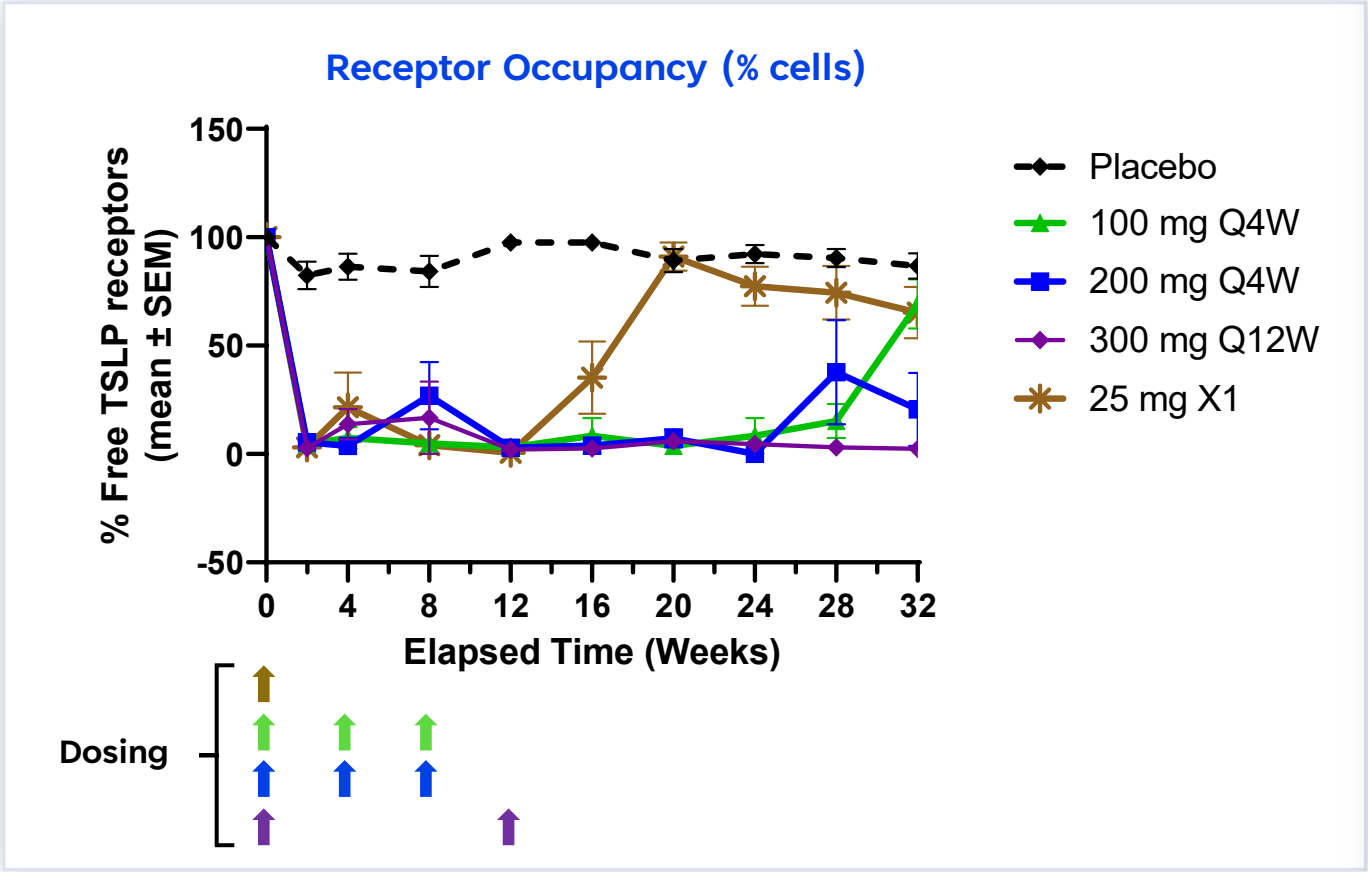
Verekitug MAD data support potentially-differentiating extended interval dosing

Observed PK data aligned with SAD study-based PK model simulations

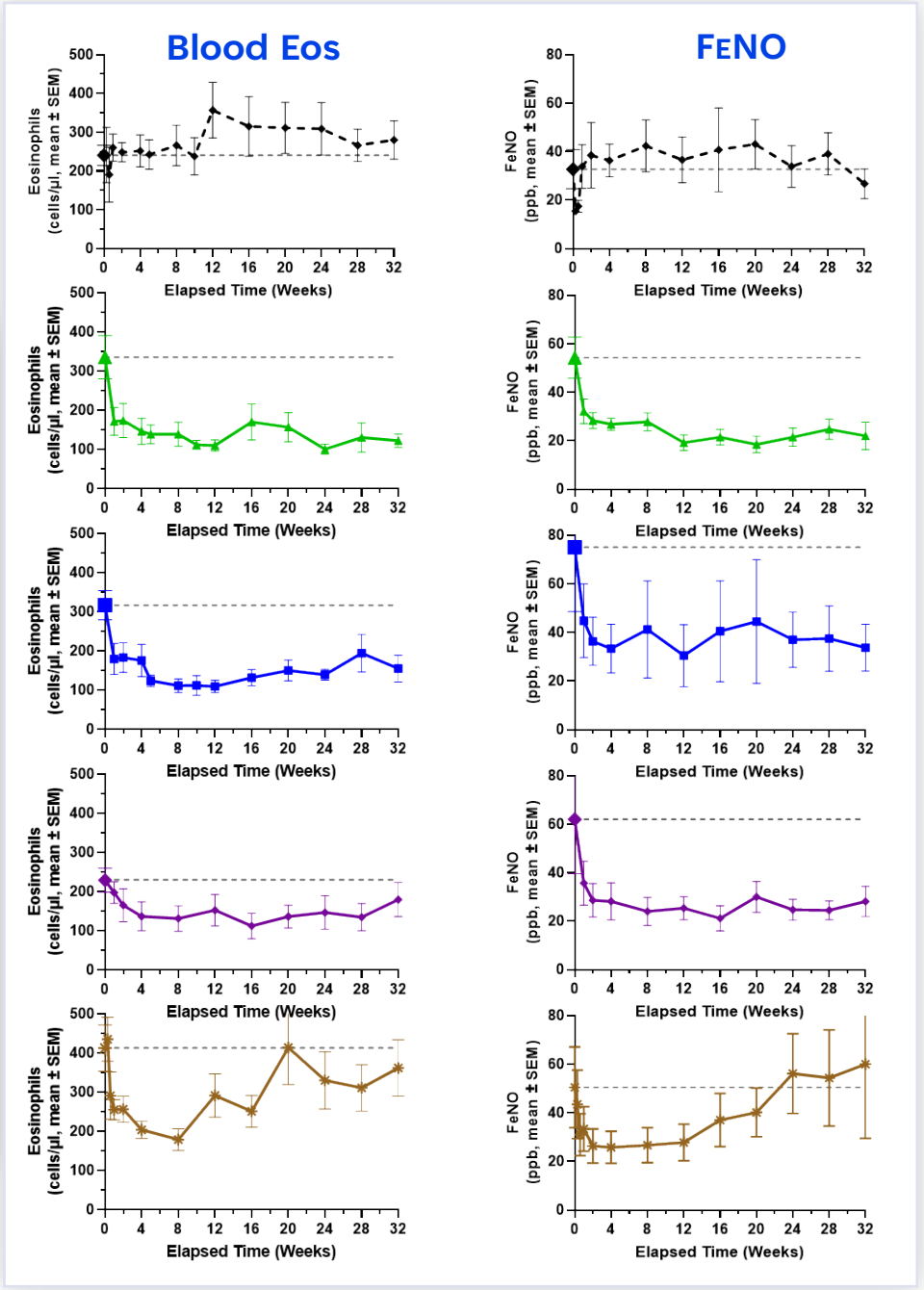


Symbols: observed mean values from Phase 1b MAD study
Solid lines: predicted PK from Phase 1 SAD clinical trial in healthy volunteers
LLOQ: lower limit of PK qualification

32-week data showed substantial PD effects for up to 24 weeks after last dose



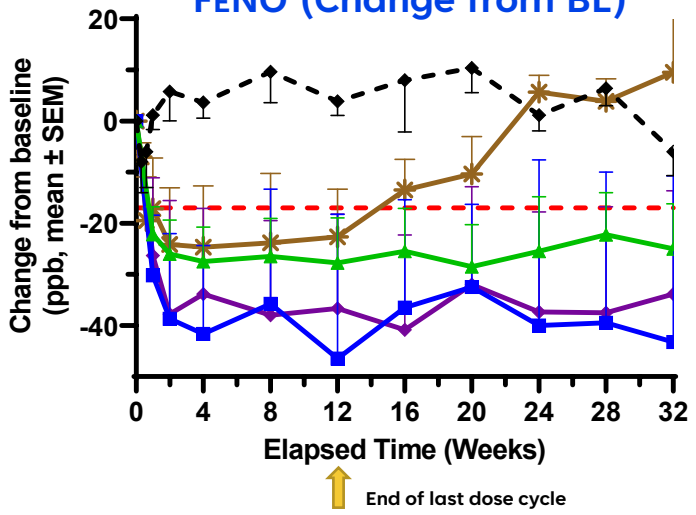
Note: Data from per protocol dosing shown



Dashed line = baseline value

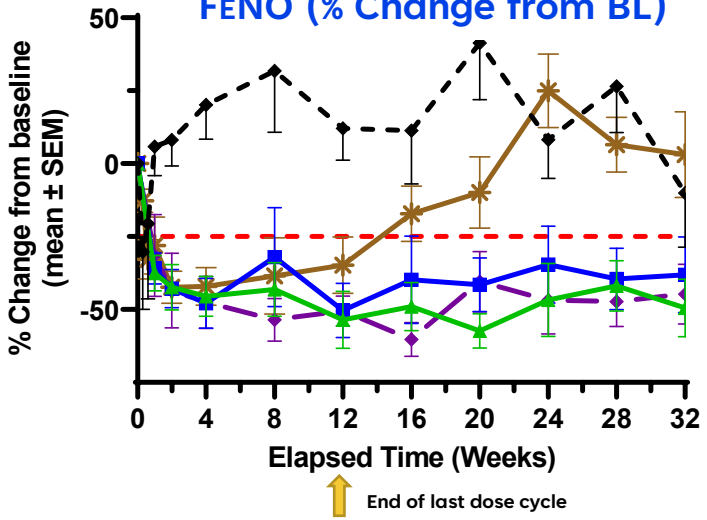
In Phase 1, verekitug led to a larger decrease in FeNO than reported with tezepelumab

FeNO (Change from BL)



-28 at W12
-47 at W12
-37 at w12

FeNO (% Change from BL)

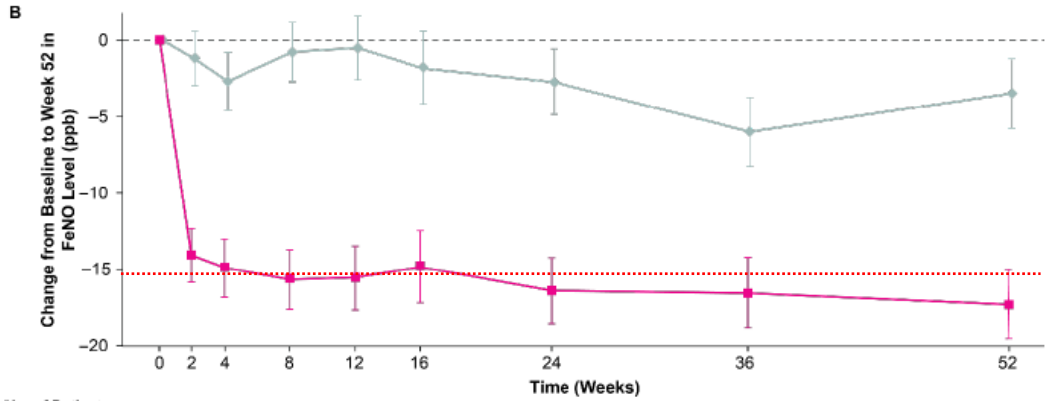


Placebo
100 mg Q4W
200 mg Q4W
300 mg Q12W
25 mg X1

-54% at W12
-51% at W12
-51% at W12

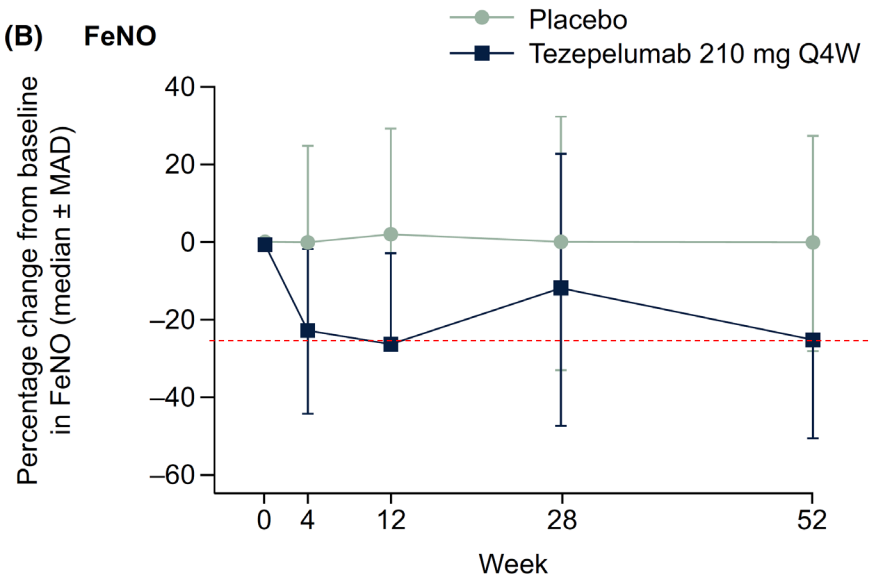
*Note: Data from per protocol dosing shown - Teze data with Q4W dosing up to 52-weeks

Tezepelumab (Phase 2 and Phase 3)



~-17 ppb at W12

Baseline mean: ~41 ppb
Menzies-Gow et al., NEJM 2021



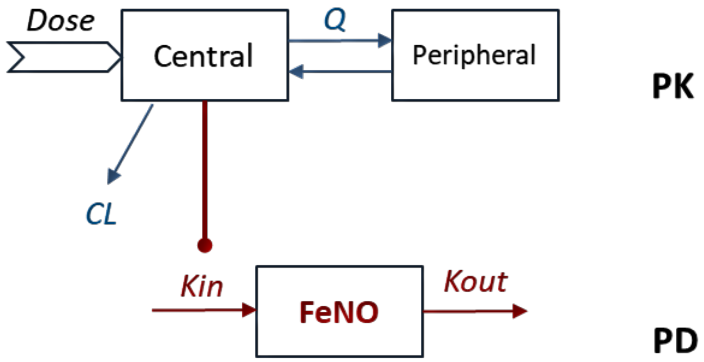
~-25% at W12

Baseline mean: ~34 ppb
Corren et al., Allergy 2022

Data shown are from different trials involving different patients and dosing regimens; no head-to-head clinical studies have been conducted. Differences exist between trial designs and subject characteristics, and caution should be exercised when comparing data across studies.

Verekitug has shown high potency in asthma patients

Modeled effect of verekitug on FeNO is substantially greater than that published for tezepelumab



$$\frac{dFeNO}{dt} = K_{in} \cdot \left[1 - \frac{Emax \,.C(t)}{EC_{50} - C(t)}\right] - K_{out}.FeNO$$

Verekitug FeNO PK/PD Model Parameters with Tezepelumab

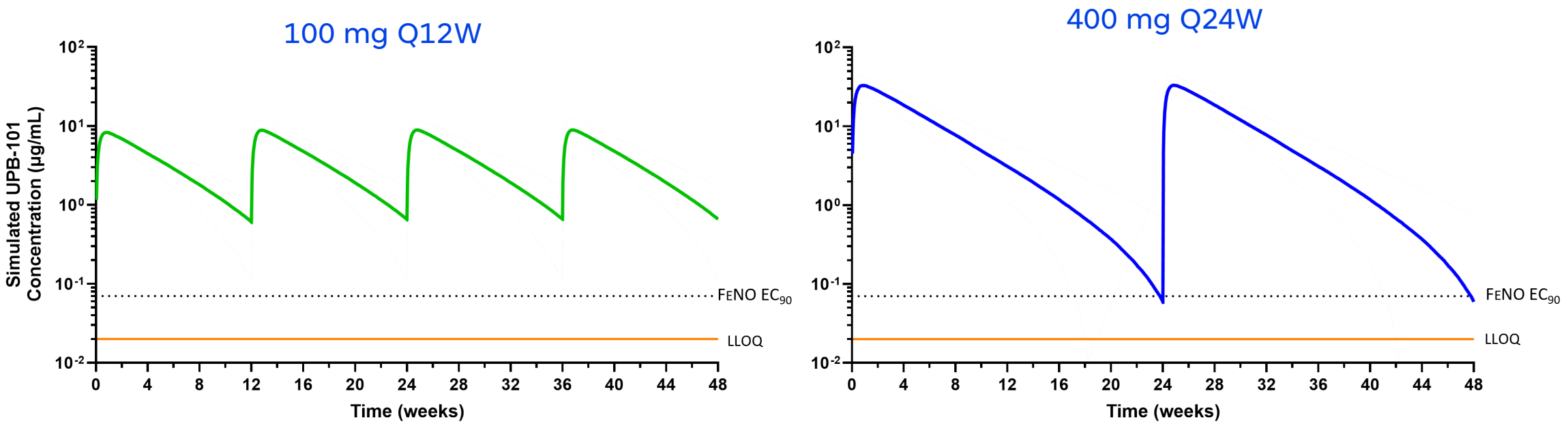
Verekitug			Tezepelumab[1]		
E_{MAX} (reduction from BL)	EC_{50} (µg/ml)	EC_{90} (µg/ml)	E_{MAX} (reduction from BL)	EC_{50} (µg/ml)	EC_{90} (µg/ml)
43.4 %; 95% CI [36.6-50.4]	0.008	0.07	27.8 %; 95% CI (23.1-32.2)	2.5	22.5

- ~1.5 times greater maximal reduction in PD (FeNO)
- >300-fold lower EC_{50} /EC_{90} compared to tezepelumab

No head-to-head clinical studies have been conducted. Differences exist between modeled data and trial design, and caution should be exercised when comparing data across studies.

[1]Ly et al., *J Clin Pharm* 2021

PK modeling predicts selected doses will sustain concentrations above the FeNO EC_{90} throughout the dosing interval



Solid line: median
LLOQ: Lower Limit of PK Quantification

Phase 2 Clinical Trials

Summary of ongoing verekitug Phase 2 Clinical Trials

	Severe Asthma Phase 2 Study	CRSwNP Phase 2 Study
Design **Duration** **Doses**	• 4 arm, randomized (1:1:1:1), parallel group • 24 week minimum→ 60 week maximum treatment • PBO, 100 mg Q24W, 400 mg Q24W, 100 mg Q12W	• 2 arm, randomized (1:1), parallel group • 24 week treatment • PBO, 100 mg Q12W
Population	• Age range: 18-75 years	• Age range: 18-75 years
Primary EP	• Annualized Asthma Exacerbation Rate (AAER)	• Change from baseline in bilateral endoscopic NPS at week 24
Secondary Eps	• Change from baseline in pre–bronchodilator FEV_1 • FENO • ACQ-6 • Safety	• Change from baseline in NCS • Patient-reported smell • Sinus opacification score (CT) • Need for surgical therapy • Need for systemic corticosteroids
Planned Sample Size	436	70
Next Milestone	Phase 2 topline data 2H 2026	Phase 2 topline data 2H 2025

Planned Phase 2 trial in COPD will focus on patients with elevated eos, with a primary endpoint of annualized exacerbation rate, and include lung function, symptoms and quality of life as secondary endpoints. Potential efficacy will also be explored in patients without elevated eos.

NPS – Nasal Polyp Score; **FEV_1**- Forced Expiratory Volume in first second; **ACQ-6**- Six Element Asthma Control Questionnaire;
NCS – Nasal Congestion Score

Pipeline Strategy

Portfolio Development

TSLP signaling is linked to a variety of indications

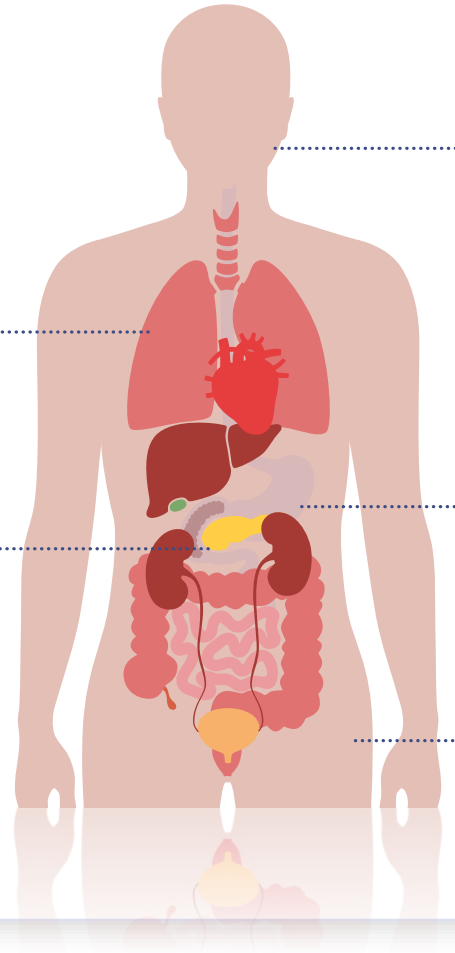
Verekitug TSLP receptor inhibitor potentially has broad applicability

Respiratory

- Severe Asthma*
- CRSwNP*
- COPD*
- Bronchiectasis
- Idiopathic Pulmonary Fibrosis (IPF)
- Systemic sclerosis (ILD)
- Sarcoidosis

Gastroenterology

- Eosinophilic Esophagitis
- Eosinophilic Gastritis/Gastroenteritis
- Ulcerative Colitis



Dermatology

- Atopic Dermatitis
- Bullous Pemphigoid
- Prurigo Nodularis
- Eczema Herpeticum
- Dermatitis Herpetiform
- Job's syndrome

Nephrology

- IgA Nephropathy

Allergy/Immunology

- Urticaria
- Mastocytosis
- Hypereosinophilic syndrome
- Churg-Strauss Syndrome

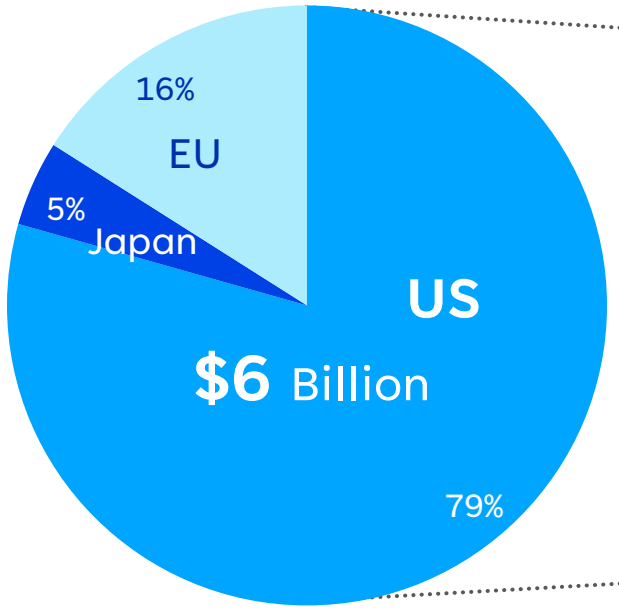
* Target indications for verekitug based on our current development strategy

Commercial Opportunity

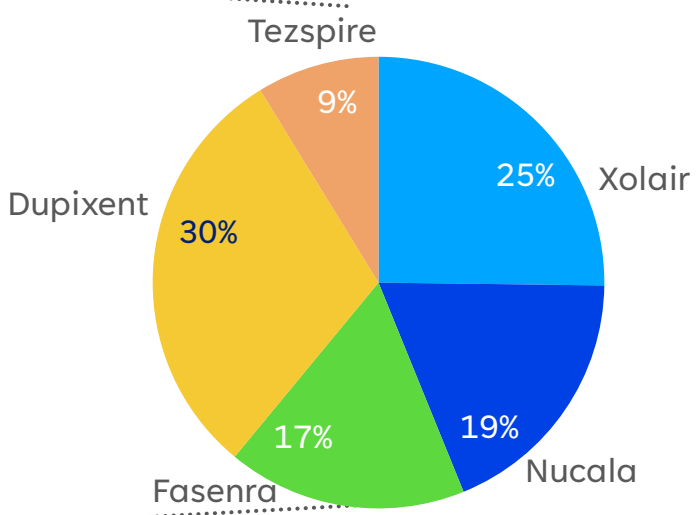
Biologics sales in major asthma markets are growing at ~6% CAGR through 2032

Verekitug is currently being developed for patients with severe asthma

Total Estimated 2023 Asthma Biologic Sales ~$7.5B across JP, EU, US[2]



Current Biologic Sales Distribution[2]

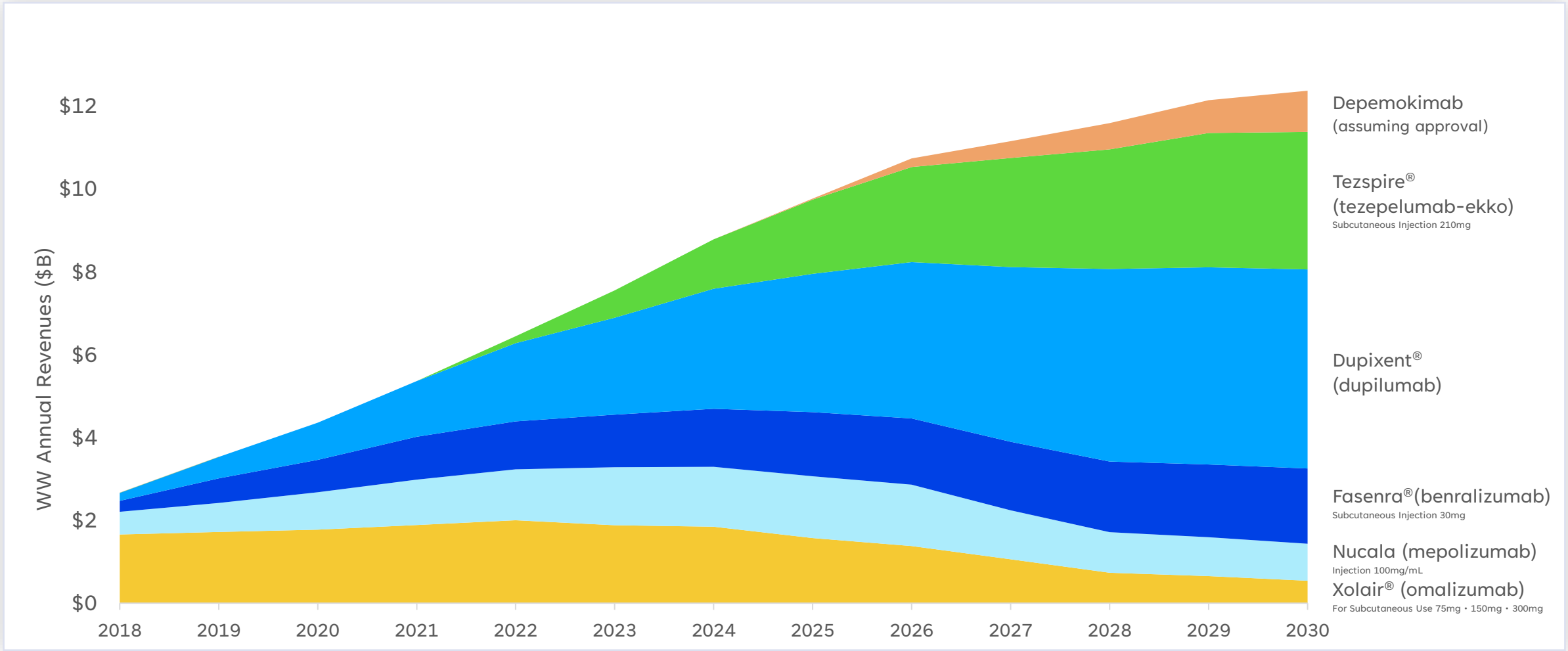


- Currently, ~1.3M biologic eligible severe asthma patients in the US[1]
- 5 of 6 asthma biologics have achieved or are projected to achieve greater than $1.0 billion in global annual sales by 2025[2]
- Tezspire is projected to reach peak global annual sales of over $3B for severe asthma alone in 2032,[2] and had achieved more than 20% of new to brand share of prescriptions in the US in its first commercial year[3].

1 Amgen Business Review Program Feb 2022
2 Datamonitor
3 Amgen Investor Presentation May 2024

Asthma biologics: A large and growing market

Market forecast to expand based on growth of both biologic use and asthma prevalence



Source: Datamonitor Healthcare Asthma Forecast

Market research suggest verekitug's clinical profile could drive high adoption

Strong Treater Support	**~90%**	*of asthma treaters are **highly "willing to use" across both Q12W and Q24W dosing intervals***
	~75-80%	*of CRSwNP treaters are **highly "willing to use" across Q12W and Q24W dosing intervals**, respectively*
High Patient Interest	**~90%**	*of asthma and CRSwNP patients would **"consider" switching** to a product with a less-frequent dosing interval*
	>95%	*of patients are moderately or highly **likely to ask their provider about a treatment option with a longer dosing interval***
MOA & Dosing Attractiveness	**~85%**	*of asthma treaters believe that the **TSLP mechanism of action has "high clinical utility,"** and respondents report that **Q12 and Q24 week dosing is considered more attractive** than all other biologic therapeutic brands*

Source: Trinity Quantitative Research with N=100 HCPs and N=120 Patients

Upstream Bio: Building a leading immunology company

- Developing verekitug, the only known clinical-stage antibody targeting the TSLP receptor, for severe respiratory diseases
- Antibody discovered by Astellas/Regeneron, acquired by Upstream
- Potential for a differentiated profile, with rapid, complete and sustained occupancy of the TSLP receptor
  - Pharmacology profile driven by potency and allowing evaluation of both 12 and 24 week dosing intervals in ongoing Phase 2 trials
  - In patients with asthma, differentiated suppression of disease-associated biomarkers, including FENO and eosinophils
- Currently in Phase 2 trials in both severe asthma and CRSwNP
  - Trials are being conducted in a broad range of patients, not limited by biomarker cutoff
- Planning for initiation of Phase 2 trial in COPD in 2H 2025
- Highly experienced team with deep knowledge of the therapeutic and competitive landscape
- $220.7 million in cash, cash equivalents and short-term investments as of September 30, 2024, plus October 2024 IPO proceeds of $268.7 million expected to fund operations through 2027; 53.6 million shares outstanding

TSLP – Thymic Stromal Lymphopoietin; **CRSwNP** – Chronic Rhinosinusitis with Nasal Polyps; **COPD** – Chronic Obstructive Pulmonary Disease; **FENO** – Fractional Exhaled Nitric Oxide; **PK** - Pharmacokinetic

Thank you