



#### **Corporate Presentation I Dec 2021**

Developing Therapeutic Antibodies Targeting Allergic Inflammatory and Proliferative Disease

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### **Allakos Opportunity**

Multiple Commercial **Opportunities for** Lirentelimab

- Lirentelimab (AK002) is a first in class anti-Siglec-8 therapeutic antibody targeting eosinophils and mast cells
- Potential to treat a broad range of serious, complex inflammatory diseases
- Clinical proof of concept demonstrated in eosinophilic gastritis (EG) / duodenitis (EoD), eosinophilic esophagitis (EoE), mast cell gastritis, severe allergic conjunctivitis, chronic urticaria, and indolent systemic mastocytosis

Lead Indication in Phase 3 with Data in Q4'21/Early Q1'22

- Phase 2 ENIGMA study for EG and/or EoD met all primary and secondary endpoints compared to placebo
- Phase 3 study in patients with EG and/or EoD and a Phase 2/3 study in patients with EoE are in progress
- EG and/or EoD and EoE are potential multi-billion dollar market opportunities with no approved therapies

	Milestones	
Upcoming Data	Q4'21/Early Q1'22 - Phase 3 Data EG and/or EoD	Q4 2021 - Initiated Phase 3 SC Lirentelimab EG and/or EoD
Catalysts and Expected	Q4'21/Early Q1'22 - Phase 2/3 Data EoE	Q4 2021 - Initiated Phase 2 SC Lirentelimab Atopic Dermatitis
Milestones	Q2 2021 - Initiated Phase 3 EoD	Study



### **Experienced Management Team**

Robert Alexander, PhD	CEO, ZS Pharma
Chief Executive Officer	Director, Alta Partners; Business Development, Genentech
Adam Tomasi, PhD	CSO & Head of Corporate Development, ZS Pharma
President & Chief Operating Officer	Principal, Alta Partners; Drug Discovery, Gilead, Cytokinetics
Baird Radford	SVP, Finance, Aimmune Therapeutics
Chief Financial Officer	CFO, HeartFlow; VP, Intuitive Surgical
Craig Paterson, MD	CMO, Vivelix
Chief Medical Officer	SVP, Medical and Clinical Development, Salix Pharmaceuticals
Tim Varacek	SVP, Sales and Commercial Operations, ZS Pharma
Chief Commercial Officer	VP, Sales, InterMune
Mark Asbury	Chief Legal Officer, ZS Pharma, Pharmacyclics
Chief Legal Officer	Associate General Council, Genentech
Ruby Casareno, PhD	Director, Manufacturing, Portola
SVP, CMC	Director of Process Development and Manufacturing, OncoMed
Sally Bolmer, PhD	SVP, Development and Regulatory Affairs, Human Genome Sciences
SVP, Reg. Affairs and Drug Development	Executive Director, Regulatory Affairs, Centocor



### **Clinical Pipeline and Milestones**

Indication

EGIDs	IND	Phase 1	Phase 2	Phase 3	Milestone
Eosinophilic Gastritis (EG) and/or EoD					Data Expected Q4'21 / Early Q1'22
Eosinophilic Duodenitis (EoD)					Initiated Q2 2021
Eosinophilic Esophagitis (EoE)					Data Expected Q4'21 / Early Q1'22
SC Lirentelimab in EG and/or EoD					Initiated Q4 2021
Others	IND	Phase 1	Phase 2	Phase 3	Milestone
Phase 2 – Atopic Dermatitis (SC Lirentelimab)					Initiated Q4 2021
Phase 2/3 – Chronic Urticaria (SC Lirentelimab)				I	Initiation Expected Mid 2022
Phase 2 – Asthma (SC Lirentelimab)					Initiation Expected Q4 2022
Phase 1 Mast Cell Gastrointestinal Disease (MGID)					Completed 2019
Phase 1 Severe Allergic Conjunctivitis (SAC)					Completed 2019
Phase 1 Indolent Systemic Mastocytosis (ISM)					Completed 2019



### **Mast Cells and Eosinophils**

#### Effector Cells Central to Initiating and Maintaining Inflammatory Responses



### Lirentelimab Targets Siglec-8 on Mast Cells and Eosinophils

Siglec-8 is an inhibitory receptor selectively expressed on mast cells and eosinophils





### Mast Cells and Eosinophils Are Key Drivers of Inflammatory Disease



### Eosinophils and Mast Cells Play a Significant Role in Many Diseases



Indolent Systemic Mastocytosis



## EGID Commercial Opportunity



### **Eosinophilic Gastrointestinal Diseases (EGIDs)**

Evidence suggests that EGIDs may be significantly underdiagnosed or misdiagnosed as other GI diseases



#### EG, EoD, EC, and EoE

## Chronic Eosinophilic Inflammation of the Stomach, Duodenum, Colon, or Esophagus

- Eosinophils and mast cells are important drivers of disease
- Symptoms may include abdominal pain, nausea, early satiety, loss of appetite, bloating, abdominal cramping, vomiting, diarrhea, and dysphagia
- Currently no FDA-approved treatment
- Current standard of care: diet and/or steroids
- Potential multi-billion dollar market opportunity

EGID Biopsies Have Elevated and Activated Eosinophils & Mast Cells

Eosinophils and mast cells both appear to play a pathogenic role in EGIDs

Lirentelimab is the only therapy that directly targets eosinophils and mast cells

akos



### **Strengths of Prevalence Study**





500+ patients screened and evaluated across 20 sites, with 400+ undergoing endoscopy PRO measured a broad constellation of symptoms and identified patients with moderate-to-severe symptoms Standardized endoscopy and biopsy protocol with predefined criteria for eosinophilia

- First large prospective study looking at prevalence of EG/EoD
- Consistent findings across U.S. geographical locations
- Study population highly representative of a typical community GI practice



# High Proportion of Chronic GI Patients Meet the Criteria for EG/EoD



#### 33% (181/556) of patients with chronic functional GI symptoms met histologic criteria for EG/EoD



Patients who met symptom criteria and  $\geq$ 30 eos/hpf in 5 gastric hpfs and/or  $\geq$ 30 eos/hpf in 3 duodenal hpfs; 7 patients did not meet MGID histologic criteria Patients who met symptom criteria and  $\geq$ 30 mast cells/hpf in 5 gastric hpfs and/or  $\geq$ 30 mast cells/hpf in 3 duodenal hpfs and <30 eos/hpf

### Prevalence Study Suggests Significant Undiagnosed EG/EoD Population

Large potential patient population for lirentelimab





SOURCE: 1. AAMC.org; 2. InCrowd market research survey of 150 adult gastroenterologists, fielded Aug 2020. 3. EI-Serag, Becher A, and Jones J. AP&T. 2010.; 4. Pimentel M. Am J Manag Care. 2018.; 5. Buono JL, et al. J Med Econ. 2017; 6. Mönkemüller K, Malfertheiner P. World J Gastroenterol. 2006.

### Prevalence Study Should Lead to a Change in Clinical Practice and Improved Detection of EG/EoD



## Phase 2 ENIGMA Study Results in EG and/or EoD

Published in the New England Journal of Medicine Oct 2020



### **ENIGMA Phase 2 Study**

#### **Study Design**

- Multi-center, randomized, double-blind, placebo-controlled study in EG and/or EoD
- Active moderate to severe symptoms
- Biopsy confirmed EG and/or EoD
  - Stomach: ≥30 eos/high powered field (hpf) in 5 hpfs
  - Duodenum: ≥30 eos/hpf in 3 hpfs
- 65 patients 3 arms
  - 0.3, 1.0, 3.0, 3.0 mg/kg lirentelimab (N = 21)
  - 0.3, 1.0, 1.0, 1.0 mg/kg lirentelimab (N = 22)
  - Placebo (N = 22)
- 4 monthly doses

#### **Endpoints**

#### Histologic Primary Endpoint

 Mean percent change in gastrointestinal eosinophil counts from baseline

#### Responder Secondary Endpoint

- Proportion of patients who have:
  - >70% decrease in tissue eosinophils AND >30% benefit in Total Symptom Score (TSS)

#### • Symptom Secondary Endpoint

Mean percent change in TSS from baseline

### Symptoms Assessed Using a Disease-Specific PRO

- Developed in accordance with FDA guidance on PRO development
- Captures the symptoms of EG/EoD patients on a daily basis
- Measures 8 symptoms each on a scale of 0-10; Total Symptom Score (TSS) 80 points:





### **Primary Endpoint Met for All Lirentelimab Groups**

Significant reductions in tissue eosinophil counts vs. placebo

Treatment Arm	Baseline Eosinophil Counts / hpf	Mean % $\Delta$ in Eosinophil Counts	p - value
High Dose <sup>*</sup> Lirentelimab (n=20)	76	-97%	<0.0001
Low Dose <sup>*</sup> Lirentelimab (n=19)	80	-92%	<0.0001
Combined Lirentelimab (n=39)	78	-95%	<0.0001
Placebo (n=20)	75	+10%	-



### Lirentelimab Met Patient Reported Symptoms Secondary Endpoint

Statistically significant improvements in symptoms observed 1 day after first infusion and maintained throughout the study

Treatment Arm	Baseline TSS*	Mean % Change in TSS*	p - value
High Dose <sup>*</sup> Lirentelimab (n=20)	34	-58%	0.0012
Low Dose <sup>*</sup> Lirentelimab (n=19)	35	-49%	0.0150
Combined Lirentelimab (n=39)	34	-53%	0.0012
Placebo (n=20)	30	-24%	-



### Lirentelimab Met Treatment Responder Secondary Endpoint

Treatment responder defined as: >75% reduction in tissue eosinophil counts AND >30% reduction in symptoms (TSS)

Treatment Arm	Treatment Responders	p - value
High Dose <sup>*</sup> Lirentelimab (n=20)	70%	0.0009
Low Dose <sup>*</sup> Lirentelimab (n=19)	68%	0.0019
Combined Lirentelimab (n=39)	69%	0.0008
Placebo (n=20)	5%	-



### **ENIGMA Phase 2 Safety Summary**

- Generally, well tolerated
- Most common adverse event (AE) was infusion-related reaction (IRR)
  - 60% of lirentelimab patients vs 23% placebo
  - 93% mild to moderate (flushing, feeling of warmth, headache, nausea, dizziness)
  - Mostly on first infusion, greatly reduced or did not occur on subsequent infusions
  - 1 drug-related serious adverse event, an IRR which recovered within 24 hours with no further sequelae
- Treatment-emergent SAEs: 9% on lirentelimab, 14% on Placebo
- No other significant AEs



### **Continued Benefit Observed in Long Term Extension**



TSS % Change in Patients with ≥94 Weeks of Treatment (N=25)



### **Improvement Observed Across All Symptoms**





## End of Phase 2 - ENIGMA FDA Meeting Outcomes



### **End of Phase 2 Meeting Outcomes**

#### Histologic Co-Primary Endpoint

- Consistent with EoE guidance, FDA recommended using a responder analysis
- Histologic response thresholds set at  $\leq$  4 eos/hpf in the stomach and/or  $\leq$  15 eos/hpf in the duodenum

#### Symptom Co-Primary Endpoint

- The same PRO questionnaire will be used in Phase 3 as was used in ENIGMA
- FDA recommended using a Total Symptom Score consisting of the 6 most frequent and severe symptoms (TSS-6): abdominal pain, nausea, bloating, early satiety, abdominal cramping, loss of appetite; vomiting and diarrhea are measured but excluded from the co-primary endpoint

#### Duration of study

- Consistent with EoE guidance, FDA recommended a 6-month study

#### Change in nomenclature

Eosinophilic Gastroenteritis is now referred to as Eosinophilic Duodenitis



## Phase 3 ENIGMA 2 Eosinophilic Gastritis (EG) and/or Duodenitis (EoD) Study



### Phase 3 ENIGMA 2 Study

#### **Study Design**

- Multi-center, randomized, double-blind, placebo-controlled study in EG and/or EoD
- Active moderate to severe symptoms
- Biopsy confirmed EG and/or EoD
  - Stomach: ≥30 eos/high powered field (hpf) in 5 hpfs
  - Duodenum: ≥30 eos/hpf in 3 hpfs
- 160 adult patients 2 arms
  - 1.0, 3.0, 3.0, 3.0, 3.0, 3.0 mg/kg
    lirentelimab (N = 80)
  - Placebo (N = 80)
- 6 monthly doses

#### **Endpoints**

- Histologic Co-Primary Endpoint
  - Proportion of responders:
    - Stomach: ≤4 eos/hpf in 5 hpfs, and/or
    - Duodenum: ≤15 eos/hpf in 3 hpfs

#### • Symptom Co-Primary Endpoint

Absolute change in patient reported TSS-6

#### Key Secondary Endpoints

- Percent change in tissue eosinophils
- Treatment responders: patients who achieve tissue eosinophil thresholds AND >30% improvement in TSS-6



# Symptoms Assessed With the Same PRO Questionnaire Used in Phase 2 ENIGMA

- Developed in accordance with FDA guidance on PRO development
- Captures the symptoms of EG/EoD patients on a daily basis
- Measures symptoms each on a scale of 0-10
- Co-primary symptomatic endpoint will consist of the TSS-6 (in blue):



### Phase 2 ENIGMA Results Analyzed Against Phase 3 Endpoints (ITT)

Co-Primary Endpoints		Lirentelimab 3.0 mg/kg	Placebo	p - value
Histologic Endpoint <sup>1</sup>	Proportion of Responders	95%	0%	<0.0001
Symptom Endpoint <sup>2</sup>	Mean Absolute Change in TSS-6	-16.6	-8.1	0.0162
	Mean Percent Change in TSS-6	-59%	-27%	0.0033



## Phase 2/3 KRYPTOS Eosinophilic Esophagitis (EoE) Study



### Strong Proof of Concept from ENIGMA Study — Eosinophil Reductions and Symptom Improvement in Patients With EoE





### Phase 2/3 KRYPTOS Study

#### Follows 2019 FDA EoE Guidance

#### **Study Design**

- Multi-center, randomized, double-blind, placebo-controlled study in EoE
- Active moderate to severe symptoms
- Biopsy confirmed EoE
  - Esophagus: ≥15 eos in 1 hpf
- 300 patients 3 arms
  - 1.0, 3.0, 3.0, 3.0, 3.0, 3.0 mg/kg
    lirentelimab (N = 100)
  - 1.0, 1.0, 1.0, 1.0, 1.0, 1.0 mg/kg
    lirentelimab (N = 100)
  - Placebo (N = 100)
- 6 monthly doses

#### Endpoints

- Histologic Co-Primary Endpoint
  - Proportion of responders:
    - Esophagus: ≤ 6 eos/hpf in 1 hpf

#### Symptom Co-Primary Endpoint

Absolute change in patient reported Dysphagia
 Symptom Questionnaire (DSQ)

#### • Key Secondary Endpoints

- Percent change in esophageal tissue eosinophil count
- Percent change in DSQ score

![](_page_33_Picture_21.jpeg)

## Phase 3 EODYSSEY Eosinophilic Duodenitis (EoD) Study

![](_page_34_Picture_1.jpeg)

### Phase 3 Eosinophilic Duodenitis (EoD) Study

#### **Study Design**

- Multi-center, randomized, double-blind, placebo-controlled study in EoD
- Active moderate to severe symptoms
- Biopsy confirmed EoD ± colonic involvement
  - Duodenum: ≥30 eos/hpf in 3 hpfs
  - Stomach: <30 eos/high powered field (hpf) in 5 hpfs (Do NOT have EG)
  - Colonic involvement assessed by colonoscopy: biopsies collected from terminal ileum, colon (ascending, transverse, descending, sigmoid) and rectum
- 80 adult patients 2 arms
  - 3.0, 3.0, 3.0, 3.0, 3.0, 3.0 mg/kg lirentelimab (N = 40)
  - Placebo (N = 40)
- 6 monthly doses

#### **Endpoints**

- Histologic Co-Primary Endpoint
  - Proportion of responders:
    - Duodenum:  $\leq$  15 eos/hpf in 3 hpfs

#### • Symptom Co-Primary Endpoint

Absolute change in patient reported TSS-6

#### Key Secondary Endpoints

- Percent change in tissue eosinophil counts
- Treatment responders: patients who achieve tissue eosinophil thresholds AND >30% improvement in TSS
- Exploratory: change in colonic eosinophil counts

![](_page_35_Picture_22.jpeg)

## Phase 1 Subcutaneous Healthy Volunteer Study

![](_page_36_Picture_1.jpeg)

### **Phase 1 Subcutaneous Healthy Volunteer Study**

Lirentelimab appears suitable for once monthly dosing

#### Study Design

- Phase 1 single-dose, placebo-controlled study
- 50 healthy volunteers
- Doses assessed:
  - SC: Lirentelimab 0.3, 1.0, 3.0, 5.0 mg/kg,300 mg fixed and placebo
  - IV: Lirentelimab 1.0, 3.0 mg/kg

#### Results

- Prolonged peripheral blood eosinophil suppression
- Lirentelimab was well tolerated
  - No injection site reactions or injection reactions
  - No treatment related adverse events
  - No serious adverse events

![](_page_37_Picture_14.jpeg)

## Clinical Proof of Concept in Additional Indications

![](_page_38_Picture_1.jpeg)

### **Proof of Concept Studies in Other Eosinophil and Mast Cell Diseases**

#### Chronic Urticaria<sup>1</sup>

- Xolair<sup>®</sup>-Naïve Chronic Spontaneous Urticaria (CSU)
- Xolair<sup>®</sup>-Refractory Chronic Spontaneous Urticaria (CSU)
- Cholinergic Urticaria
- Symptomatic Dermographism

#### • Severe Allergic Conjunctivitis<sup>2</sup>

- Atopic keratoconjunctivitis
- Vernal keratoconjunctivitis
- Perennial allergic conjunctivitis
- Showed improvements in concomitant asthma, rhinitis, and atopic dermatitis
- Indolent Systematic Mastocytosis<sup>3</sup>
- Mast Cell GI Disease<sup>4</sup>

![](_page_39_Picture_13.jpeg)

Altrichter S, et al. ACAAI 2019. Annals of Allergy, Asthma & Immunology. 2019 November; 123(5) Supplement:S27-S28.; Altrichter S, et al. EAACI 2019. Allergy. 2019 Aug 08;74(S106): 1-965.
 Leonardi A, et al. EAACI. 2020. Allergy. 2020 Sep 07;75(S109): 5-99.
 Siebenhaar F, et al. EAACI 2019. Allergy. 2019 Aug 08;74(S106): 1-965; Siebenhaar F, et al. DAK 2019. Allergy Journal. 2019 Sep 10;28(6), 67–113.;

edsoe AC, et al. DDW 2020. Gastroenterology. 2020 May 01;158(6) Supplement 1: S52-S53.

### **Strong Balance Sheet and Significant IP Protection**

Cash, Cash Equivalents and Investments in Marketable Securities as of Sept 30, 2021

\$505.6M

#### **Q3 2021 Operating Expenses**

\$62.6M

![](_page_40_Picture_5.jpeg)

Lirentelimab US patents first to expire 2035

![](_page_40_Picture_7.jpeg)

Lonza currently manufactures lirentelimab

![](_page_40_Picture_9.jpeg)

### **Completed and Near-term Milestones**

![](_page_41_Figure_1.jpeg)

### Summary

- Late-stage clinical biotech developing lirentelimab (AK002), a wholly owned mAb that selectively targets Siglec-8 expressed on eosinophils and mast cells
- Initial focus on EG and/or EoD, prevalence study suggests ~2.5M EG and/or EoD patients in the US
- Positive phase 2 clinical data and near-term phase 3 data readouts in Q4'21 / Early Q1'22
  - Phase 2 results with lirentelimab in EG and/or EoD showed a statistically significant improvement in tissue eosinophil reduction (-95% vs. +10%) and symptom reduction (-53% vs. -24%)
  - Strong proof of concept in EoE:
    - 13/14 (93%) of patients had esophageal eosinophils  $\leq$  6 /hpf
    - 53% decrease in dysphagia vs. placebo 17%
- Multiple opportunities including atopic dermatitis, chronic spontaneous urticaria, asthma and other mast cell and eosinophil-driven diseases