Innovative development in mast cell disorders

November 14, 2024

Today's agenda and speakers

1. **WELCOME & INTRODUCTION TO BLUEPRINT'S MAST CELL PORTFOLIO**
   Fouad Namouni, MD; President Research & Development
2. **TARGETING MAST CELLS**
   Percy H. Carter, PhD; Chief Scientific Officer
3. **CLINICAL DEVELOPMENT FOR BLU-808**
   Becker Hewes, MD; Chief Medical Officer
4. **A CONVERSATION WITH DR O'BYRNE**
   Paul O'Byrne, MD; Dean & VP, Faculty of Health Sciences at McMaster University

Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding plans, strategies, timelines and expectations for the company's future business growth, including the company's vision for mast cell driven diseases and the possibility of capturing multiple blockbuster opportunities; statements regarding whether any of the company's product candidates will successfully address medical needs; statements regarding the company's potential to drive innovation in allergic and inflammatory disease and its potential to revolutionize the allergy/inflammation space with BLU-808; statements regarding plans and expectations for the company's current or future approved drugs and drug candidates, including plans and timing for reporting clinical data; the potential benefits of any of the company's current or future approved drugs or drug candidates in treating patients; and the company's strategy, goals, business plans and focus.

The words "aim," "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks and uncertainties related the company's ongoing and planned research and discovery activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; the company's ability and plans to continue to expand a commercial infrastructure, and successfully launch, market and sell current or future approved products; the company's ability to successfully expand the approved indications for AYVAKIT/AYVAKYT or obtain marketing approval for AYVAKIT/AYVAKYT in additional geographies in the future; the delay of any current or planned clinical trials or the development of the company's current or future drug candidates; the company's advancement of multiple early-stage efforts; the company's ability to successfully demonstrate the safety and efficacy of its drug candidates and gain approval of its drug candidates on a timely basis, if at all; the preclinical and clinical results for the company's drug candidates, which may not support further development of such drug candidates either as monotherapies or in combination with other agents or may impact the anticipated timing of data or regulatory submissions; the timing of the initiation of clinical trials and trial cohorts at clinical trial sites and patient enrollment rates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; the company's ability to obtain, maintain and enforce patent and other intellectual property protection for AYVAKIT/AYVAKYT or any drug candidates it is developing; the company's ability to successfully expand its operations, research platform and portfolio of therapeutic candidates, and the timing and costs thereof; and the success of the company's current and future collaborations, financing arrangements, partnerships or licensing arrangements. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the company's filings with the Securities and Exchange Commission (SEC), including the company's most recent Annual Report on Form 10-K, as supplemented by its most recent Quarterly Report on Form 10-Q and any other filings that the company has made or may make with the SEC in the future. The forward-looking statements in this presentation are made only as of the date hereof, and except as required by law, the company undertakes no obligation to update any forward-looking statements contained in this presentation as a result of new information, future events or otherwise. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

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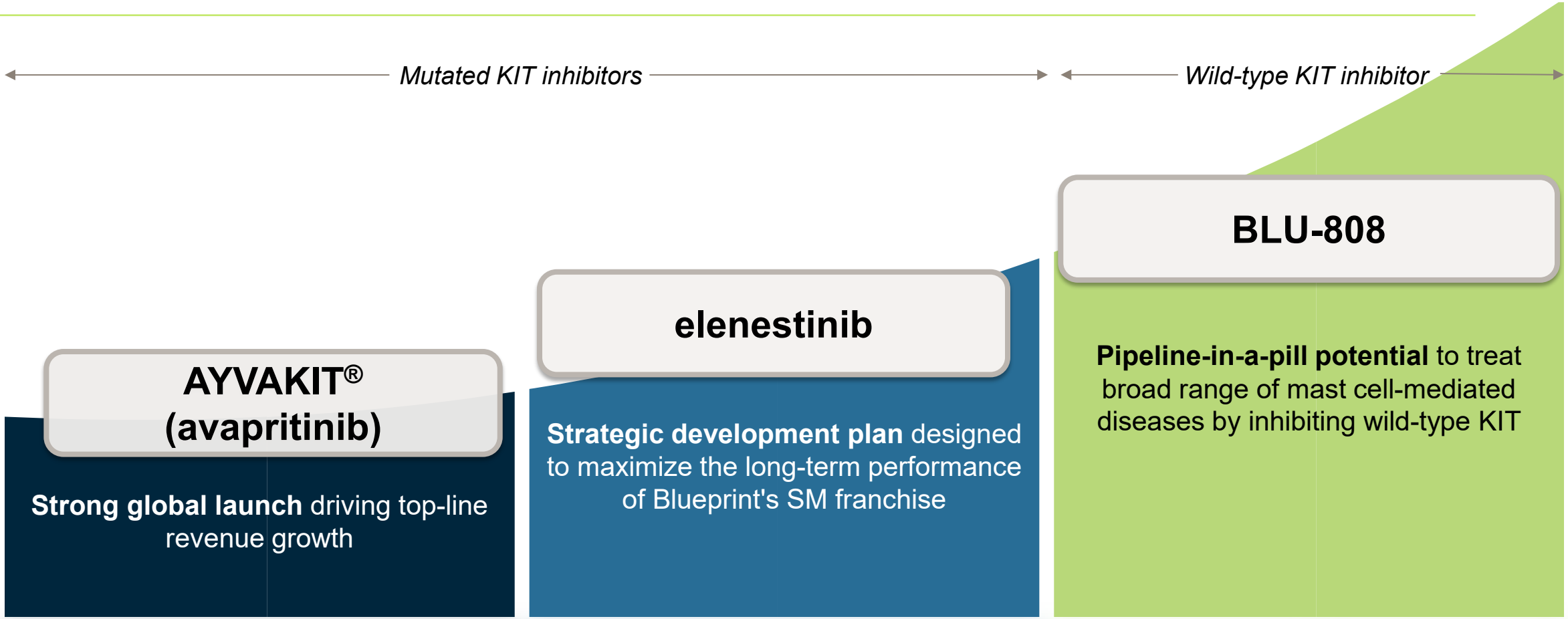
Blueprint Medicines: leaders in mast cell diseases



Avapritinib is approved under the trade name AYVAKYT® in Europe. AdvSM, advanced systemic mastocytosis; ISM, indolent systemic mastocytosis; SM, systemic mastocytosis

AYVAKIT experience anchors mast cell portfolio approach

Clear understanding of mast cell biology and the central role of the KIT receptor

Aim to deliver tunable dosing to optimize benefit-risk across complex diseases

Develop robust datasets to drive clinical, regulatory, and commercial success

Our portfolio of KIT inhibitors, designed to potently and selectively target the mast cell, are developed with the premise that ***KIT inhibition requires titration and tunability***

Innovating the SM treatment approach of tomorrow

SYMPTOM IMPROVEMENT

- Reducing symptom frequency and severity as measured by the ISM-SAF
- Impacting quantitative measures of mast cell burden
- Improving quality of life

CURRENT PARADIGM

DISEASE MODIFICATION

- Improve bone health
- Reduce anaphylaxis frequency and severity
- Address chronic inflammation
- Minimize risk of disease progression

FUTURE PARADIGM

Registration-enabling HARBOR Part 2 is designed to measure broad clinical impact

Primary endpoint	• Mean change in ISM-SAF TSS from baseline • Leverages AYVAKIT regulatory precedent
Novel endpoints	• Reduction in anaphylaxis frequency • Improvement in bone health • Additional biomarkers measuring inflammation
Multiple active doses	• Two active arms, 75 & 100 mg elenestinib selected based on Part 1 data, vs placebo • Studying titratable doses to meet provider preference for flexibility to tailor treatment

On track to initiate registration-enabling HARBOR Part 2 study of elenestinib in ISM by end of 2024

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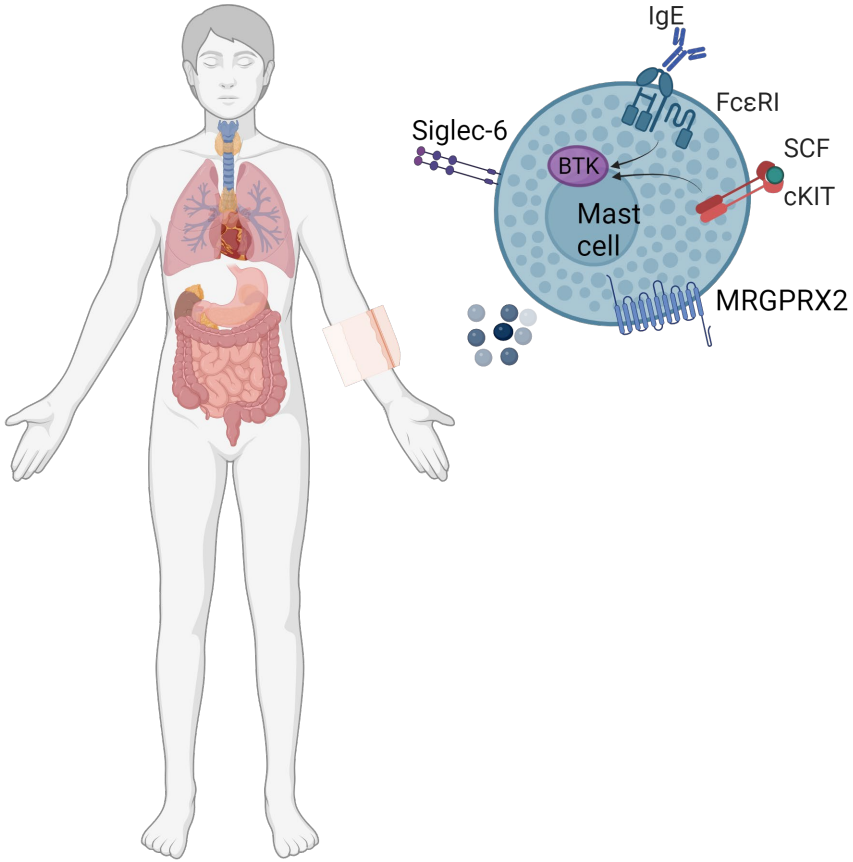
Mast cells are found throughout the body



Mast cells…

- Reside in border tissues and react to various stimuli


Respiratory

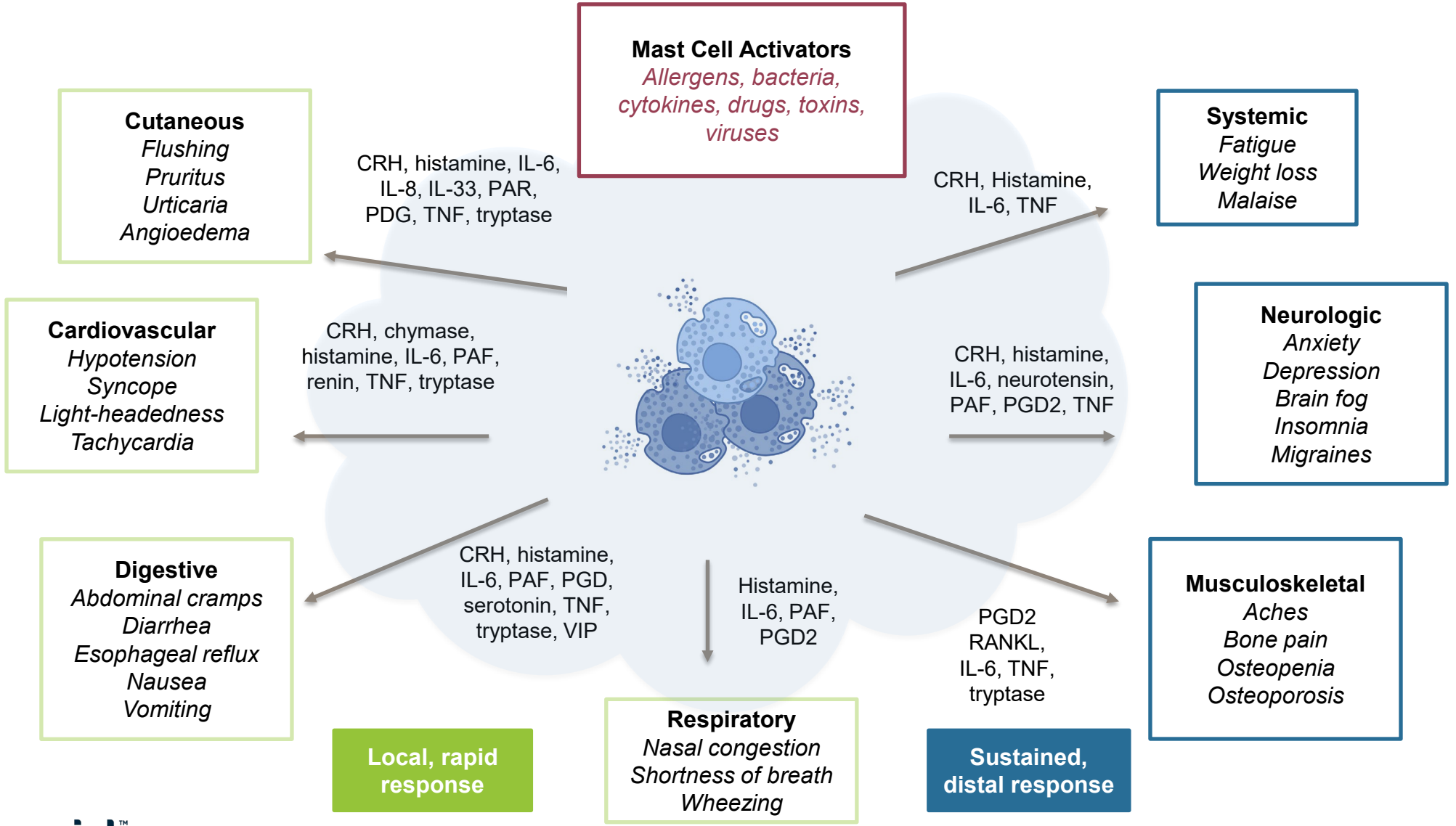

Skin


Gastrointestinal

- Differ across organ systems:
  - » Receptor expression
  - » Granule contents
  - » Response to agonists
  - » Disease relevance
  - » Density/numbers

Unlike other receptors, **KIT is universally expressed across tissue types**, and controls mast cell proliferation, maturation, and survival.

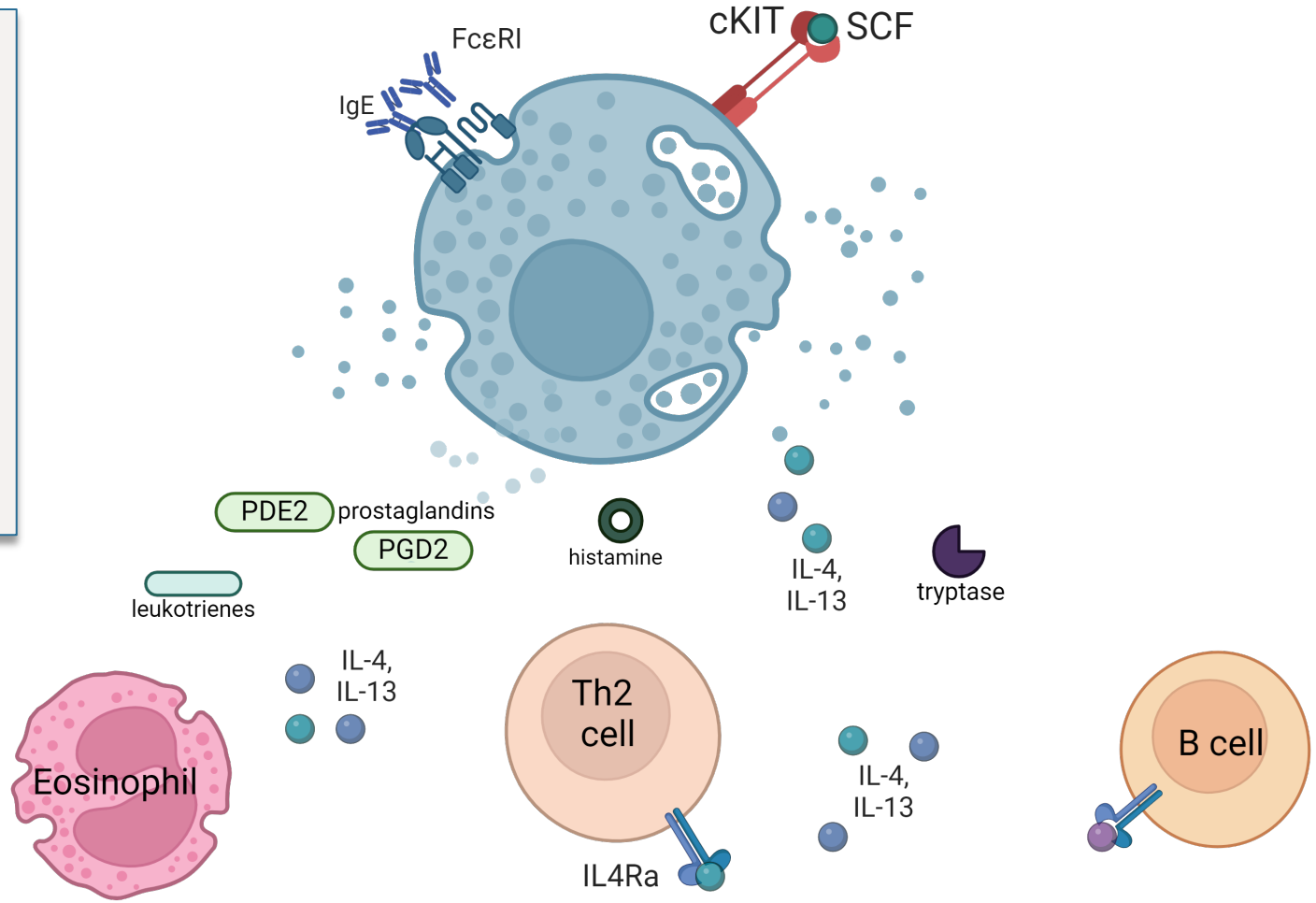
Heterogeneity of tissue response to mast cell activation



Adapted from Theoharides, T. et al, (2015) *New England Journal of Medicine*

Mast cells play a known role in type 2 inflammation

- Mast cells release mediators that further **activate inflammation**
- Inflammatory responses can lead to **long-term effects** including tissue remodeling
- Targeting **KIT, the regulator of mast cell survival and differentiation**, is a promising approach to improve disease outcomes



Oral wild-type KIT inhibitor BLU-808 has first- and best-in-class potential

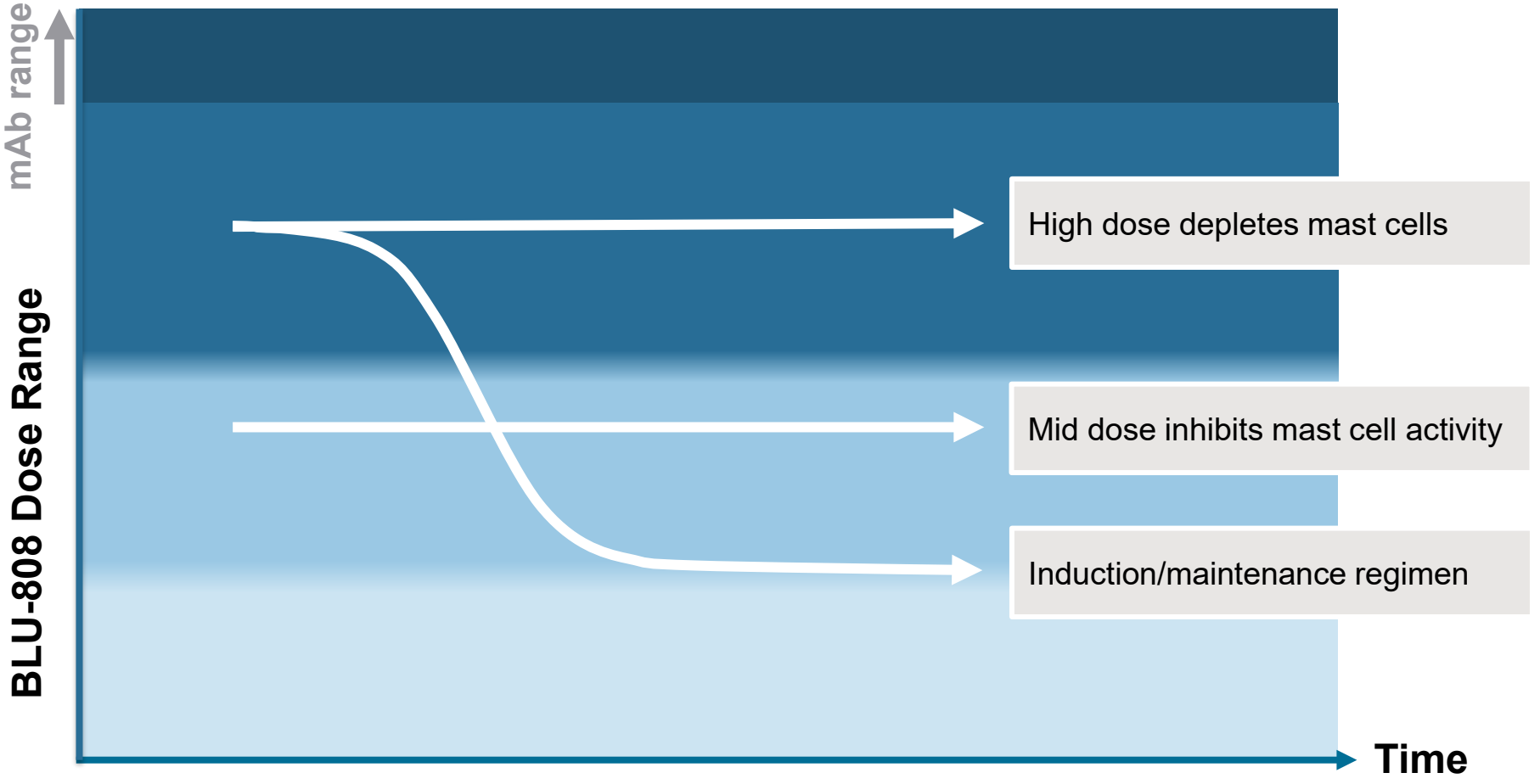
	BLU-808	Key point
Potency		
pKIT cellular IC_{50} (nM)	0.37	Sub-nM KIT inhibition in cellular assay
WT KIT-dependent proliferation IC_{50} (nM)	1.3	Inhibits KIT-dependent growth in cellular assay
Inhibition of CD63 extracellular expression IC_{50} (nM)[b]	2.7	Blocks degranulation as measured by surface marker expression
Inhibition of histamine degranulation IC_{50} (nM) [b]	8.6	Blocks degranulation as measured by histamine release
Selectivity		
S(10) @ 3 µM	0.042	Highly selective across the kinome
PDGFRA / PDGFRB / FLT3 cellular selectivity[a]	>300x/>400x/>9600x	Selective against key kinases closely related to KIT
CSF1R Kd selectivity	>800x	
Brain penetrance ($Kp_{u,u}$)	0.021	Peripherally restricted
Preclinical PK supports once daily oral dosing		

Designed with the potential to support flexible dosing and potential use in combinations

Grassian, A et al, AAAAI 2023

[A] Determined in a cellular assay. CSF1R, colony stimulating factor 1 receptor; FLT3, FMS-like tyrosine kinase 3; IC_{50}, half-maximal inhibitory concentration; PDGFRA/B, platelet-derived growth factor receptor alpha/beta; pKIT, phosphorylated KIT; S(10) @ 3 µM, selectivity score at a concentration of 3 µM; $Kp_{u,u}$, unbound brain to plasma partition, where values <1 indicate preferentially distributed to periphery vs CNS. [B] Human-derived CD34+ mast cells.

Tunable BLU-808 dosing aims to deliver appropriate balance between efficacy and side effects across diseases



A small molecule provides a tunable approach where dose and regimen can be optimized to treat a range of different diseases

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Aim to maximize BLU-808 value with an early development plan to derisk broad scope of utility

Is BLU-808 clinical profile consistent with preclinical data?

Phase 1 SAD/MAD study in healthy volunteers

- Demonstrate tunable therapeutic index with dose-dependent safety, PK, and PD

Where do we strategically develop BLU-808 to maximize value?

POC studies in multiple indications

- Prioritize indications where wild-type KIT mechanism has been de-risked (e.g., chronic urticaria)
- De-risk broader set of indications by characterizing BLU-808 activity and mast cell biology in organ systems beyond the skin
- Explore BLU-808 combination potential in complex disease

Initial BLU-808 POC indications

Areas where targeting wtKIT has been de-risked

- Chronic spontaneous urticaria
- Chronic inducible urticaria

Explore other biology to unlock broader potential

- Allergic asthma
- Allergic rhinitis
- Allergic conjunctivitis
- Mast cell activation syndrome (MCAS)

Broad Universe of Allergic and Inflammatory Diseases Potentially Addressable with BLU-808

Mast cell activation syndrome

Chronic spontaneous urticaria

Allergic rhinitis

Allergic asthma

Allergic conjunctivitis

Chronic inducible urticaria

Nasal polyps

Food allergy

Psoriasis

Insect venom allergy

Eosinophilic gastrointestinal disorders

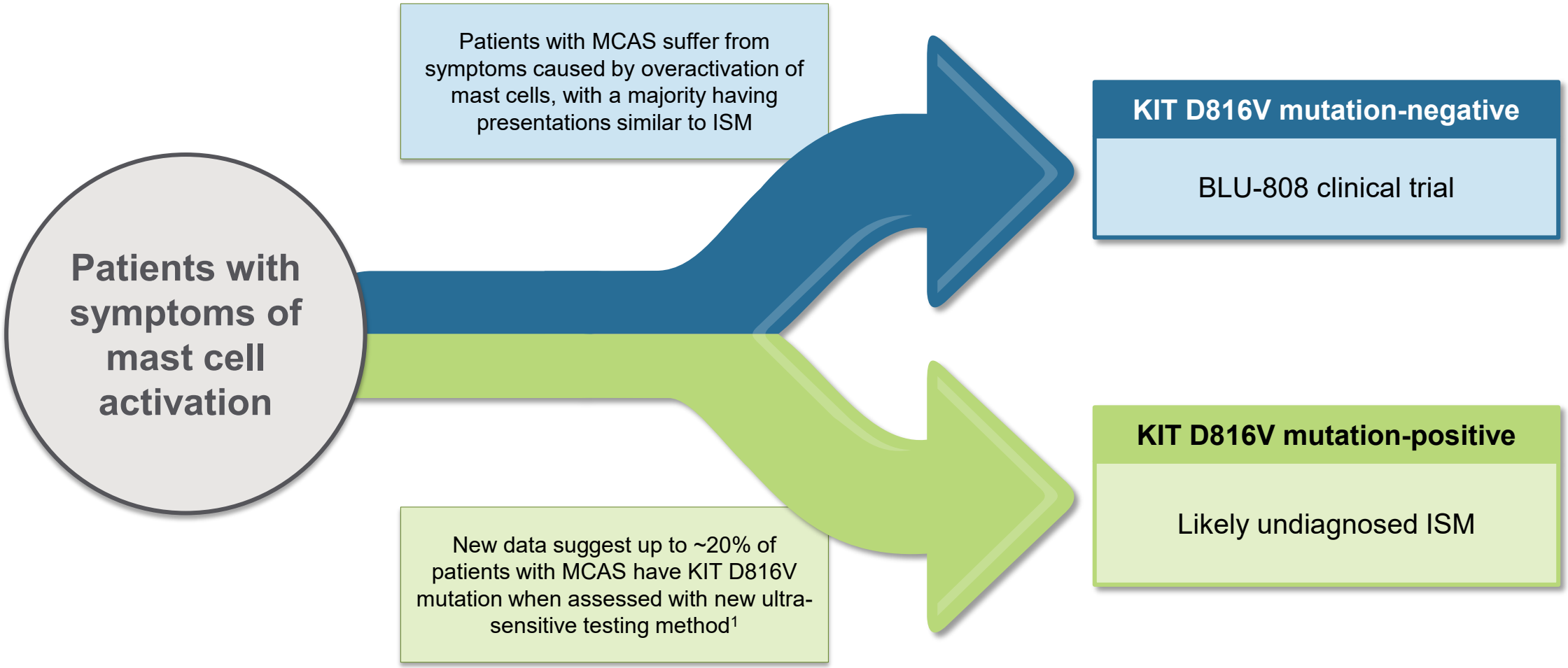
Irritable bowel syndrome with diarrhea

Chronic obstructive pulmonary diseases

Atopic dermatitis

Prurigo nodularis

Mast Cell Activation Syndrome POC approach leverages our SM leadership



[1]Orfao, A, ECNM (2024)

Healthy volunteer study underway to validate the BLU-808 target product profile

Safety

Well tolerated profile

Pharmacokinetics

Good drug-like properties supportive of once daily oral dosing, or informative for induce-maintain strategy

Pharmacodynamics

Dose-dependent signs of mast cell engagement, including tryptase and other biomarkers

HV study designed to demonstrate **wide therapeutic window** with dose-dependent safety, PK and PD to demonstrate the tunable power of BLU-808, and **de-risk POC studies**

Healthy volunteer data anticipated in early 2025

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Mast cells: the wave of the future in treatment of allergic asthma

Paul O'Byrne, MD

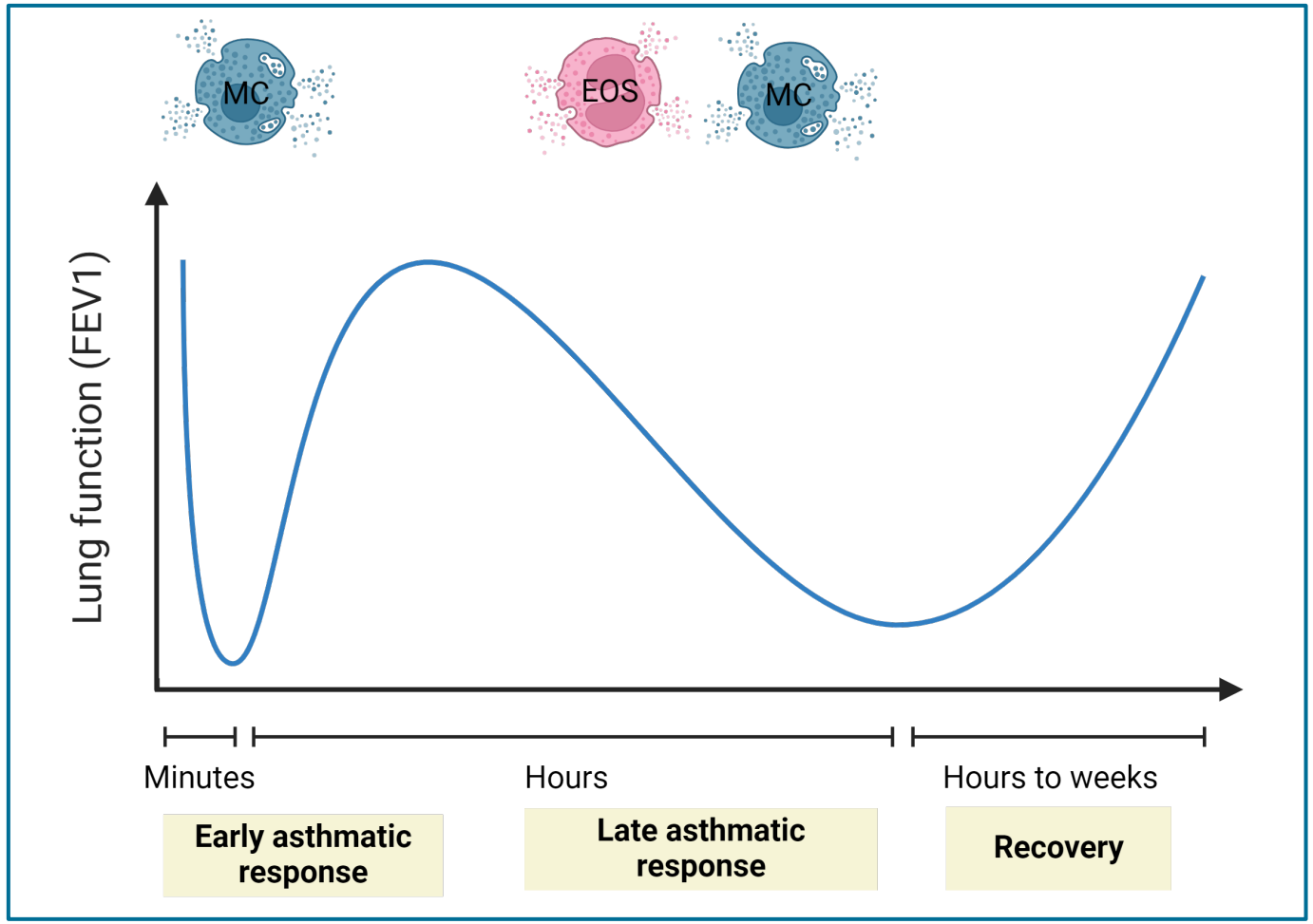
Dean and VP; Faculty of Health Sciences
at McMaster University

Allergic and inflammatory symptoms are driven by mast cell activation

Early phase is primarily mast cell-driven and is characterized by IgE-mediated degranulation products (histamine, growth factors, tryptase, etc)

Late phase is characterized by an influx of inflammatory cells driven in part by mast cell-derived products, and Th2 cytokines

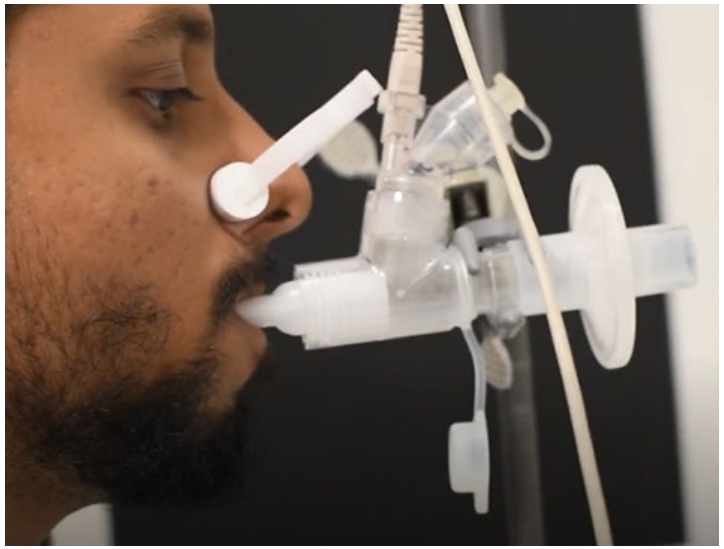
Symptoms include nasal itching, sneezing, congestion, ocular symptoms, wheezing



Created with BioRender.com

How does an allergen challenge study work?

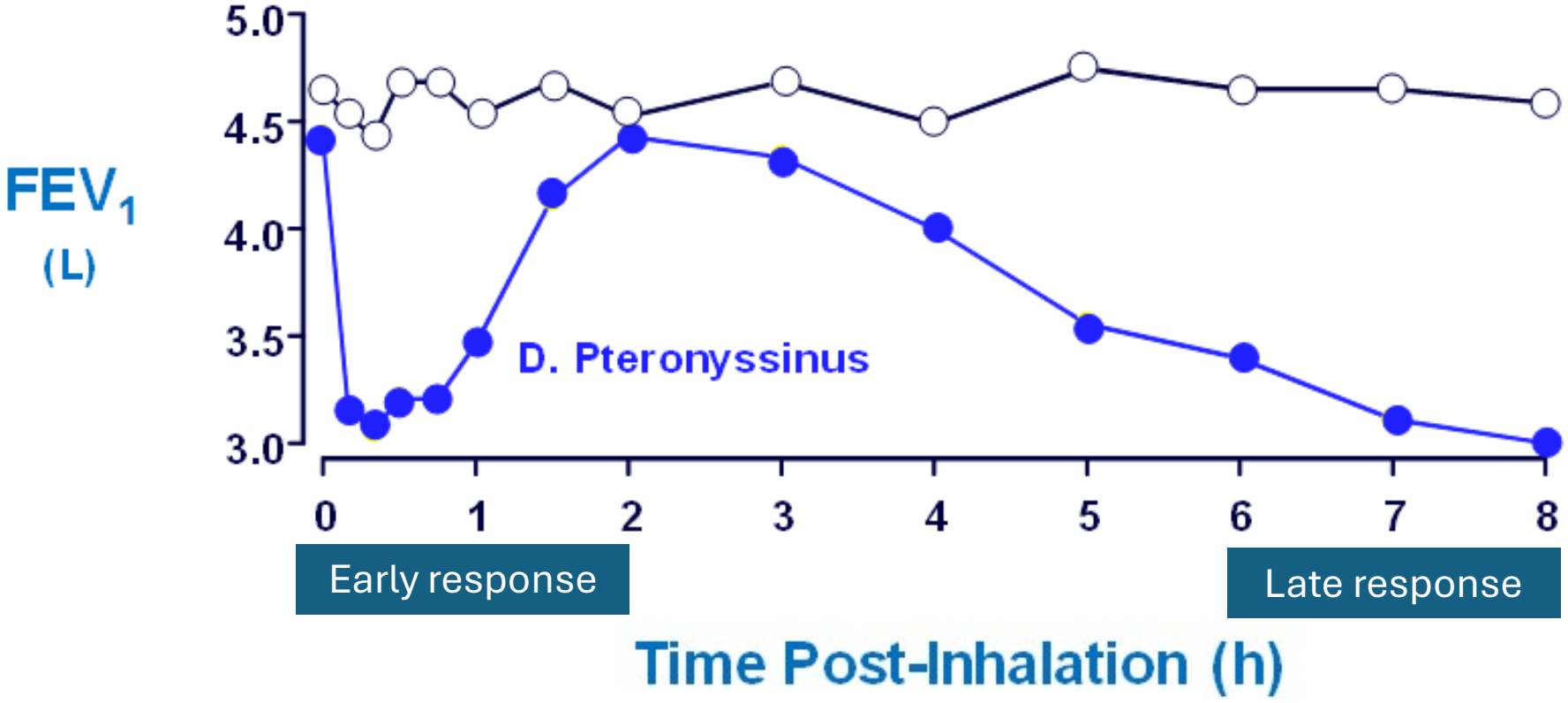
The patient's most reactive allergen is identified.



Following treatment with the experimental drug or placebo, the patient is exposed to the allergen.

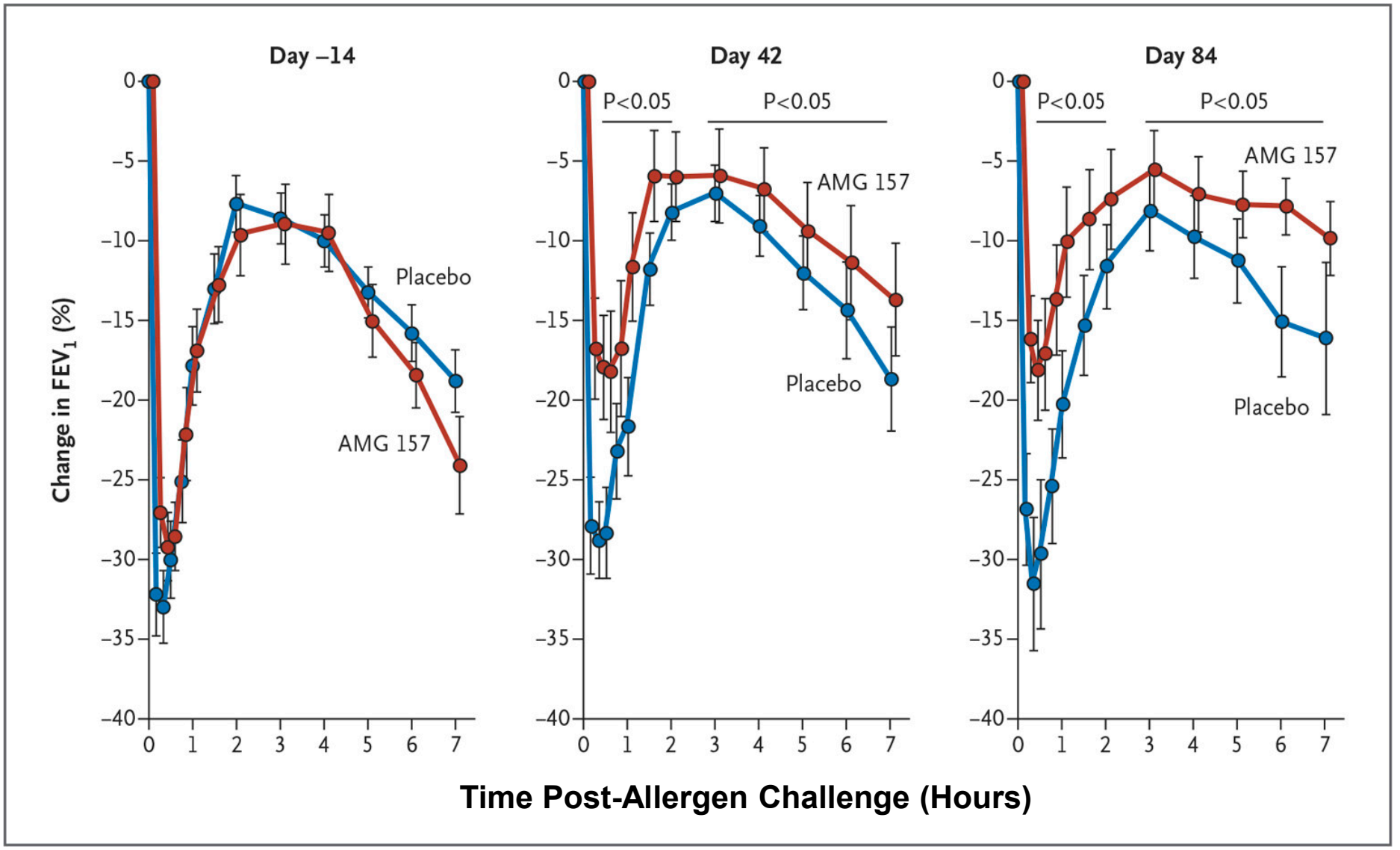
Respiratory capacity is measured (FEV1).

Allergen-induced bronchoconstriction is a hallmark of asthmatic response



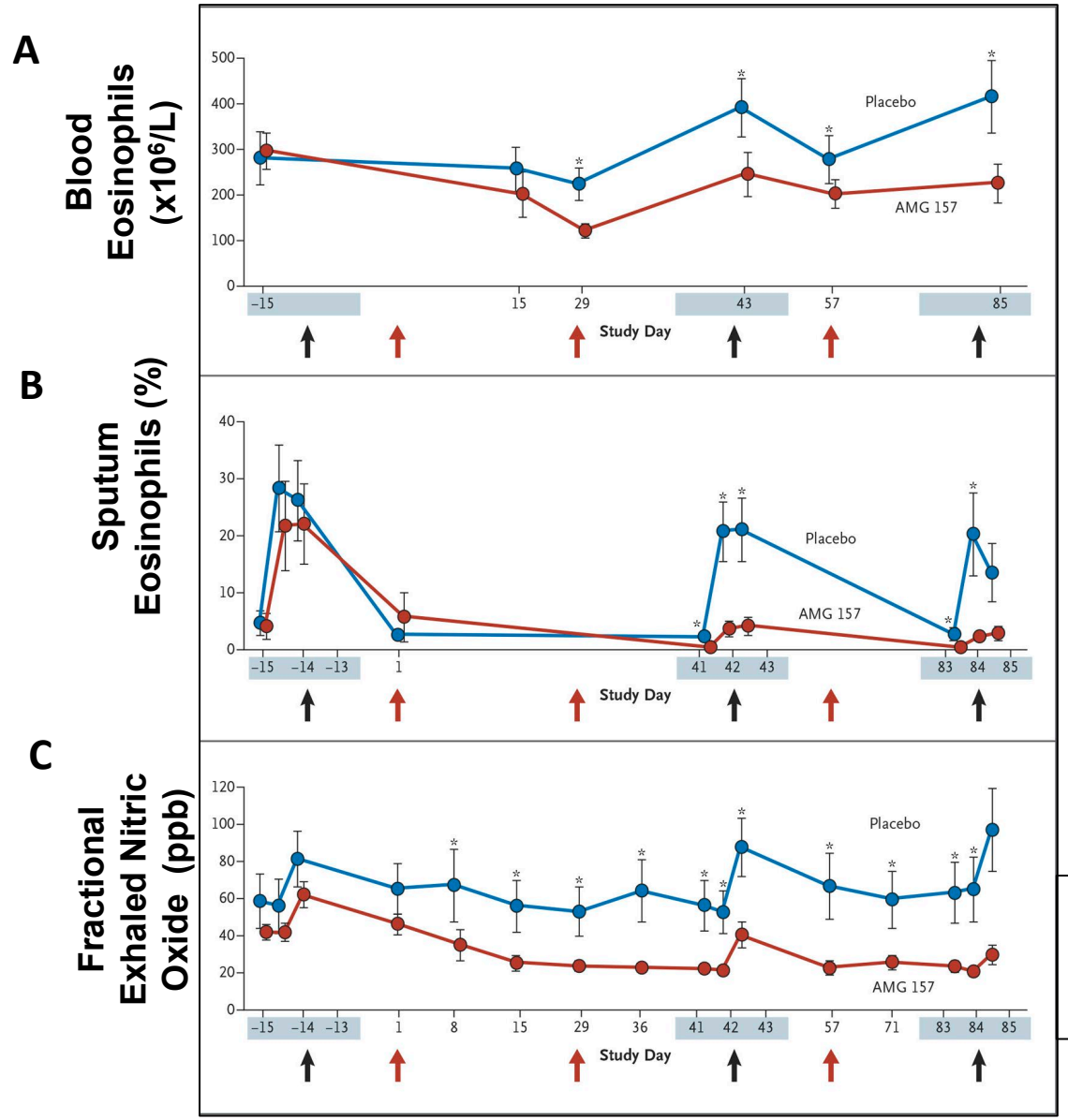
- Mild, stable allergic asthmatic that are not on regular treatment
- Sensitized to an environmental allergen:
  - house dust mite
  - ragweed
  - cat

Allergen challenge study shows improved response with anti-TSLP receptor treatment



Gauvreau GM, et al. N Engl J Med 2014: 370:2102-10.

Challenge study shows eosinophil levels are reduced with anti-TSLP receptor treatment



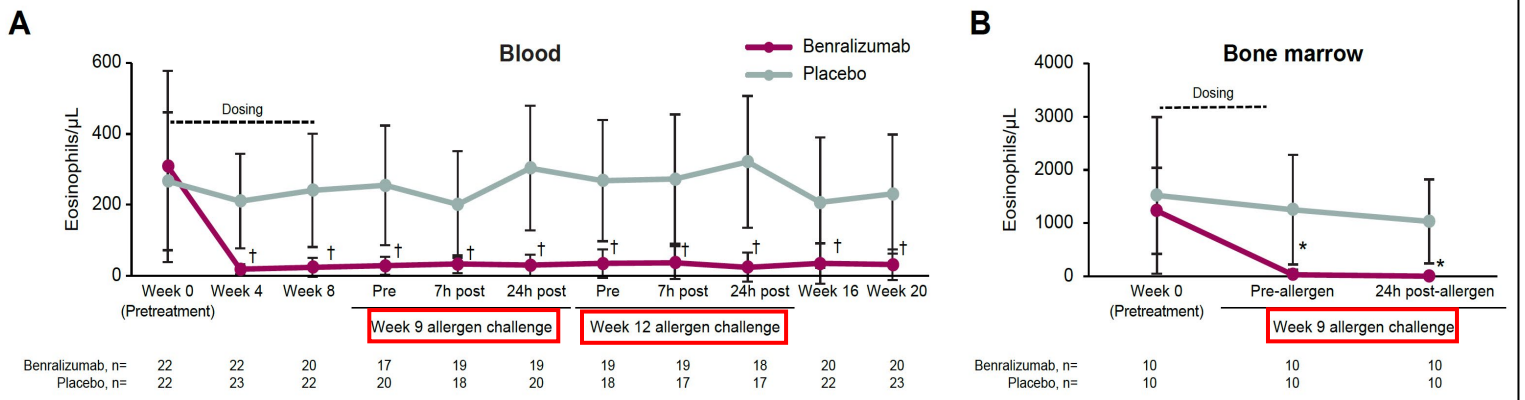
Treatment with AMG-157 reduced levels of eosinophils across tissue compartments

Gauvreau GM, et al. N Engl J Med 2014: 370:2102-10.; AMG-157: tezepelumab, anti-TSLP receptor antibody

Eosinophil levels are reduced with treatment, but symptoms remain

Benralizumab for allergic asthma: a randomised, double-blind, placebo-controlled trial

Gail M. Gauvreau[1], Roma Sehmi[1], J. Mark FitzGerald[2,12], Richard Leigh[3], Donald W. Cockcroft[4], Beth E. Davis[4], Irvin Mayers[5], Louis-Philippe Boulet[6], Dhuha Al-Sajee[1], Brittany M. Salter[1], Ruth P. Cusack[1], Terence Ho[1], Christiane E. Whetstone[1], Nadia Alsaji[1], Imran Satia[1], Kieran J. Killian[1], Patrick D. Mitchell[7], Iain P. Magee[4], Celine Bergeron[2], Mohit Bhutani[5], Viktoria Werkström[8], Tomasz Durżyński[9], Kathryn Shoemaker[10], Rohit K. Katial[11], Maria Jison[10], Paul Newbold[10], Christopher McCrae[9] and Paul M. O'Byrne[1]



Treatment with benralizumab depleted eosinophils across tissue compartments

Gauvreau GM, et al. Eur Respir J 2024; 64:2400521. benralizumab : anti-IL 5 receptor antibody

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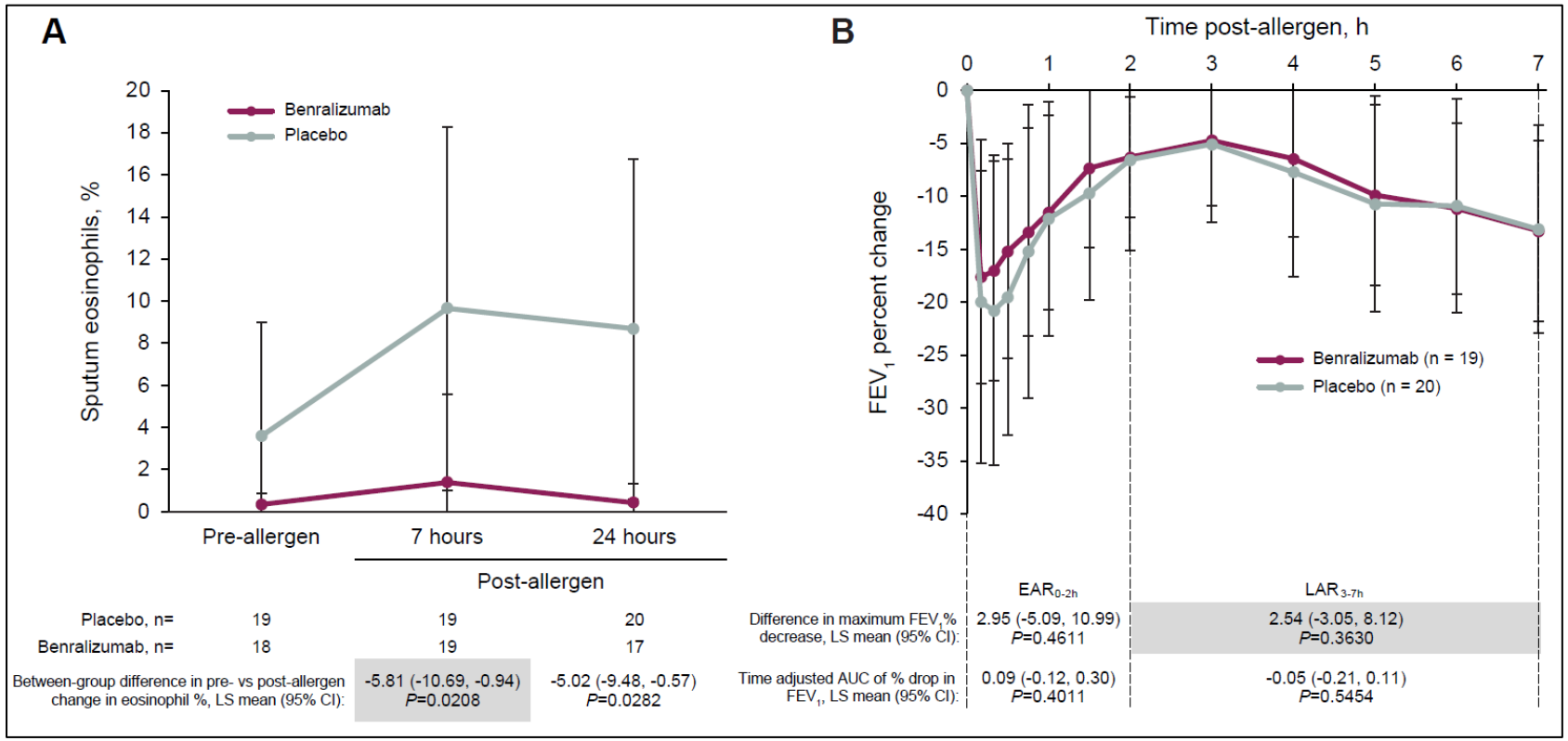

Placebo, n=	19	19	20
Benralizumab, n=	18	19	17
Between-group difference in pre- vs post-allergen change in eosinophil %, LS mean (95% CI):		-5.81 (-10.69, -0.94) *P*=0.0208	-5.02 (-9.48, -0.57) *P*=0.0282
Difference in maximum FEV_1% decrease, LS mean (95% CI):		2.95 (-5.09, 10.99) *P*=0.4611	2.54 (-3.05, 8.12) *P*=0.3630
Time adjusted AUC of % drop in FEV_1, LS mean (95% CI):		0.09 (-0.12, 0.30) *P*=0.4011	-0.05 (-0.21, 0.11) *P*=0.5454

- No significant reduction in asthmatic response despite reduction of eosinophils
- Clear signal that mast cells play an important role in early and late phases of asthmatic response

Gauvreau GM, et al. Eur Respir J 2024; 64:2400521

Blueprint's strategic approach to development in mast cell diseases

Blueprint is a **leader in mast cell therapies**, using our success in SM with AYVAKIT as a competitive edge to advance strategic development of elenestinib and BLU-808.

Our approach to solving the challenges of mast cell biology is designed to **achieve tunability through dose flexibility** to optimize benefit-risk profile.

We are committed to maximizing value while maintaining our disciplined financial approach, by generating **important early data that de-risks further development.**

In fond memory of Dr. Marcus Maurer

At Blueprint Medicines, we mourn the loss of Dr. Marcus Maurer, a true pioneer. His unwavering commitment to improve the lives of patients inspired innovation across the field of mast cell biology.


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Thank you