Olezarsen: A Potential New Medicine for Patients with FCS

September 26, 2023

Nasdaq: IONS

Forward-Looking Statements

This presentation includes forward-looking statements regarding the therapeutic and commercial potential of olezarsen, Ionis' technologies, and Ionis' other products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on our Form 10-K for the year ended December 31, 2022, and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available at www.ionispharma.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

Agenda

Topic	Speaker
Welcome	Wade Walke, Ph.D.
Introduction	Brett Monia, Ph.D.
FCS: Biology and Significant Unmet Need	Sam Tsimikas, M.D.
Phase 3 Balance Study: Topline Results	Sam Tsimikas, M.D.
FCS Go-to-Market Plan	Onaiza Cadoret
Concluding Remarks	Brett Monia, Ph.D.
Q&A	

Introduction

Brett Monia, Ph.D.

Chief Executive Officer

Positive Results from Olezarsen Balance Study Further Advances Two of Our Key Priorities

Establish an integrated commercial organization

Deliver a steady cadence of new medicines to the market

Expand and **diversify** our technology platform

Strengthen our financial foundation to support our strategic priorities

Positive Results from Olezarsen Balance Study Further Advances Two of Our Key Priorities

- **Establish** an integrated commercial organization
- **Deliver** a steady cadence of new medicines to the market
- **Expand** and **diversify** our technology platform
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Olezarsen: Positioned to Address Underserved Patients with FCS[1,2]

Urgent Medical Need

- Severe, genetically driven disease
- Patients at extreme risk for acute, potentially fatal pancreatitis
- Olezarsen has the potential to be the first drug approved for FCS in the US

Positive Balance FCS data

- Robust, dose-dependent reductions in APOCIII
- Statistically significant reductions in triglycerides at 80 mg dose
- 100% reduction in acute pancreatitis attacks in 80 mg dose group
- Favorable safety and tolerability

Next steps: regulatory & commercial

- Preparing for first U.S. launch in FCS
- NDA submission planned in early 2024
- Positioned to be Ionis' first wholly owned commercial medicine
- Phase 3 studies supporting SHTG indication ongoing

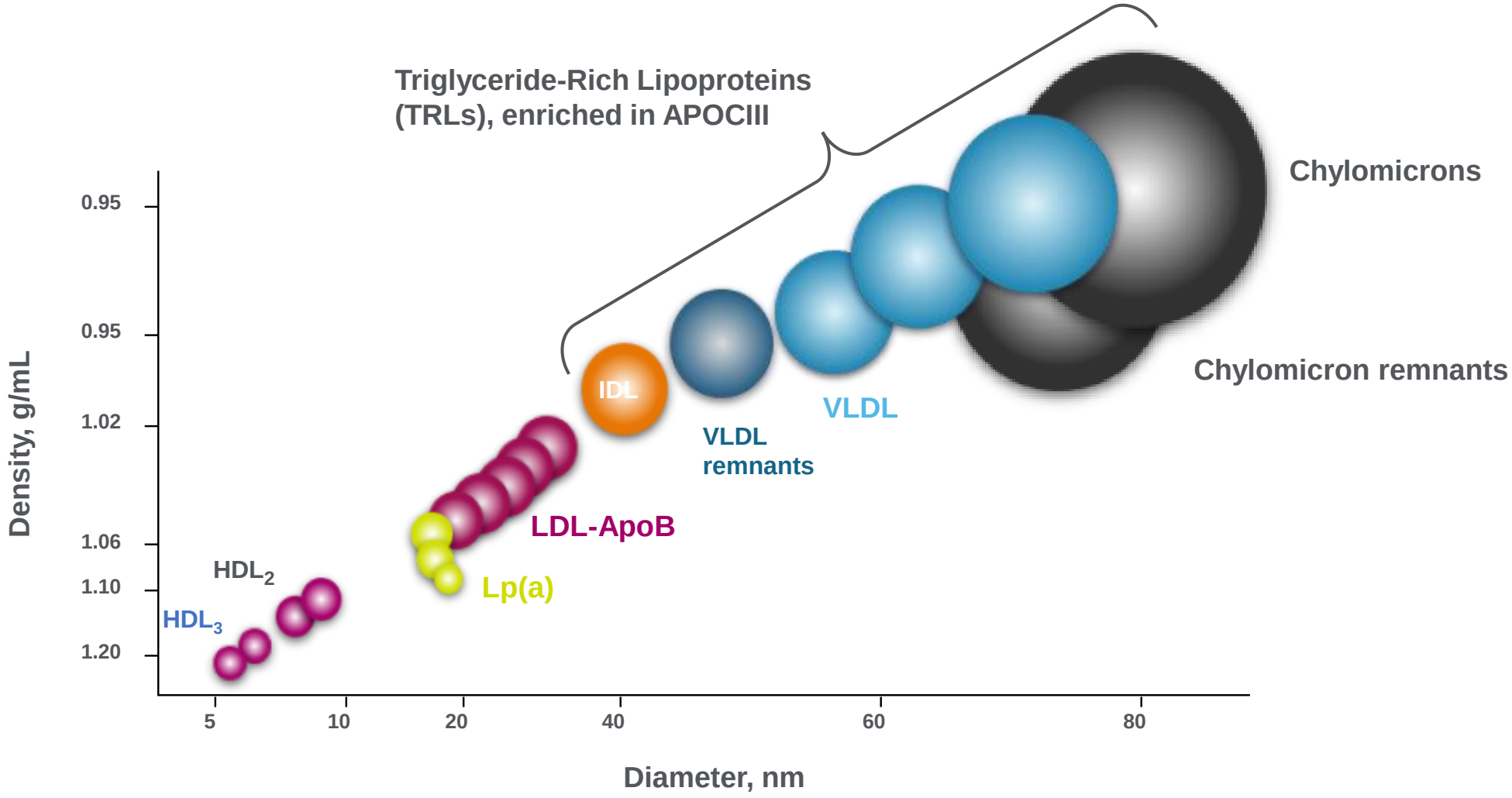
1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval.

FCS: Biology and Significant Unmet Need

Sam Tsimikas, M.D.

Senior Vice President, Global Cardiovascular Development

Triglyceride Rich Lipoproteins & Elevations in Plasma Triglycerides



apoB, apolipoprotein B-III; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); VLDL, very low-density lipoprotein.
Figure modified Feingold KR et al, endocrinologist. Mdtext.com, Inc 2000. Classes of Lipoproteins. Accessed May 9, 2023. http://www.ncbi.nlm.nih.gov/books/NBK305896/

FCS: A Severe, Rare, Genetically Driven Disease

FCS Overview[1,2]

- 1 – 2 per million patients worldwide[3]
- Monogenic, associated with deficient LPL activity caused by mutations in *APOA5, APOC2, GPD1, GPIHBP1, LMF1* or *LPL*
- TG levels often 10-100 times higher than normal levels

Associated with Multiple Debilitating Symptoms and Reduced QoL[2]

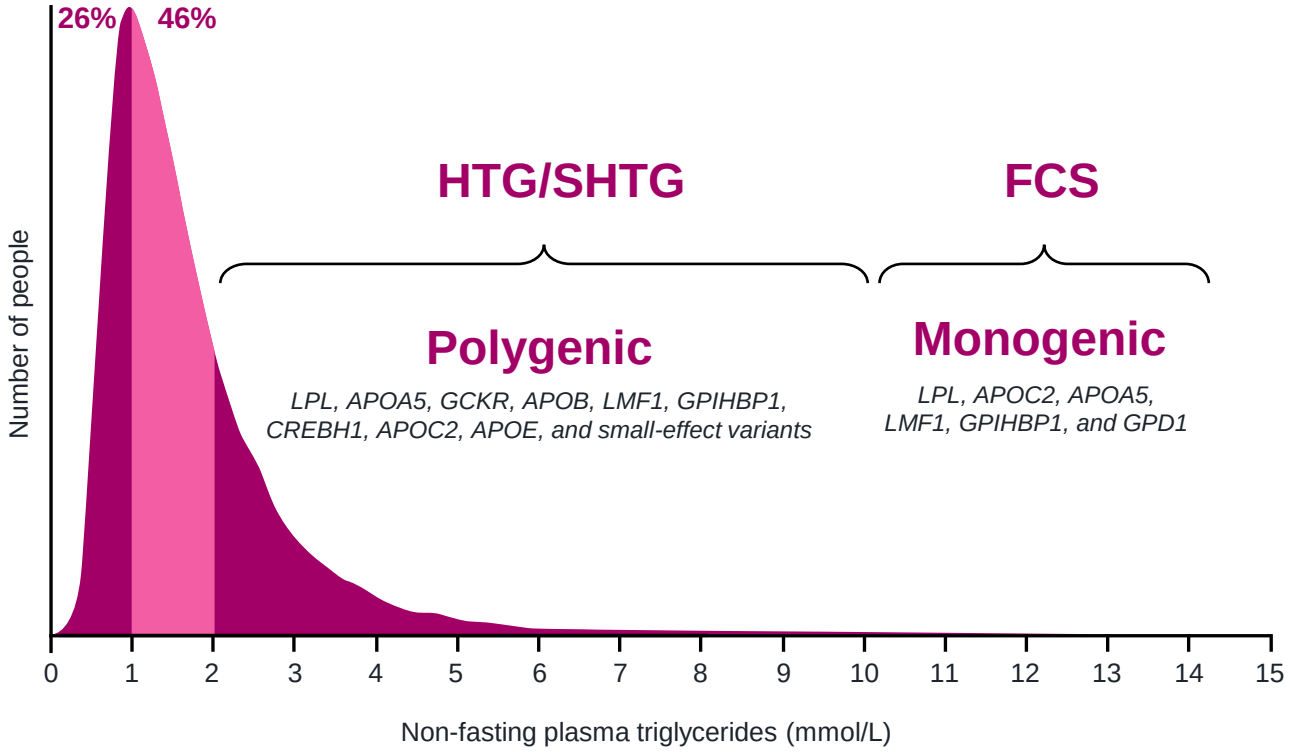
- Extreme risk for acute, potentially fatal, pancreatitis
- Causes daily, debilitating abdominal pain, neurocognitive impairment, eruptive xanthomas and poor QoL

FCS Represents Clear Unmet Medical Need[1,3]

- No approved treatments in the US
- FCS patients are refractory to triglyceride-lowering therapies
- Standard of care is limited to restrictive, extremely low-fat diet
  - 15 – 20g of dietary fat per day – equivalent to ~2 Tbsp olive oil; no alcohol

1. Pallazola et al. Eur J Preventive Cardiol 2020 27:2276-2278. 2. Gaudet D, et al. N Engl J Med. 2014;371:2200-2206. 3. endocrine.org (accessed 9/24/23).
4. Williams L, et al. J Clin Lipidol. 2018;12:908-919.

FCS Patients Have a Distinct Genetic Profile Compared to Other Patients with Elevated Triglycerides



1 mmol/L = ~89 mg/dL
1.6 mmol/L = ~150 mg/dL
5.6 mmol/L = 500 mg/dL

FCS (monogenic)

- **Deficient TG Metabolism (i.e., LPL activity)**
- **Functional TRL clearance**

HTG/SHTG (polygenic)

- **Functional but reduced TG metabolism**

and/or

- **Functional but reduced TRL clearance**

Hegele, et al, Lancet Diabetes Endocrinology, 2014; HTG: hypertriglyceridemia; SHTG: severe hypertriglyceridemia

Olezarsen Targets APOCIII, a Key Regulator of Triglyceride Clearance and Metabolism[1,2]

APOCIII inhibits triglyceride metabolism and clearance via two mechanisms:

- **APOCIII inhibits LPL activity** (metabolism)
- **APOCIII inhibits TRL clearance**

By reducing APOCIII production, olezarsen increases both triglyceride metabolism and TRL clearance

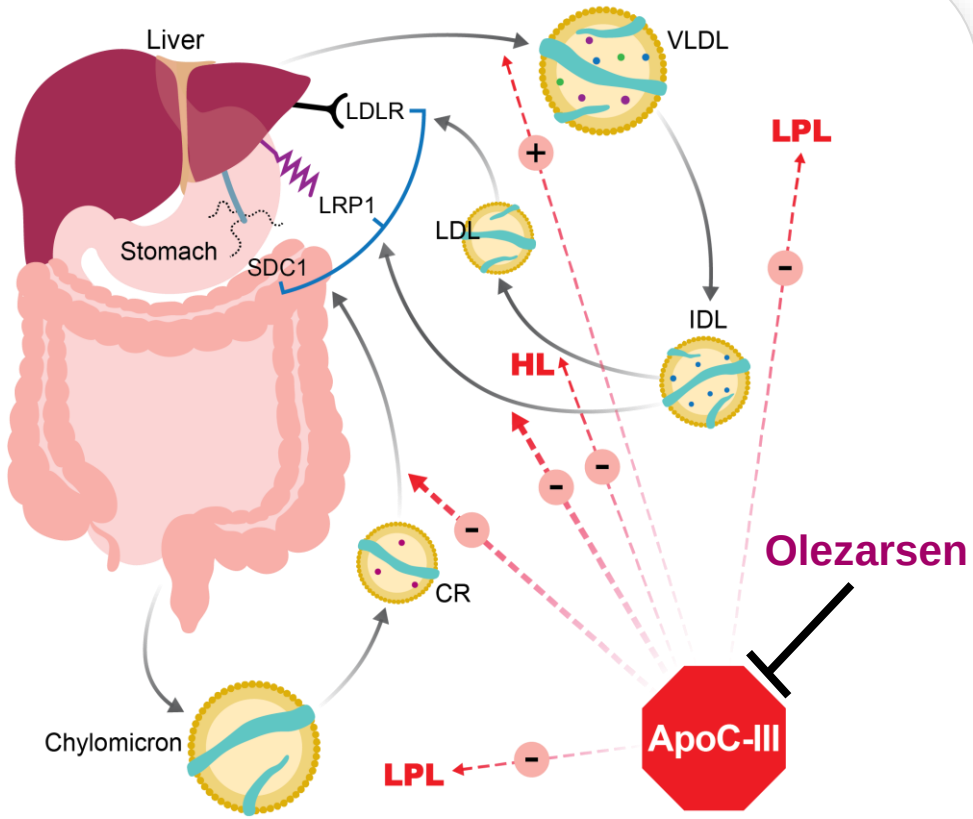


Image adapted from: Gordts PL, et al J Clin Invest. 2016;126:2855

1. Gordts PL et al. J Clin Invest 2016;126:2855–66. 2. Kohan AB. Curr Opin endocrinologistcrinol Diabetes Obes. 2015;22:119-125.

APOCIII Loss of Function Reduces Post-Prandial Triglycerides

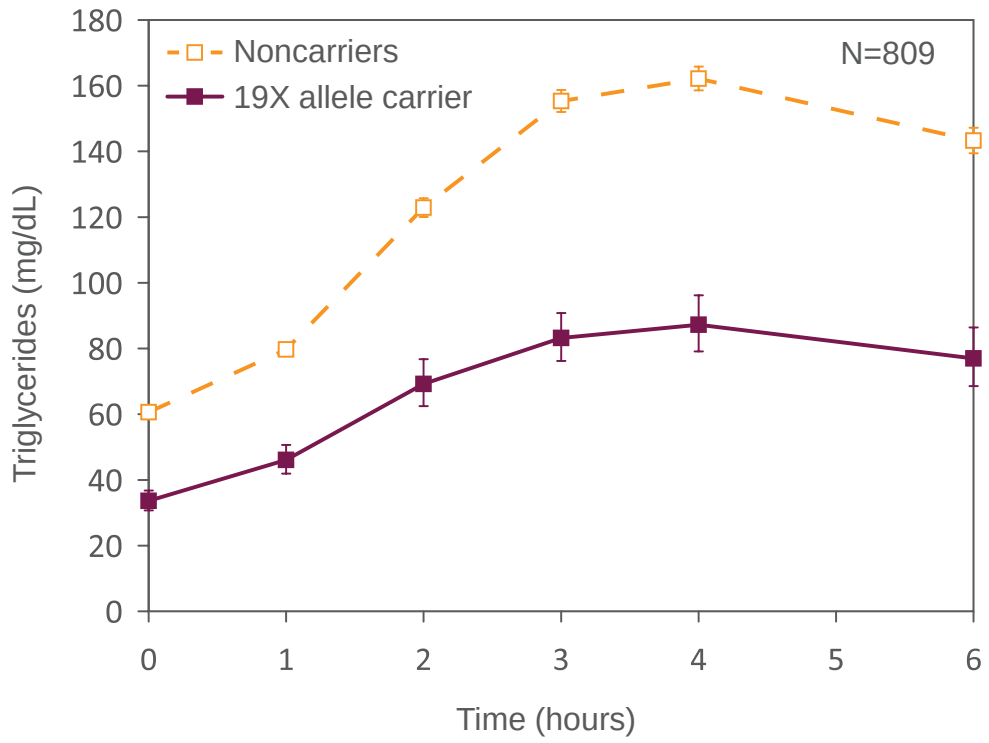
A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Toni I. Pollin,[1] Coleen M. Damcott,[1] Haiqing Shen,[1] Sandra H. Ott,[1] John Shelton,[1] Richard B. Horenstein,[1] Wendy Post,[2] John C. McLenithan,[1,3] Lawrence F. Bielak,[4] Patricia A. Peyser,[4] Braxton D. Mitchell,[1] Michael Miller,[1] Jeffrey R. O'Connell,[1] Alan R. Shuldiner[1,3]

Key Results:

- Reduced APOCIII levels in heterozygotes by 50%
- Decreased fasting and postprandial TGs
- Decreased non-HDL-C, LDL-C, VLDL-C, IDL-C

TG Levels Before and During High-fat Challenge by R19X *APOCIII* Genotype



Pollin TI, et al. Science. 2008;322:1702-1705.

Olezarsen Development Program Designed to Generate Robust Data in Patients with FCS and SHTG[1]

FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS)

Balance
a familial chylomicronemia syndrome study

- Significant reductions in TGs, clinically meaningful reductions in AP and favorable safety and tolerability
- OLE progressing well
- Ph 2b study supporting FCS NDA exposure database, on track to complete 2H:2023
- On track for US and EU filings in 2024
- Launch preparations underway

SEVERE HYPERTRIGLYCERIDEMIA (SHTG)

CORE
a hypertriglyceridemia study

- First pivotal study in patients w/ TGs ≥500 mg/dL enrolling
- Pivotal registrational study
- ~540 patients

CORE2
a hypertriglyceridemia study

- Confirmatory study in patients w/ TGs ≥500 mg/dL enrolling
- Pivotal registrational study
- ~390 patients

Essence
TIMI-73b

- Supportive Ph3 study in patients w/ TGs ≥200 mg/dL
- Adds to patient exposure database
- ~1,300 patients

---------- *Data expected in late 2024/early 2025* ----------

1.Timing expectations are based on current assumptions and are subject to change. Phase 2b study in patients w/ TGs >150mg/dL for 1 year, supportive of olezarsen safety database, clinicaltrials.gov/NCT05355402. CORE study, clinicaltrials.gov/NCT05079919. CORE2 study, clinicaltrials.gov/NCT05552326. ESSENCE study, clinicaltrials.gov/NCT05610280.

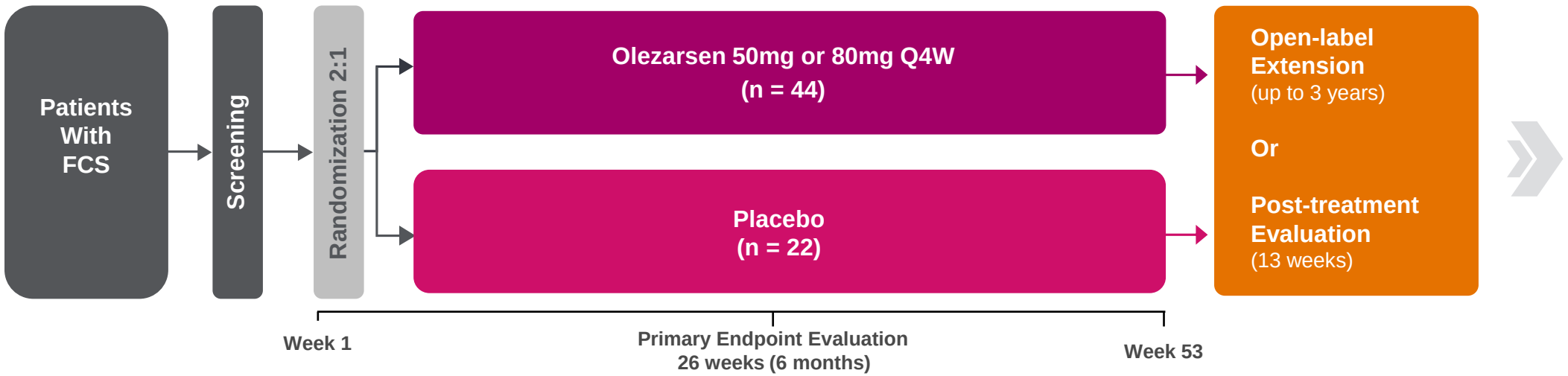
Phase 3 Balance Study: Topline Results

Sam Tsimikas, M.D.

Senior Vice President, Global Cardiovascular Development

Phase 3 Balance Study in Patients with FCS

Balance
a familial chylomicronemia syndrome study



- Randomized, double-blind, placebo-controlled study of monthly subcutaneous olezarsen in 66 patients with FCS, fasting TG ≥ 880 mg/dL (10 millimoles per liter (mmol/L) and a history of pancreatitis
  - Patients were expected to be on background lipid-lowering therapy
- Primary outcome measure: Percent change in fasting triglycerides (TG) from baseline to 6 months
- Key secondary endpoints:
  - Change from baseline: fasting TG (12 months)
  - Reduction in pancreatitis events

Patient Disposition: >90% of Patients Completed Study

	Placebo	Olezarsen 50 mg	Olezarsen 80 mg
N	23	21	22
Completed Treatment	22 (95.7%)	19 (90.5%)	19 (86.4%)
Discontinued Study Treatment	1 (4.3%)	2 (9.5%)	3 (13.6%)
Voluntary withdrawal	0	1 (4.8%)	1 (4.5%)

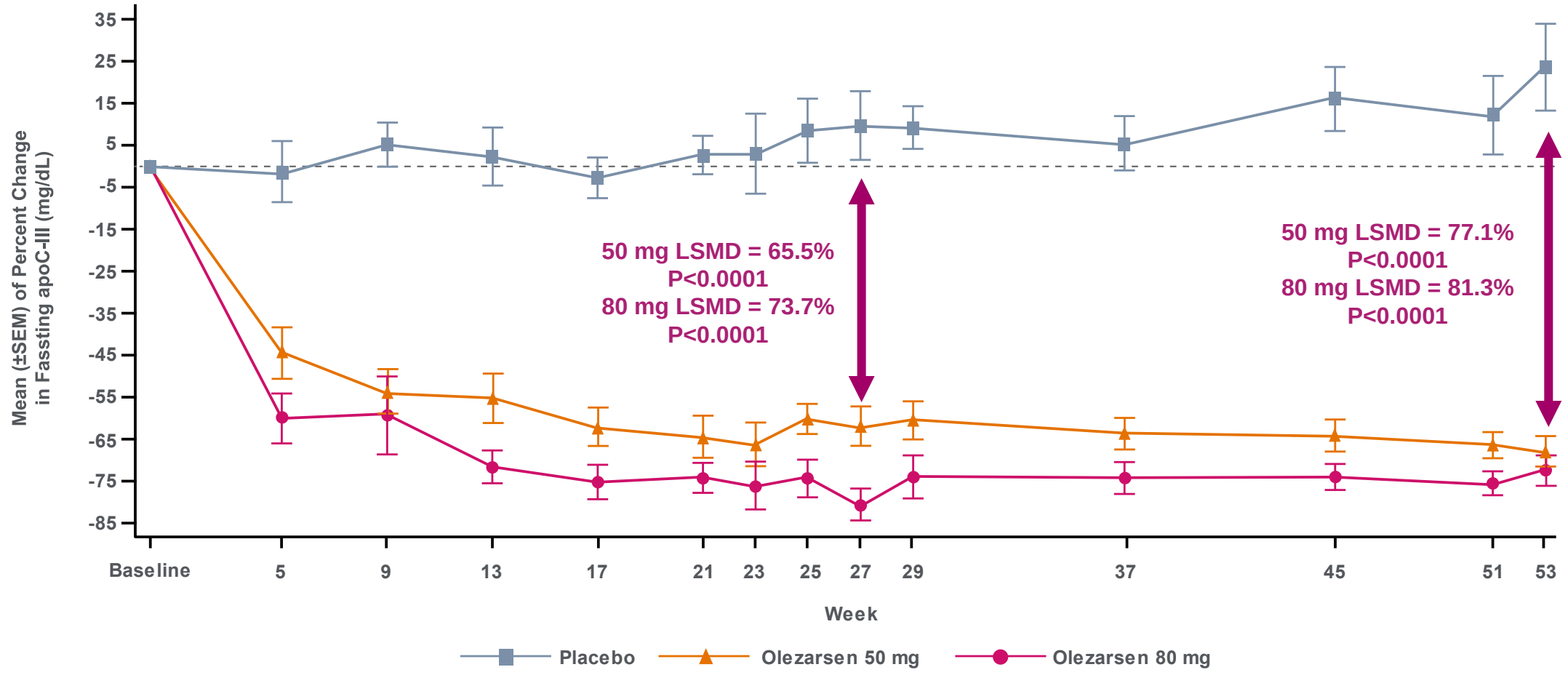
100% of patients who completed the study chose to go into the open label extension study

Baseline Characteristics

Baseline Characteristics	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
Age, Mean years (SD)	44.0 (14.67)	43.2 (12.11)	47.7 (13.30)
Age Category, n (%) • < 65 • ≥ 65	 20 (87.0%) 3 (13.0%)	 20 (95.2%) 1 (4.8%)	 20 (90.9%) 2 (9.1%)
Sex, n (%) • Female • Male	 12 (52.2%) 11 (47.8%)	 15 (71.4%) 6 (28.6%)	 11 (50.0%) 11 (50.0%)
Race, n (%) • White • Asian • Native Hawaiian/other Pac Islander • Other	 22 (95.7%) 0 0 1 (4.3%)	 17 (81.0%) 3 (14.3%) 1 (4.8%) 0	 17 (77.3%) 3 (13.6%) 0 2 (9.1%)
Body Weight (kg), Mean (SD)	67.8kg (16.1)	61.2 (11.6)	68.4 (16.7)
BMI (kg/m^2), Mean (SD)	24.2 (4.1)	22.4 (3.5)	25.1 (6.0)

Baseline Characteristics	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
History of AP, prior 10 years, n (%)	15 (65.2%)	15 (71.4%)	17 (77.3%)
≥2 documented AP events, prior 5 years, n	9	6	6
Fasting TG ≥ 880 mg/dL at Baseline, n (%)	21 (91.3%)	20 (95.2%)	21 (95.5%)
Previous treatment with volanesorsen	10 (43.5%)	8 (38.1%)	8 (36.4%)

Olezarsen Treatment Resulted in Robust and Significant Reduction in Serum APOCIII Levels at 6 and 12 Months



LSMD = Least squares mean difference

Positive Results For Primary and Key Secondary Endpoints

Measurement	Time
Triglyceride (TG):	**Month 6***
Percent change in fasting TG (80 mg)	**p=0.0009**
Percent change in fasting TG (50 mg)	p=0.0775
Pancreatitis:	**Weeks 1-53**
Reduction in pancreatitis events (80 mg)	**100%** (olezarsen: 0 events, placebo: 11 events**)
Reduction in pancreatitis events (50 mg)	**92%** (olezarsen: 1 event, placebo: 11 events**)

*Primary endpoint. P-values are based on differences in least-squares mean change from baseline
**There were a total of 8 patients in the study who had one or more pancreatitis events

Olezarsen Safety and Tolerability Profile

- More TEAEs were seen in the placebo group compared to the olezarsen groups, primarily due to a higher number of pancreatitis events in the placebo group
- No serious TEAEs related to study drug
- No clinically meaningful thrombocytopenia, renal or hepatic safety signals
- Low incidence of mild injection site reactions
- 1 non-drug related death in olezarsen treatment group

Incidence, n (%)	Placebo	Olezarsen 50 mg	Olezarsen 80 mg
N	23	21	22
Any TEAE[1]	22 (95.7)	18 (85.7)	19 (86.4)
Related to study drug	5 (21.7)	6 (28.6)	7 (31.8)
Leading to study drug discontinuation	0	1 (4.8)	2 (9.1)
Any Serious TEAE	9 (39.1)	4 (19.0)	3 (13.6)
Related to study drug	0	0	0
Fatal TEAE	0	1 (4.8)	0
Related to study drug	0	0	0

1. Treatment emergent adverse event (TEAE) is defined as an adverse event that first occurred or worsened after the first dose of investigational product;

Olezarsen: Positioned to Address Underserved Patients with FCS

- Robust, dose-dependent reductions in APOCIII
- Statistically significant reductions in triglycerides at 80 mg dose
- 100% reduction in acute pancreatitis attacks at 80 mg dose
- Favorable safety and tolerability observed in Balance study
- On track to submit regulatory fillings in US and EU in 2024
- Olezarsen is positioned to be Ionis' first wholly owned commercial medicine

FCS Go-to-Market Plan

Onaiza Cadoret

Executive Vice President, Chief Global Product Strategy and Operations Officer

FCS is a Severe, Rare Disease of Significant Unmet Need[1-3]

FCS:

It is Rare: Estimated 1-2 per million patients worldwide

It is Severe: Acute, potentially fatal pancreatitis is the most severe manifestation

It is Debilitating: Patients suffer chronic, debilitating physical, cognitive and emotional symptoms that impact relationships, employment and well-being

It Has No Effective Treatments: Patients in the US have no effective treatments approved

1. endocrine.org (accessed 9/24/23). 2. Gaudet D, et al. N Engl J Med. 2014;371:2200-2206. 3. Williams L, et al. J Clin Lipidol. 2018;12:908-919.

FCS Patients Feel Defined by their Disease[1,2]

FCS causes **physical, emotional, and cognitive symptoms**:

- Acute pancreatitis, abdominal pain, nausea, vomiting
- Fear, social isolation, frustration
- Brain fog, memory loss, and impaired judgement are all frequently reported symptoms of high TGs

> Patients are scared of having an acute pancreatitis event and are very motivated to take action" – *KOL Endocrinologist*

> I don't even have to have my TG levels checked. When I am in danger, my body tells me. And there's very little I can do about it." – *FCS patient*

> FCS patients are the most difficult to treat as their dietary fat allowance is extremely restricted; the equivalent to 5-6 almonds" – *Dietician*

1. Aquest FCS Research. 2. US Pricing Research

FCS Patients are at Increased Acute Pancreatitis Risk, Suffer Worse Outcomes Compared to Patients with Normal TGs[1]

Acute pancreatitis is a significant burden for patients with FCS

Higher AP Risk[2]

67% of FCS Patients

Have experienced an AP event in their lifetime

Higher Recurrence[3]

Up to 10-fold

Increased risk of recurrent attacks

More Deadly[1]

~2 times

More likely to result in death vs. other AP causes

1. Nawaz H, et al. *Am J Gastroenterol.* 2015;110:1497-1503. 2. Gaudet D, et al. N Engl J Med. 2014;371:2200-2206. 3. Toth PP, *et al*. *Atherosclerosis* 2014;237:790-797.

Positive Phase 3 Balance Study Results Support Broad Patient Access[1,2]

> There is no treatment for these individuals other than dietary restrictions which, from a QoL perspective, must be terrible. The drugs available don't lower TGs enough to reduce organ damage or pancreatitis."

> The clinical benefit of current standard of care is pretty minimal… Medications have little effect, and it is hard to follow those diets."

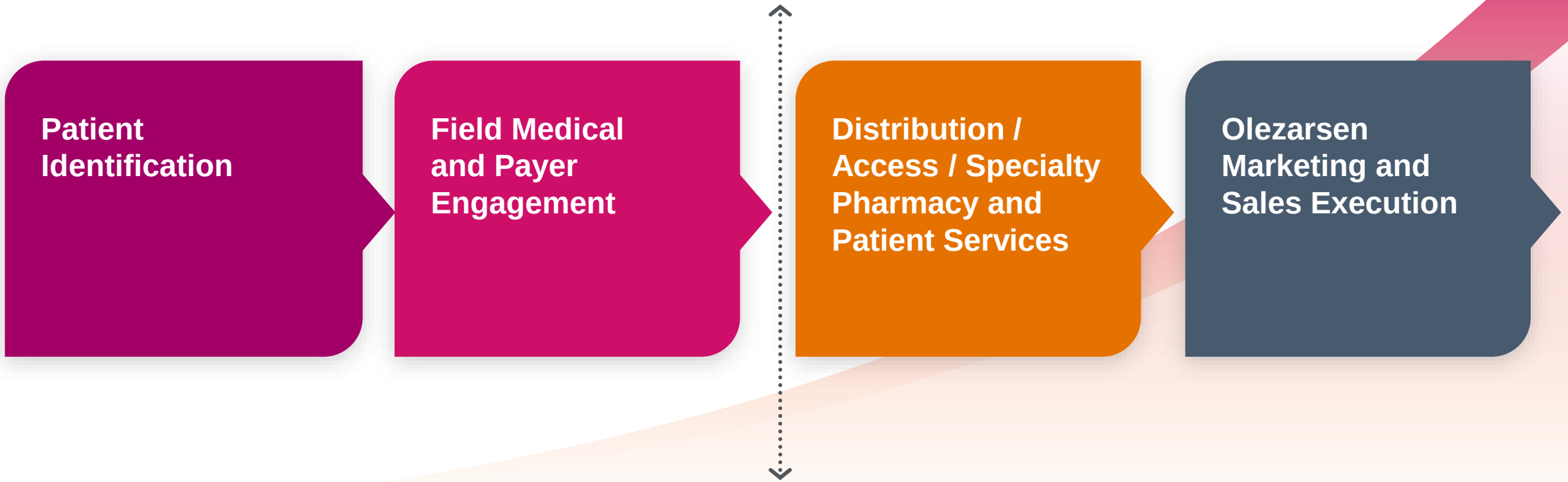
> A trend in improving acute pancreatitis would be great… outcomes data would be a homerun."

- Payers understand the need for an effective treatment to prevent acute pancreatitis in FCS patients
- Positive Phase 3 data demonstrating substantial reductions in outcomes on acute pancreatitis expected to be well received by the payer community

1. Aquest FCS Research. 2. US Pricing Research

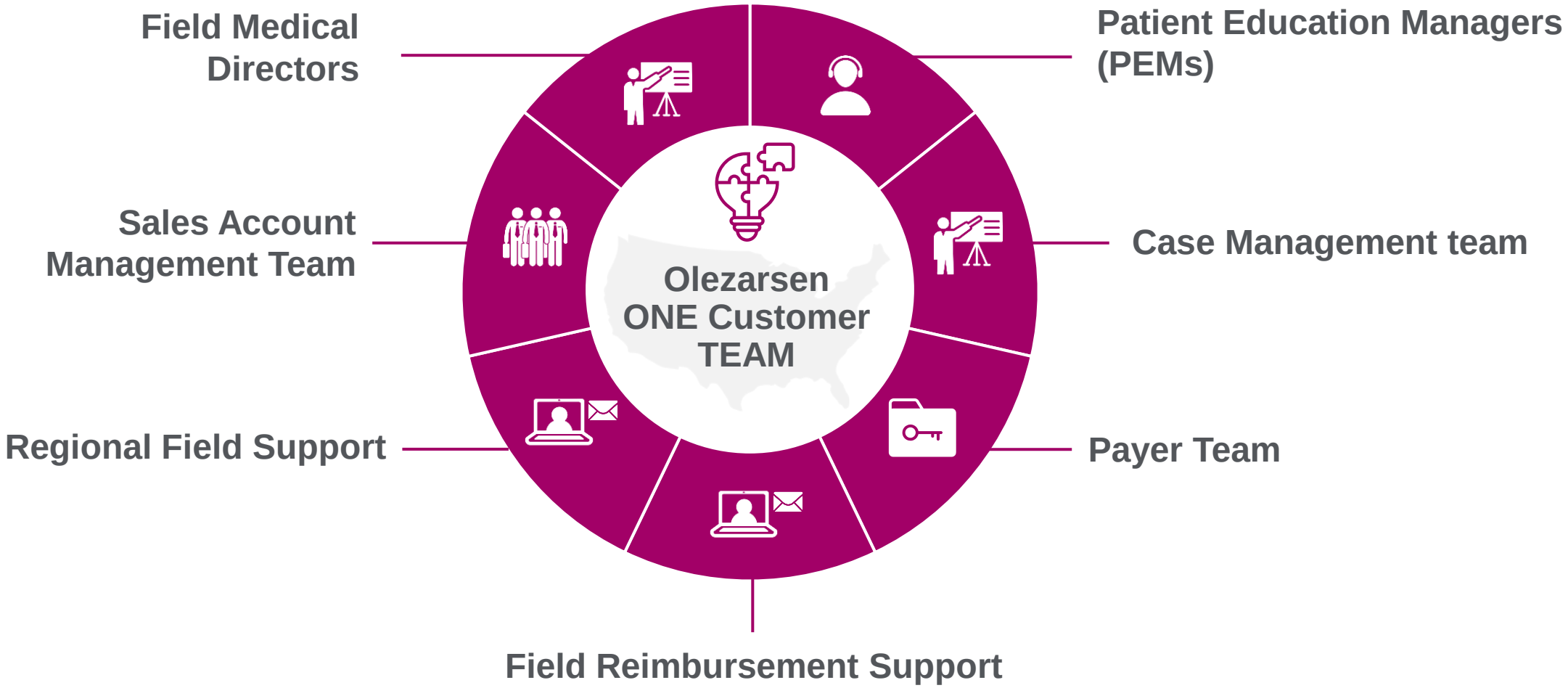
Prepared to Deliver Olezarsen to FCS Patients

Olezarsen Go-to-Market Approach



PDUFA

Commercial and Medical Affairs Operations Designed to Deliver Exceptional Customer Experience



Olezarsen: A Potential New Treatment for Patients with FCS[1,2]

01 FCS patients have a clear and urgent unmet medical need

02 Olezarsen demonstrated robust APOCIII reductions, significant TGs reductions and 100% reduction in acute pancreatitis in the 80 mg dose group

03 Olezarsen has the potential to be the first drug approved for FCS in the US

04 Ionis poised to launch the first of many medicines from our wholly owned pipeline to patients

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval.

Closing Remarks

Brett Monia, Ph.D.

Chief Executive Officer

Well Positioned to Deliver Value by Executing on our Strategic Priorities

- Established integrated commercial organization ready for first independent launch
- Eplontersen, olezarsen and donidalorsen nearing the market
- The pipeline is poised to deliver an abundance of new products to patients in the near- mid and longer-term
- Positioned to drive increasing value to all of Ionis' stakeholders

Q&A

Brett Monia, Ph.D.

Chief Executive Officer

Ionis Innovation Day

Westin New York Grand Central

Wednesday, October 4

8:00am – 3:00pm ET