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Potential for Sebetralstat to Address Pseudo-allergic Reaction Burden Secondary to Icatibant in HAE

Sally L. Hampton,[1] Paul K. Audhya,[1] Michael D. Smith,[1] Christopher M. Yea[1]

[1]KalVista Pharmaceuticals, Salisbury, United Kingdom, and Cambridge, MA, USA

Background

- All approved on-demand medications for hereditary angioedema (HAE) attacks require parenteral administration[1,2]
- Parenteral administration adds to the complexity in treatment decision-making and delays attack treatment in patients with HAE due to the time required to prepare and administer parenteral treatment, not having on-demand treatment on hand, a fear of needles, lack of a private area to administer the injection, associated pain and discomfort, and the occurrence of injection-site reactions[3,4]
  - An oral on-demand treatment has the potential to improve patient outcomes by reducing many of the barriers associated with parenteral on-demand treatment[5]
- Icatibant is the most widely approved on-demand treatment for HAE, being licensed in more than 46 countries[6]
  - In pivotal phase 3 randomized controlled trials, icatibant-associated injection site reactions were reported in 96% to 100% of patients[8,9]
  - The available evidence suggests that icatibant-associated injection site reactions (**Figure 1**) are a pseudo-allergic reaction arising from cutaneous mast cell degranulation and histamine release, via Mas-Related G-Protein Coupled Receptor X2 (MRGPRX2) induction (**Figure 2**)[10-12]

Figure 1. Icatibant-associated injection site reaction in a patient with HAE[10]

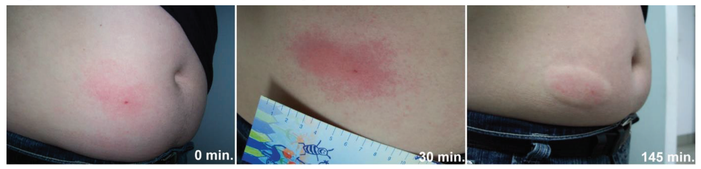

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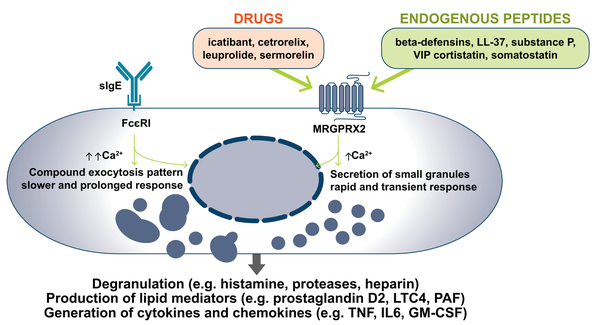
Figure 2. Mediation of drug hypersensitivity by mast cells



GM-CSF, granulocyte-macrophage colony-stimulating factor; FcεRI, high-affinity IgE receptor; IgE, immunoglobulin E; IL6, interleukin-6; LL-37, cathelicidin; LTC4, leukotriene C4; MRGPRX2, MAS-related G protein–coupled receptor X2; PAF, platelet activating factor; TNF, tumor necrosis factor; VIP, vasoactive intestinal peptide.

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Objectives

- Review the general safety profiling with sebetralstat utilizing *in vitro* assays to support sebetralstat clinical development
- Assess the potential to cause pseudo-allergic reactions

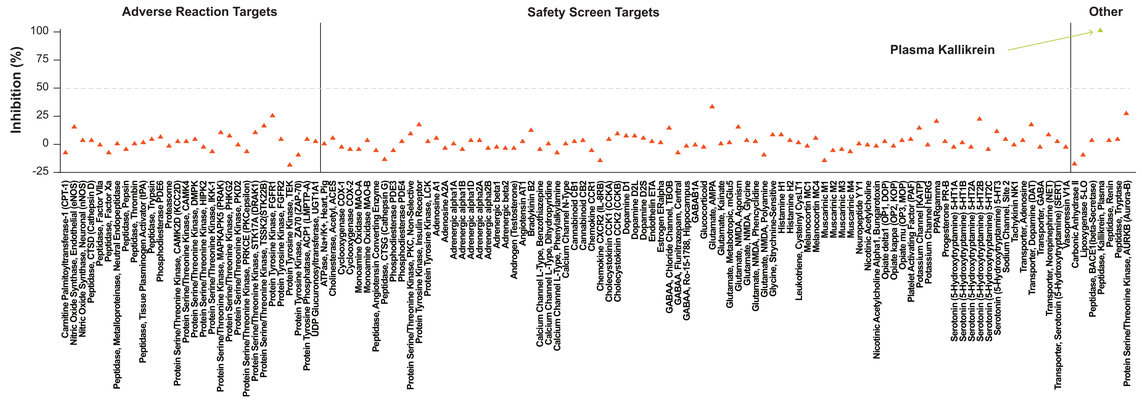
Methods

- The general safety profiling of sebetralstat (10 µM) was examined against commercial adverse reaction and safety screen targets panels comprising 123 molecular targets that are related to undesirable adverse effects (Eurofins Panlabs). Plasma kallikrein enzyme target was included as a positive control
- MRGPRX2 activation was examined by monitoring calcium mobilisation in the PathHunter® human CHO-K1 cell line stably expressing MRGPRX2 using a calcium-sensitive dye loaded into cells in a live cell, non-imaging assay format
  - Cells were seeded into 384-well microplates and incubated at 37°C, and loaded with dye prior to testing
  - Cells were incubated with Cortistatin 14 (positive control), icatibant (HOE-140; n=3), or sebetralstat (n=2), and calcium mobilisation following receptor activation was monitored in duplicate on a FLIPR Tetra (MDS) for 2 minutes with test compound being added to the cells 5 seconds into the assay (Eurofins DiscoverX Corp)
  - Half-maximal effective concentration (EC_{50}) and percentage activity at concentrations of 3 to 100 µM were calculated

Results

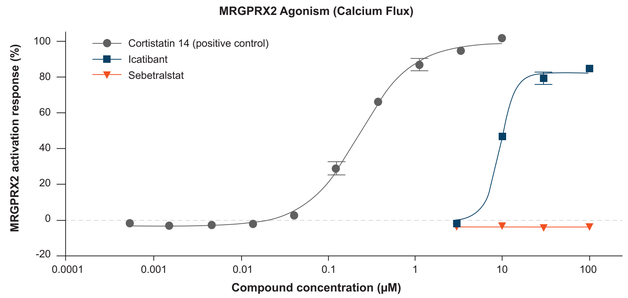
- With the exception of 102% inhibition of plasma kallikrein (positive control), sebetralstat did not significantly inhibit the activity or binding at any of the 123 safety profiling targets (ie, <50% inhibition at 10 µM), representing a window of >1,656-fold selectivity of sebetralstat (**Figure 3**)

Figure 3. *In vitro* safety profiling panel assays at 10 µM sebetralstat



- The mean (SD) EC_{50} of MRGPRX2 activation was 10.57 (2.35) µM for icatibant (n=3) and >100 µM for sebetralstat (n=2) (Representative graph presented in **Figure 4**)

Figure 4. MRGPRX2 agonism for icatibant and sebetralstat



Conclusions

- ***In vitro* assays demonstrated the high selectivity of sebetralstat across a wide panel of molecular targets associated with drug adverse reactions and safety concerns**
- **Sebetralstat did not activate MRGPRX2 at clinically relevant concentrations, indicating that pseudo-allergic reactions are unlikely when sebetralstat is used as on-demand treatment by a wider group of people living with HAE (assuming regulatory approval)**
- **The findings of these *in vitro* assays were corroborated by the clinical safety observed in sebetralstat clinical trials**

References

1. Busse PJ et al. *J Allergy Clin Immunol Pract.* 2021;9:132-150.
2. Maurer M et al. *Allergy.* 2022;77(7):1061-1990.
3. Christiansen S et al. *Ann Allergy Asthma Immunol.* 2024:S1081-1206(24)01732-0.
4. Betschel SD et al. *Allergy Asthma Clin Immunol.* 2024;20(1):43.
5. Valerieva A et al. *Clin Transl Allergy.* 2024;14(9):e12391.
6. Maurer M et al. *Clin Exp Allergy.* 2022;52(9):1048-1058.
7. Firazyr 30 mg solution for injection in pre-filled syringe. Summary of product characteristics. Takeda Pharmaceuticals International AG Ireland Branch; 2013.
8. Cicardi M et al. *N Engl J Med.* 2010;363(6):532-541.
9. Lumry WR et al. *Ann Allergy Asthma Immunol.* 2011;107(6):529-537.
10. Porebski G et al. *Front Immunol.* 2021;12:676354.
11. McNeil BD et al. *Nature.* 2015;519(7542):237-241.
12. Kolkhir P et al. *J Allergy Clin Immunol.* 2023;151(2):410-412.
13. Riedl MA et al. *New Engl J Med.* 2024;391(1):32-43.
14. Davie RL et al. *J Med Chem.* 2022;65(20):13629-13644.

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