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Pharmaceuticals

# Corporate Overview

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March 2024

# Forward-Looking Statements

This presentation and the accompanying oral commentary contain forward-looking statements that are based on our management's beliefs and assumptions and on information currently available to our management. Forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified. In some cases, you can identify forward-looking statements by terminology such as "may," "will," "should," "could," "expect," "plan," "anticipate," "believe," "estimate," "predict," "intend," "potential," "would," "continue," "ongoing" or the negative of these terms or other comparable terminology. Forward-looking statements include all statements other than statements of historical fact contained in this presentation, including information business plans and objectives, timing and success of our planned nonclinical and clinical development activities, timing and results of nonclinical studies and clinical trials, efficacy and safety profiles of our product candidates, any expectations about safety, efficacy of sebetralstat and our ability to obtain regulatory approvals for sebetralstat and other candidates in development, the ability of sebetralstat to treat hereditary angioedema (HAE), the potential therapeutic benefits and economic value of our product candidates, potential growth opportunities, competitive position, industry environment and potential market opportunities, our ability to protect intellectual property and the impact of global business or macroeconomic conditions, including as a result of inflation, rising interest rates, instability in the global banking system, and geopolitical conflicts, including the conflicts in Ukraine and the Middle East, on our business and operations.

Forward-looking statements are subject to known and unknown risks, uncertainties, assumptions and other factors. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. These factors, together with those that are described under the heading "Risk Factors" contained in our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission ("SEC") and other documents we file from time to time with the SEC, may cause our actual results, performance or achievements to differ materially and adversely from those anticipated or implied by our forward-looking statements.

In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this presentation, and although we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted a thorough inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain, and investors are cautioned not to unduly rely upon these statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

# Company Highlights

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- Discovery, development, and commercialization of oral, small molecule protease inhibitors
- Lead program Sebetralstat for on-demand treatment of rare disease hereditary angioedema (HAE)
- Data from Phase 3 KONFIDENT trial announced February 2024; met all primary and secondary endpoints, with favorable safety profile; NDA expected H1 2024
- Sebetralstat would be first oral option in \$900 million on-demand HAE market and has potential to transform treatment of the disease and the entire \$2.7 billion market
- Preclinical oral Factor XIIa program focused on HAE and additional indications
- All programs internally developed, with full rights and IP protection into the 2040's
- Funded into 2026 with pro forma cash of \$242 million after closing \$160.1 million public offering in February 2024.

# Program Portfolio

Product	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Status
Sebetralstat	On-Demand HAE	KONFIDENT (Trial Completed)				Data reported; NDA 1H 2024
		KONFIDENT-S (Open-Label Extension)				Trial ongoing
		Orally Disintegrating Tablets				Advancing to sNDA as lifecycle extension
Oral Factor XIIa	HAE Prophylaxis					Discovery and Optimization
Oral Factor XIIa	Thrombosis, inflammation					Future opportunities under evaluation



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# Hereditary Angioedema (HAE)

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# Hereditary Angioedema (HAE)

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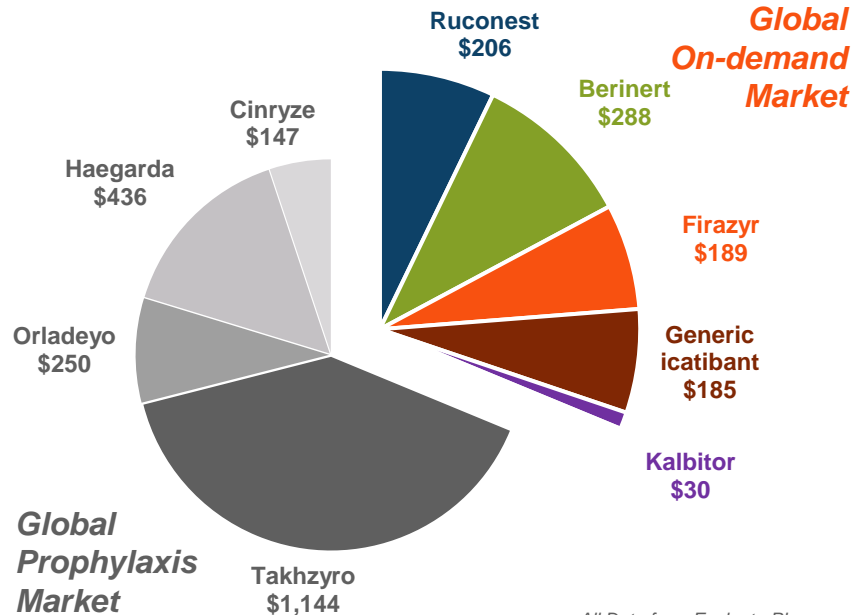
- Genetic condition causing painful and pronounced swelling in various parts of the body
  - Primarily caused by defect in C1 inhibitor activity, which leads to uncontrolled plasma kallikrein activation and bradykinin release
- Orphan disease: incidence 1 in 10,000 to 1 in 50,000<sup>1</sup>
  - 6,500 – 8,000 patients in US; similar in EU
  - Incidence consistent worldwide; patients have average of ~2 attacks per month
- Approved on-demand therapies are injected or infused - high unmet need for efficacious and safe oral administration
  - On-demand + prophylaxis is majority share in US, although burden of treatment remains high
  - On-demand only is majority share ex-US

<sup>1</sup>[www.haei.org](http://www.haei.org)

# On-Demand is \$900 Million Market, With Growth Potential

**On-demand was \$900 Million revenue market in 2022**

**At branded prices, US on-demand market alone would be \$1+ billion**



**US units 2022**

<b>Ruconest</b>	<b>29,200</b>
<b>Berinert</b>	<b>35,400</b>
<b>Firazyr</b>	<b>10,500</b>
<b>Gx icanitabant</b>	<b>49,300</b>
<b>Total units</b>	<b>124,400</b>

**Firazyr WAC/dose: \$10,800**

All Data from Evaluate Pharma, public filings and certain Company estimates.



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# Sebetralstat: HAE On-Demand Therapy

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# Unmet Need In HAE Is Underappreciated

The goal of treatment is to minimize compromises in lifestyle, but attacks still cause anxiety and impact quality of life



Anxiety and depression are common in people living with HAE



~50% of people taking prophylaxis continue to experience HAE attacks



96% of people on prophylaxis feel they must change their plans for the day when an attack occurs<sup>3</sup>



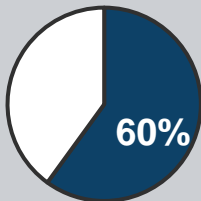

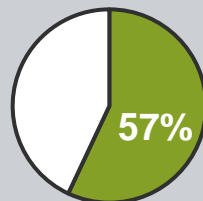
People living with HAE prefer to treat at home to avoid treating attacks in public



People typically delay injectable treatment for hours and studies show more than 40% of attacks aren't treated at all<sup>1,2,4</sup>

<sup>1</sup>Maurer M, et al. Hereditary Angioedema Attacks Resolve Faster and Are Shorter after Early Icatibant Treatment. *PLoS ONE*. 2013;8(2):e53773. <sup>2</sup>Longhurst H J et al. Real-world outcomes in hereditary angioedema: first experience from the Icatibant Outcome Survey in the United Kingdom *Allergy Asthma Clin Immunol*. 2018;14: 28. <sup>3</sup>Remaining Burden of Hereditary Angioedema (HAE) Attacks Despite Modern Long-term Prophylaxis Stephen Betschel, Sally van Kooten, Markus Heckmann, Sherry Danese, Ledía Goga, Teresa Caballero; *EAACI 2023 Hybrid Congress*. <sup>4</sup>Banerji A, et al. *Allergy Asthma Proc*. 2015;36(3):213-7. doi: 10.2500/aap.2015.36.3824

# Patients on LTP Still Have Attacks

Proportion of patients that experienced attacks on approved LTP in placebo-controlled trials			
Treatment	C1-INH (SC) 60 IU/kg <sup>1</sup>	Lanadelumab 300 mg Q2W <sup>2</sup>	Bertralstat 125 mg <sup>3</sup>
Trial design	Randomized, placebo-controlled crossover phase 3 trial (16 weeks)	Randomized, double-blind, parallel-group, placebo-controlled phase 3 trial (26 weeks)	Randomized, double-blind, parallel-group, dose-response phase 2 trial <sup>4</sup> (28 days)
Proportion of patients experiencing attacks during observed period	<p><b>C1-INH (SC) 60 IU/kg (N=45)</b></p>  <p>Entire 16-week treatment period</p>	<p><b>Lanadelumab 300 mg Q2W (N=27)</b></p>  <p>Entire 26-week treatment period</p> <p>Steady state (days 70-182)</p>	<p><b>Bertralstat 125 mg (N=14)</b></p>  <p>Entire 28-day treatment period</p>

Although LTP reduces attack frequency, many patients continue to have attacks and require ready access to effective on-demand treatment

# The Sebetralstat Treatment Vision



## EARLY

- Patients empowered to **treat early** - at **first recognition** of attack
- Halt progression of swelling at **earliest stages**



## ALL ATTACKS

- Patients **able to treat all attacks**, since it is impossible to predict which ones will escalate in severity or migrate to other anatomic locations, including the larynx
- Current **barriers to treatment are removed** including pain and inconvenience associated with parenteral therapies



## EASE OF USE

- Sebetralstat dosing is **simple** with easy-to-take **tablets**
- Patients can **easily carry, store and access** anytime, anywhere
- **Quick-dissolving oral disintegrating tablet (ODT)**, a potential future advancement



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# Topline Data from Phase 3 KONFIDENT Trial

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# Welcome to the New Era of HAE

## KONFIDENT™

Positive topline results from the largest  
clinical trial conducted in HAE

**We believe SEBETRALSTAT offers the promise to be the foundational HAE treatment**



**On-demand with or  
without prophylaxis**



**Any attack location  
or severity**



**Adults and  
adolescents**

# Sebetralstat Phase 3 Trial Design

- Double blind crossover trial assessing 300 mg and 600 mg sebetralstat versus placebo
- Primary endpoint: Time to beginning of symptom relief using PGI-C
- At least 90% powered to detect treatment differences vs placebo
- Each patient treats up to 3 attacks anytime, anywhere
  - One with each treatment in a randomized, blinded sequence
  - Patients take up to two doses per attack



**Primary endpoint:**

- Time to beginning of symptom relief (PGI-C)

**Key secondary endpoints:**

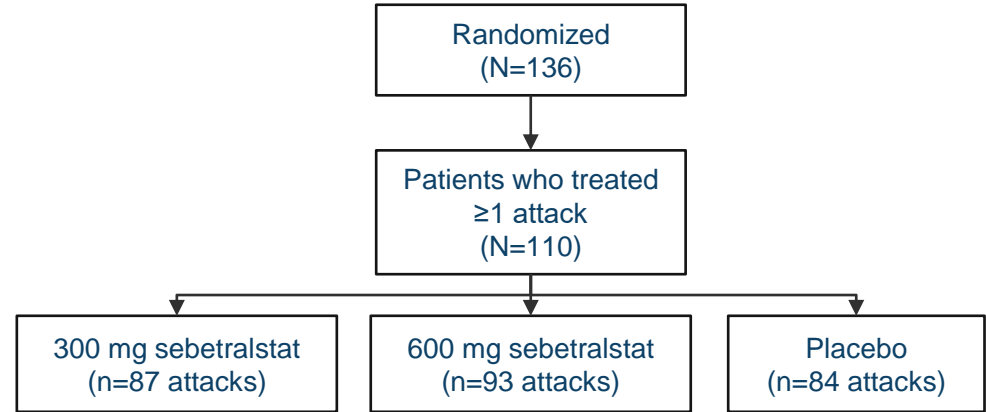
- Time to improvement (PGI-S)
- Time to resolution (PGI-S)

# Key Differences in Design Between the Sebetralstat Phase 2 and Phase 3 KONFIDENT Trials

	Phase 2 Trial	Phase 3 KONFIDENT Trial
Primary endpoint	Time to use of conventional attack treatment within 12 hours after study drug administration	PGI-C: TOSR defined as at least “a little better” (≥2 time points in a row) within 12 hours after study drug administration
Population	Adults (≥18 years of age) with HAE type 1 or 2	Adolescents and adults (≥12 years of age) with HAE type 1 or 2
LTP	No LTP allowed	Stable LTP eligible to participate (excluding androgens and tranexamic acid)
Attack locations	Peripheral, abdominal	All attack locations
Attack severity	Mild to moderate	Mild to very severe
Attack eligibility	Patient required to notify trial physician to confirm attack eligibility before dosing	Patient not required to call physician to confirm attack eligibility before dosing
Treatment	Single dose of study drug with minimum 48-hour washout between attacks	Up to 2 doses of study drug permitted as treatment for a single attack

# Enrollment and Demographics

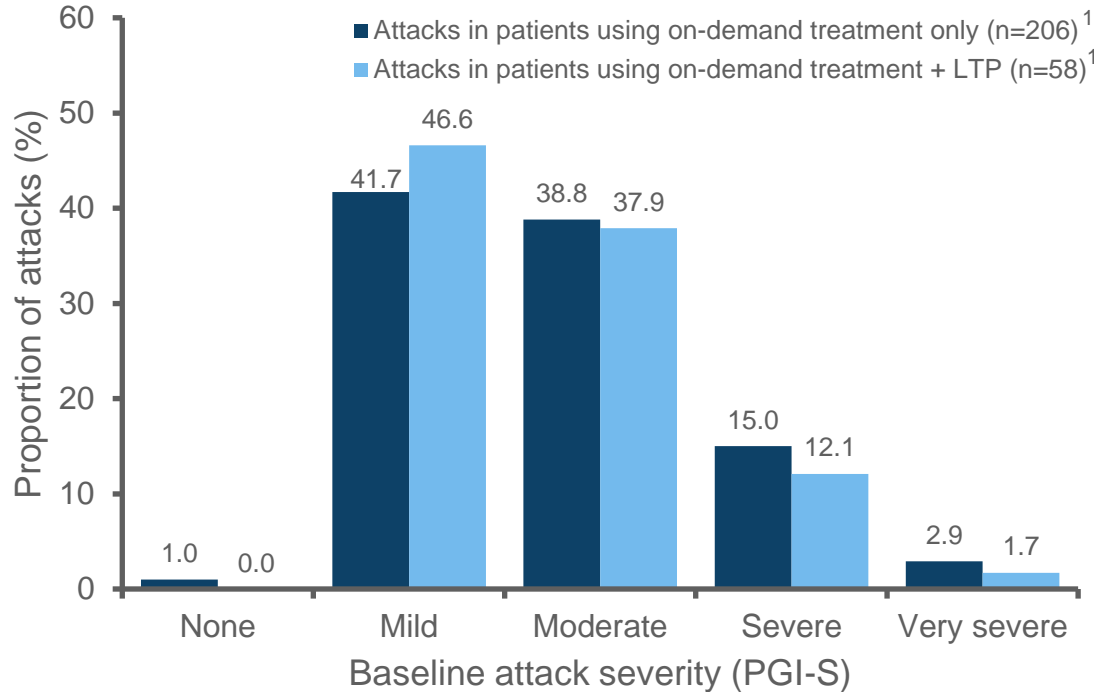
	Total (N=110)
<b>Age (years)</b>	
Mean (SD)	37.7 (15.0)
Median (min, max)	39.5 (13, 74)
<b>Age (category), n (%)</b>	
18+	97 (88.2)
12-17	13 (11.8)
<b>Sex, n (%)</b>	
Female	66 (60.0)
Male	44 (40.0)
<b>BMI (kg/m<sup>2</sup>)</b>	
Mean (SD)	27.4 (6.3)
Median (min, max)	26.2 (18.2, 45.6)
<b>Geography, n (%)</b>	
Europe	58 (52.7)
US	34 (30.9)
Asia/Pacific <sup>a</sup>	18 (16.4)



- 10 patients discontinued from the trial
- No patients withdrew due to an AE



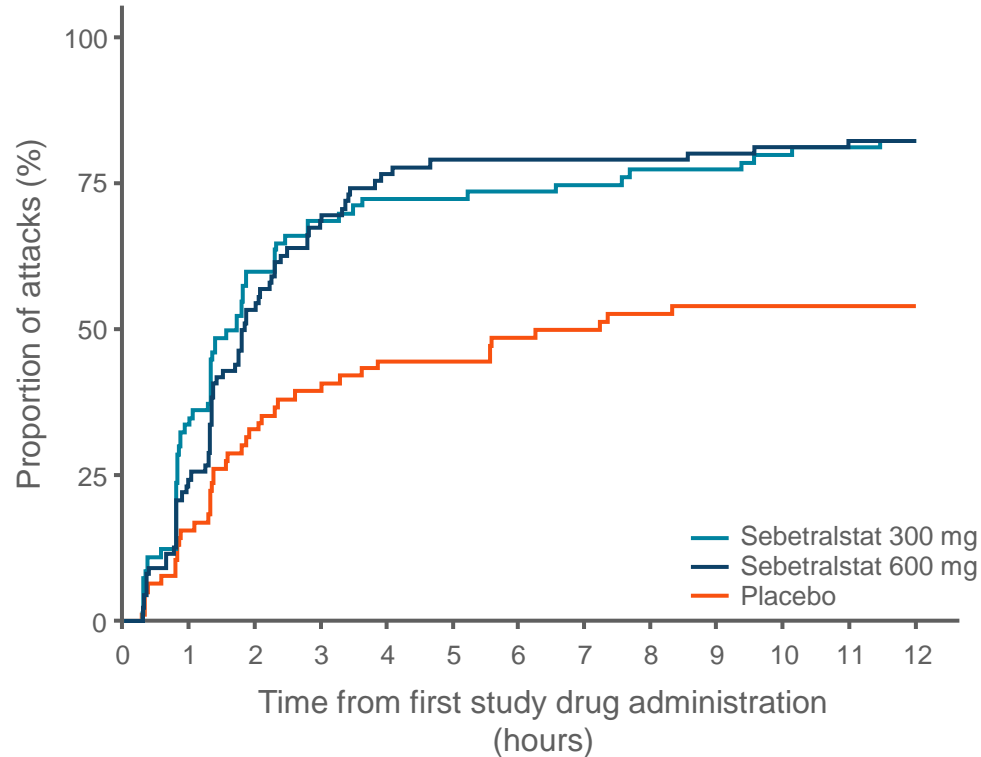
# Comparable Attack Severity in Patients Using LTP



	Total (N=110)
<b>Current treatment regimen, n (%)</b>	
On-demand only	86 (78.2)
On-demand + LTP	24 (21.8)
Berotrastat	11 (10.0)
Lanadelumab	8 (7.3)
C1INH	5 (4.5)

1. Baseline severity for 1 attack in each group not reported. Data on file.

# Primary Endpoint: Time to Beginning of Symptom Relief



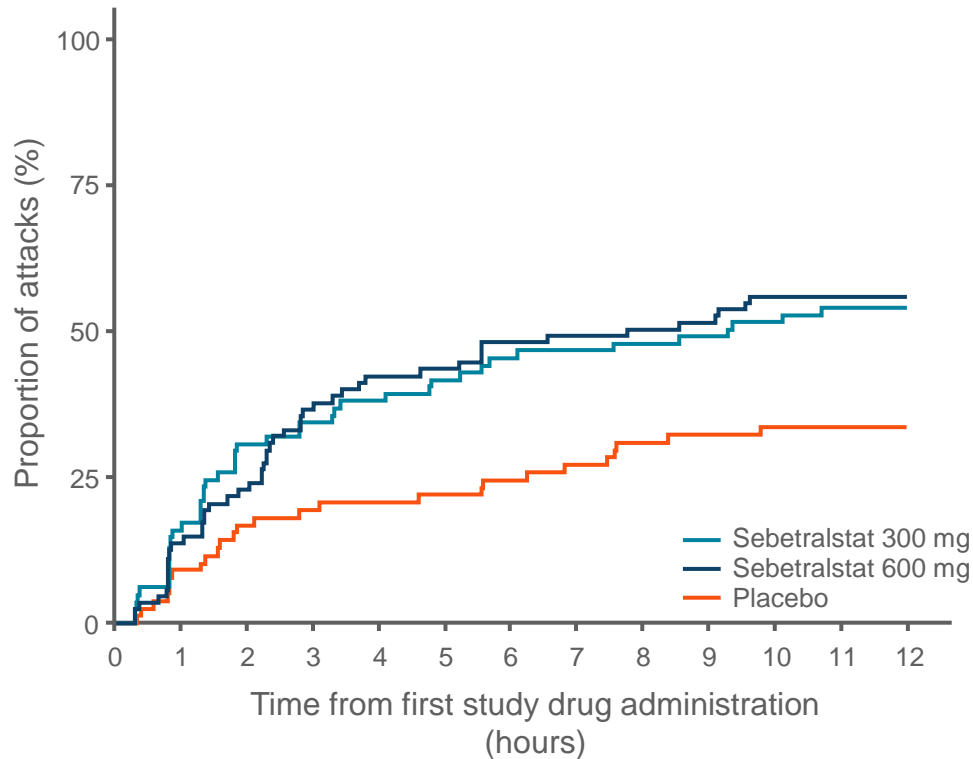
- Time to beginning of symptom relief was statistically significantly faster vs placebo for
  - 300 mg ( $p < 0.0001$ )
  - 600 mg ( $p = 0.0013$ )
- Median time (95% CI) to beginning of symptom relief was
  - 1.61 h (1.28, 2.27) for 300 mg
  - 1.79 h (1.33, 2.27) for 600 mg
  - 6.72 h (2.33, >12) for placebo

# Primary Endpoint: Consistent Treatment Effect Across Subgroups

- Trial was not powered to statistically test treatment effect within subgroups
- Treatment effect with sebetralstat was consistent across subgroups including
  - Sex, race, age, geographic region, HAE subtype, time to treatment, attack location, attack severity
- Importantly, consistent treatment effect was also observed in subgroups not previously studied with sebetralstat

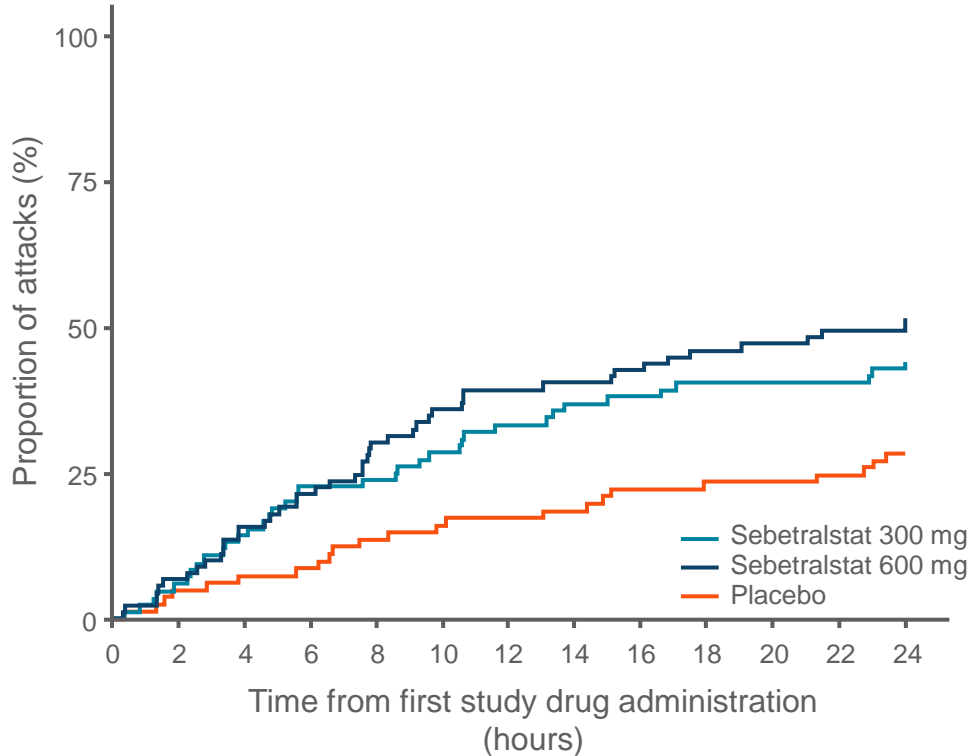
Time to beginning of symptom relief	Sebetralstat 300 mg		Sebetralstat 600 mg	
Subgroup	n	Median (95% CI)	n	Median (95% CI)
On-demand with LTP	19	1.85 (0.79, 3.47)	21	2.03 (0.78, 3.41)
Adolescent	10	2.27 (0.28, 9.36)	11	2.16 (0.33, 9.53)
Severe/very severe	14	1.40 (0.78, 2.78)	18	1.50 (0.79, 2.27)

# Key Secondary: Time to Reduction in Attack Severity



- Time to reduction in attack severity was statistically significantly faster vs placebo for
  - 300 mg ( $p=0.0036$ )
  - 600 mg ( $p=0.0032$ )
- Median time (95% CI) to reduction in attack severity was:
  - 9.27 h (4.08, >12) for 300 mg
  - 7.75 h (3.27, >12) for 600 mg
  - >12 h (>12, >12) for placebo

# Key Secondary: Time to Complete Attack Resolution



- Time to complete attack resolution was statistically significantly faster vs placebo for
  - 300 mg ( $p=0.0022$ )
  - 600 mg ( $p<0.0001$ )
- Proportion achieving complete attack resolution within 24 hours was:
  - 44.0% for 300 mg
  - 51.7% for 600 mg
  - 28.4% for placebo

# On-treatment Related Adverse Events

System organ class preferred term, n (%) E	Sebetralstat 300 mg (n=86)	Sebetralstat 600 mg (n=93)	Placebo (n=83)
<b>Gastrointestinal disorders</b>	1 (1.2) 1	1 (1.1) 1	1 (1.2) 1
Dyspepsia	1 (1.2) 1	0	0
Nausea	0	1 (1.1) 1	1 (1.2) 1
<b>General disorders and administration site conditions</b>	1 (1.2) 1	0	0
Fatigue	1 (1.2) 1	0	0
<b>Nervous system disorders</b>	0	1 (1.1) 1	2 (2.4) 2
Headache	0	1 (1.1) 1	1 (1.2) 1
Dysgeusia	0	0	1 (1.2) 1
<b>Reproductive system and breast disorders</b>	0	0	1 (1.2) 1
Menstruation irregular	0	0	1 (1.2) 1
<b>Skin and subcutaneous tissue disorders</b>	0	0	1 (1.2) 1
Rash	0	0	1 (1.2) 1

E, number of events; TEAE, treatment-emergent adverse events. On-treatment AEs were defined as TEAEs that start within 3 days of administering the final dose of study drug for an attack. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Adverse events were coded using MedDRA, Version 26.0.

See Table 14.3.1.3.2 – Safety Set. Data on file.

# Results in the Sebetralstat Phase 2 Trial and the Phase 3 KONFIDENT Trial

		Phase 2 Trial		Phase 3 KONFIDENT Trial		
<b>Population</b>		Adults 100%   adolescents 0%		Adults 88.2%   adolescents 11.8%		
<b>LTP</b>		On-demand only: 100% On-demand + LTP: Not allowed		On-demand only: 78.2% On-demand + LTP: 21.8%		
<b>Attack locations</b>	<b>Peripheral Abdominal</b>	68.1%		56.1%		
		26.5%		43.2%		
<b>Attack severity</b>	<b>Mild</b>	50.4%		42.8%		
	<b>Moderate</b>	45.1%		38.6%		
	<b>Severe</b>	Not allowed		14.4%		
	<b>Very severe</b>	Not allowed		2.7%		
<b>Dose</b>		Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
<b>Time to administration</b>		30 minutes		41 minutes		
<b>Median time to beginning of symptom relief</b>		1.6 h	9.0 h	1.61 h	1.79 h	6.72 h
<b>Second dose</b>		Not allowed	Not allowed	38.4%	41.1%	55.4%
<b>Use of conventional treatment within 12 h</b>		15.1%	30.2%	13.8%	8.6%	25.0%

# Update: KONFIDENT-S Open-Label Extension

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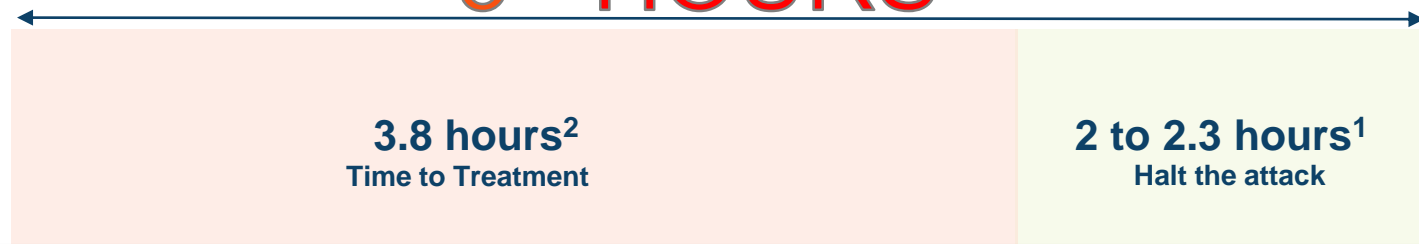
- Trial to evaluate the long-term safety of sebetralstat
- As of February 2, 2024
  - More than 110 patients enrolled
  - More than 640 attacks treated
- Median time to treatment: 10 minutes
- All attack locations well represented, including 14 laryngeal attacks treated to date



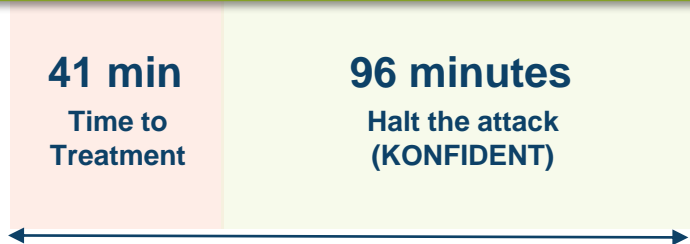
# Sebetralstat Halts the Attack When Today's Patients are Still Deciding Whether to Treat

Current on-demand

**5+ HOURS**



Attack  
Recognition



**Treatment Success Is  
Measured in Minutes  
Not Hours**

Sebetralstat

**137 MINUTES**

# Sebetralstat Can Become the Foundational HAE Therapy



## *Current treatment paradigm*



## *Future with sebetralstat*



# Sebetralstat Can Become the Foundational HAE Therapy

## Market Share



- ✓ Convert current on-demand market, including prophylaxis patients, who still experience attacks
- ✓ Branded pricing

## Increased Treatment



- ✓ ~40% of attacks are untreated, including for prophylaxis patients<sup>1</sup>
- ✓ More attacks will ultimately be treated for both prophylaxis and on-demand patients

## Prophy → On-Demand



- ✓ Patients may switch from prophylaxis to on-demand, seeking an efficacious and safe oral option
- ✓ More cost effective for many prophylaxis patients

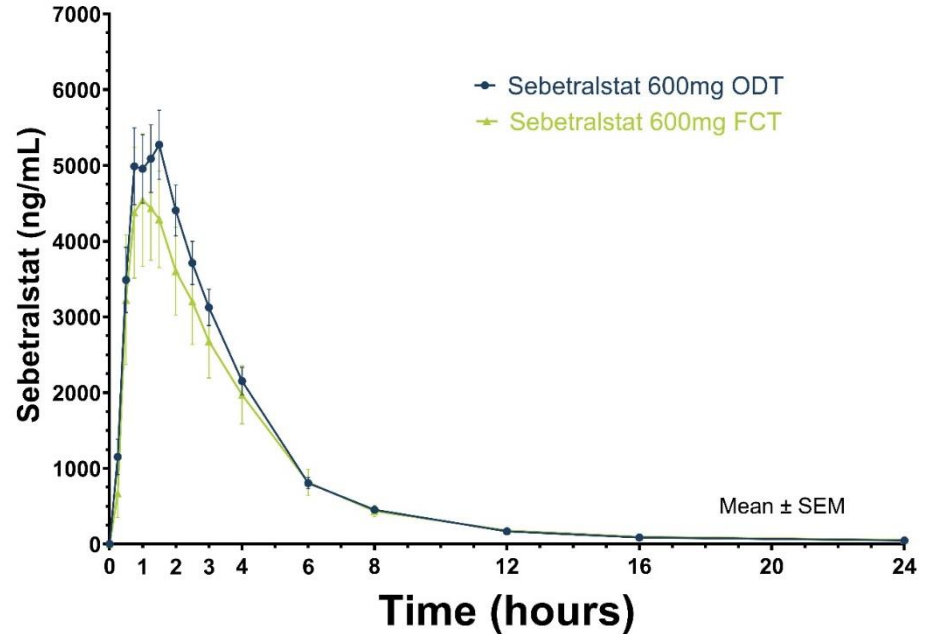
## Future Indications



- ✓ Plasma kallikrein mediated normal C1-INH angioedema
- ✓ Short-term prophylaxis
- ✓ Pediatrics 2-11

# Orally Disintegrating Tablet (ODT): A Future Enhancement

- ODT increases ease of dosing for patients - in particular, pediatrics and those with difficulty swallowing
- Phase 1 data shows similar pharmacokinetics to current film-coated tablets (FCT)
- Regulatory plan agreed with FDA for sNDA filing





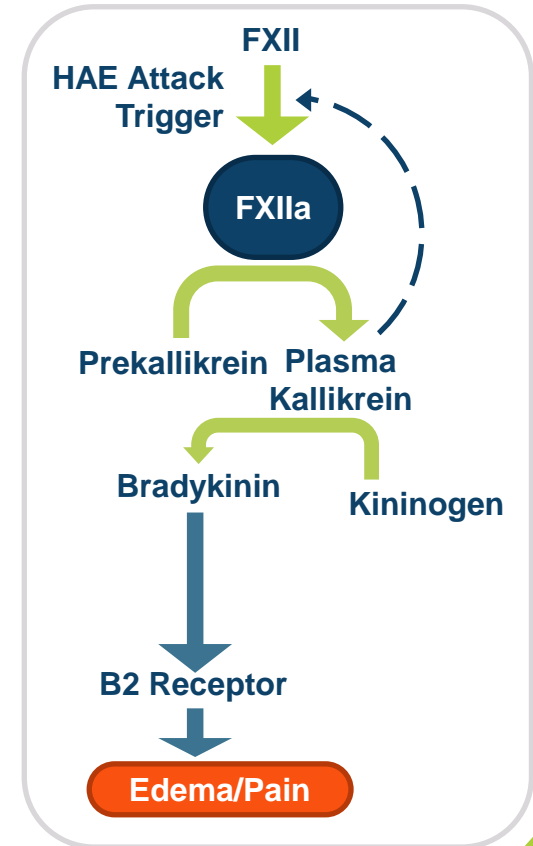
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# Factor XIIa

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# Factor XIIa is an Attractive Drug Target

- Factor XIIa (FXIIa) activates the kallikrein kinin system
  - Generates plasma kallikrein, leading to uncontrolled bradykinin release in HAE
  - FXIIa and plasma kallikrein inhibitors selectively block bradykinin generated by the plasma kallikrein kinin system, unlike bradykinin receptor antagonists
- FXIIa inhibitory antibody has been shown clinically to reduce HAE attack frequency<sup>1</sup>
  - At least as efficacious as approved therapies against other targets
  - No known chronic safety implications
- KalVista is developing oral Factor XIIa inhibitors
  - Initially for HAE, but also implicated in other inflammatory and thrombotic conditions



# KalVista Value Proposition

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- Data from Phase 3 KONFIDENT trial announced February 2024; met all primary and secondary endpoints, with favorable safety profile; NDA expected H1 2024
- Sebetralstat would be first oral option in \$900 million on-demand HAE market and has potential to transform treatment of the disease and the entire \$2.7 billion market
- Oral FXIIa inhibitor program future development opportunity in both HAE prophylaxis and other indications
- All programs internally developed, with full rights and IP protection into the 2040's
- Funded into 2026



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