



# Corporate Presentation

May 2023



*Enhancing the standard of care for retinal disorders by working to achieve the first FDA approval for bevacizumab in ophthalmology*

# Disclaimer

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# Leadership Team: Global Ophthalmic Development and Commercial Launch Excellence



**C. RUSSELL TRENARY III**

President, CEO and Director



**LAWRENCE KENYON**

Chief Financial Officer and Director



**JEFF EVANSON**

Chief Commercial Officer



**TERRY DAGNON**

Chief Operations Officer



**JOEL PRIEVE**

SVP, Commercial Operations



**ALICIA TOZIER**

SVP, Market Access and Marketing



**Surendra Sharma, MD**

SVP, Medical Affairs



**JENNIFER KISSNER**

SVP, Clinical Development



**CHRISTOPHER YONAN**

SVP, Technical Operations





# Investment Highlights

## FDA Market Approval of ONS-5010 (bevacizumab-vikg)<sup>1</sup>, an Investigational Therapy for the Treatment of Wet AMD, Targeted for August 29, 2023 PDUFA Date

### Targeting \$13.1 Billion Global Ophthalmic Anti-VEGF Market<sup>2</sup>

#### Differentiated Drug Product

- Designed to meet robust standards required for FDA ophthalmic approval
- Potential to eliminate risks associated with off-label repackaged bevacizumab, including potential impurities and particulates from compounders re-packaging processes
- Delivery ultimately expected through a convenient pre-filled syringe

#### Potential for 1<sup>st</sup> FDA Approved Ophthalmic Bevacizumab

- **U.S. FDA BLA accepted with target PDUFA action date of August 29, 2023**
- **Potential U.S. launch in Q4 2023**
- **Received validation of Marketing Authorization Application by European Medical Agency**
- Provides an economically elegant anti-VEGF solution for patients, payers and doctors

#### Attractive Market Opportunity

- **Strategic commercialization agreement with AmerisourceBergen**
- Over 50% of the U.S. market estimated to be available for conversion to ONS-5010, representing up to billions in potential yearly sales
- 12-years US regulatory exclusivity expected upon approval
- Label expansion opportunity into DME and BRVO

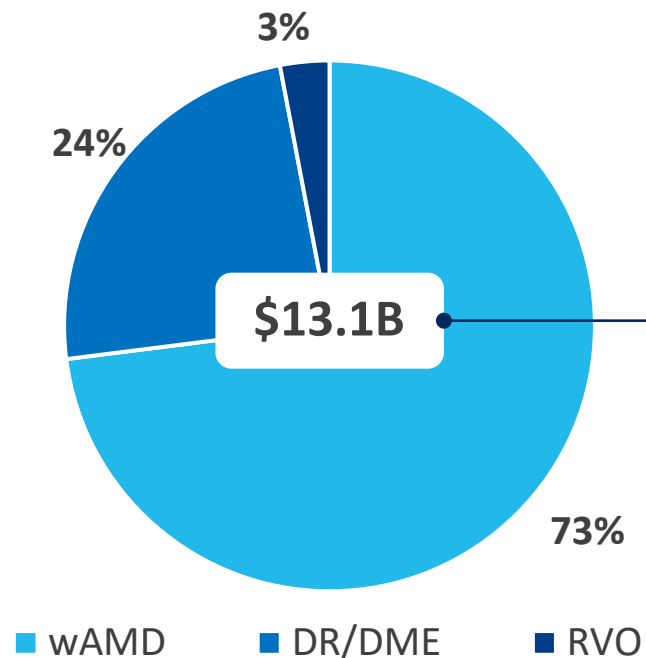
# Wet AMD Landscape

## *Current and Future*

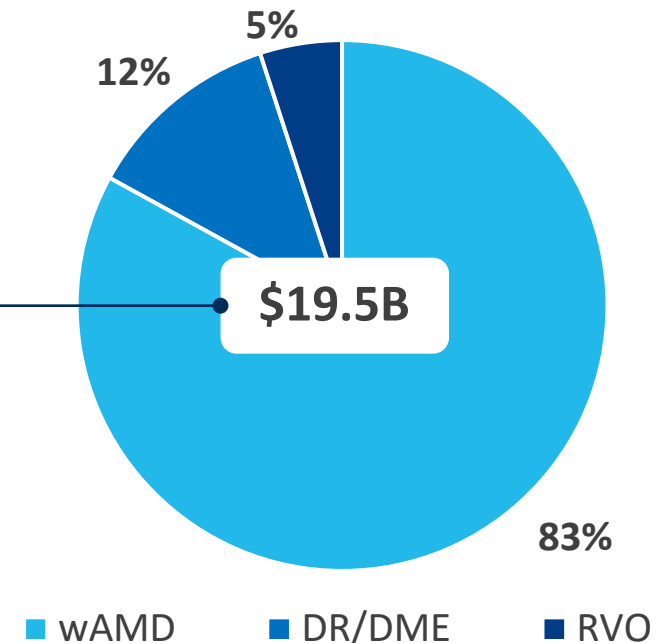
# Targeting Large and Growing Ophthalmic Markets

**ONS-5010, if Approved, will be a Significant Therapy in the Retinal Anti-VEGF Market, Currently Estimated to be in Excess of \$13.1 Billion Worldwide**

2020 9MM Anti-VEGF Revenue Share (USD)



2030 9MM Anti-VEGF Revenue Share (USD)



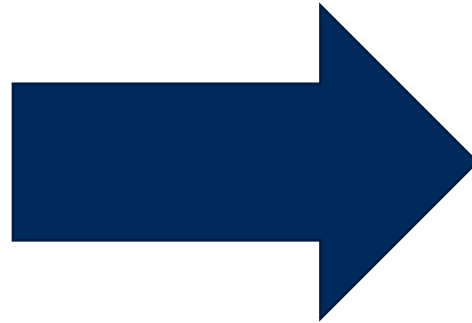
CAGR

4.1%

# The Majority of New Patient Starts are Off-Label Bevacizumab

## New Patient Starts

*66.3% of respondents (n=990) utilize off-label bevacizumab as a first-line agent<sup>1</sup>*



## Maintenance Therapy

*42.8-50.2% of overall injections continue therapy on off-label<sup>2,3</sup>*

- **Anti-VEGF is the standard-of-care** for the treatment of wAMD, DME and BRVO globally
- **~70% of Retinal Specialists in the US use off-label Avastin first-line for wAMD**
- Despite high usage, Retinal Specialists show **concern for the quality and supply of off-label Avastin**

Source: Navigant Quantitative Survey (n=152), 2019



# Public Health Concern Due to Repackaged and Off-Label Use of Bevacizumab Designed for Other Specialties and Delivery Systems

## Variability in Potency<sup>1</sup>

JAMA Ophthalmology

- 81% of samples had lower protein concentrations than required
- Samples had statistically significant variations in protein concentration among samples

## Safety and Sterility Adverse Events<sup>2</sup>

Warning Letter 

- Unvalidated hold times in syringes
- Patients have lost eyesight due to infections
- Multiple unapproved repackaged IV bevacizumab recalls due to unsterile compounding practices

## Syringe Adverse Events<sup>3</sup>

 **ASRS** American Society of Retina Specialists

- Variability in repackaging can lower quality of syringe products, resulting in adverse events
- Silicone oil droplets may be released from the syringe into the eye

## Not Held to FDA Ophthalmic Quality Standards When Repackaged



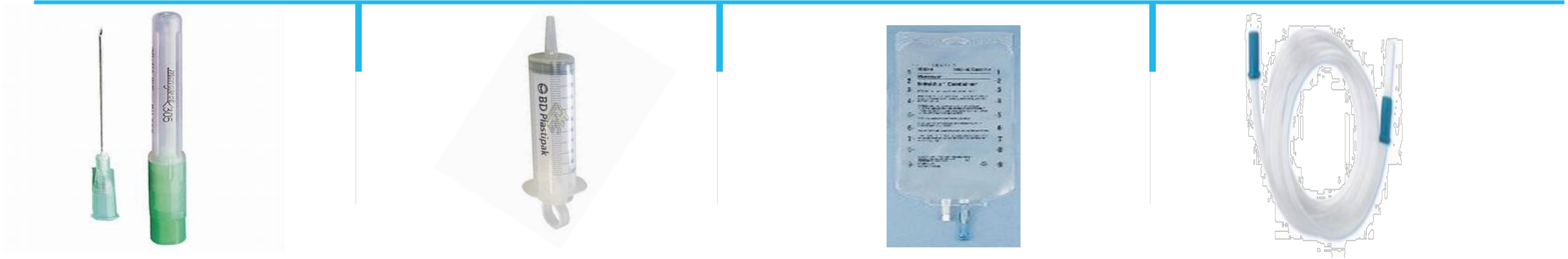
400 mg/16 mL, single-use vial;  
100 mg/4 mL, single-use vial



# Higher Particulates Allowed in Parenteral Injection Avastin® Compared to Ophthalmic Standards - Compounded by Particulates Leaching from Manufacturing Commodities and Syringes

There are significant differences in IgG [protein] concentration measured from repackaged bevacizumab syringes. A trend exists for an increase in micron-sized protein aggregates with the decrease in IgG concentration.<sup>1</sup>

## Non- Ophthalmic Standard Manufacturing Commodities



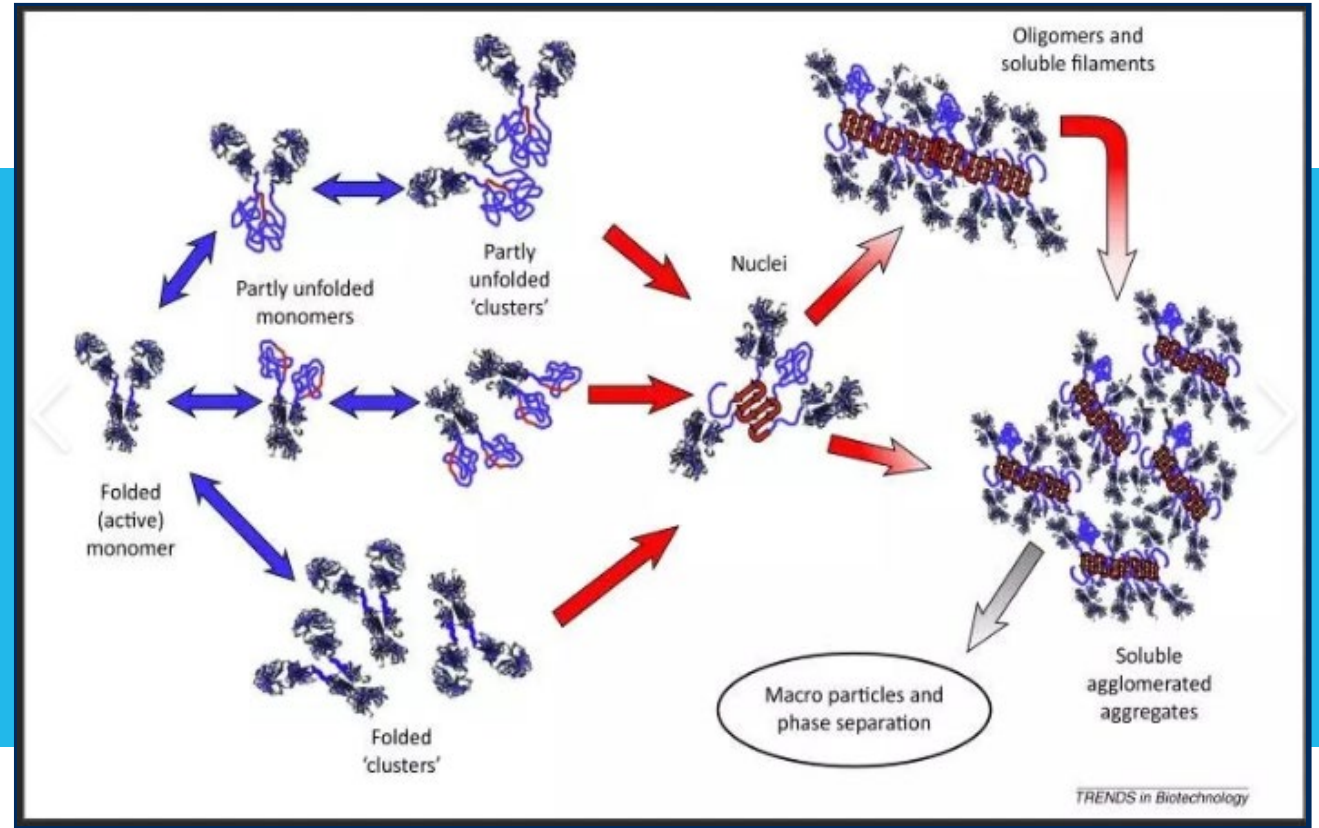
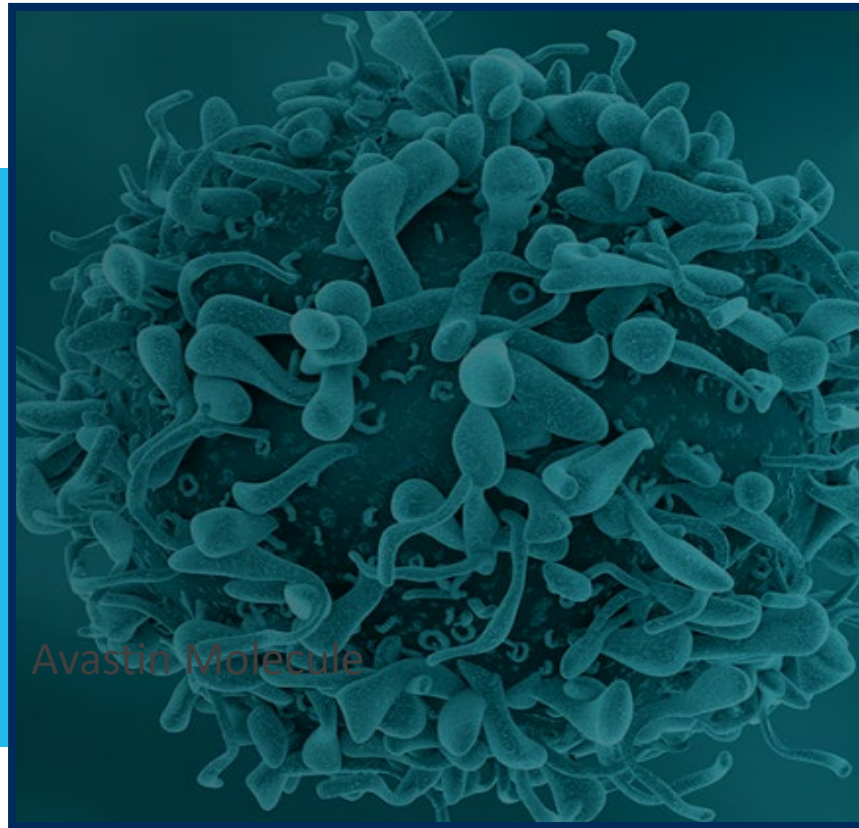
### USP <788> Particulate Matter in Injections

≥ 10 µm: Not more than **6000** particles/mL • ≥ 25 µm: Not more than **600** particles /mL • ≥ 50 µm: **Not tested**

### USP <789> Particulate Matter in Ophthalmic Solutions

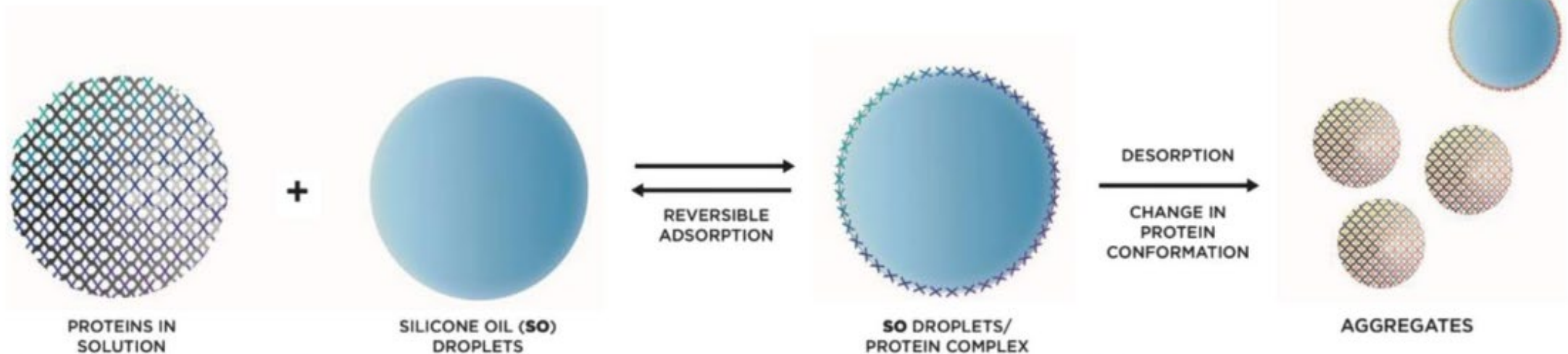
≥ 10 µm: Not more than **50** particles/mL • ≥ 25 µm: Not more than **5** particles/mL • ≥ 50 µm: Not more than **2** particles

# Monoclonal Antibody Shearing/Fragmentation During the Repackaging Process



Our results suggest that the particle formation is intensified by the amplified desorption effects of shear stress.<sup>1</sup>

# Protein Aggregation Around Particulates and Potential Decreased Efficacy



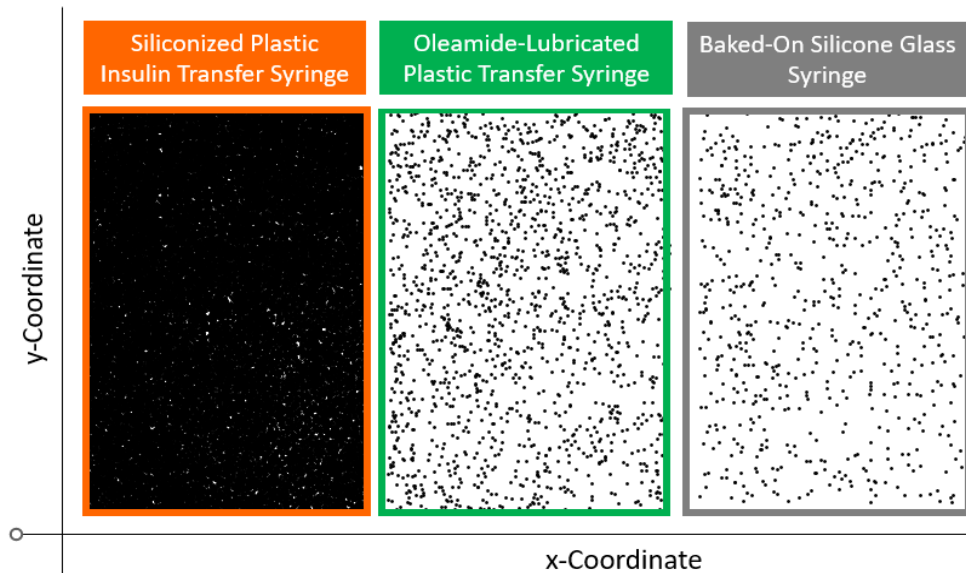
**Fig. 1** Schematic drawing illustrating possible interactions between silicone oil (SO) and proteins in solution. Proteins may undergo conformational change and film formation after interaction with the silicone oil surface. Fragmentation of SO-protein complexes results in smaller aggregates and agglomerates

Unwanted particles in the solution can cause irritation in the eye and potentially react with the active drug to lower efficacy.<sup>1</sup>

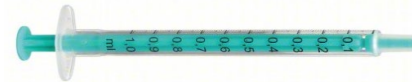


# Extended Storage of a Biologic in Pre-Filled Non-Validated Syringes Potentially Leading to Decreased Efficacy

## Quality Challenges Caused by Long Term Storage of a Biologic in Non-Validated Pre-Filled syringes



**Siliconized Plastic Insulin Syringe**



**Oleamide Lubricated Plastic Transfer Syringe**



**Baked on Silicone Glass Syringe**

Storage of a protein solution in a plastic syringe can extract leachable material from the syringe barrel and rubber plunger tip. Compounds can induce protein aggregation and potentiate adverse effects in patients such as immunogenicity. Therefore, properly developed therapeutic proteins are not stored in plastic containers.<sup>1</sup>





# U.S. Law and FDA Regulations for Compounding and Repackaging Biologics

## Effective March 23, 2020, Bevacizumab, a Biological Product, is No Longer Eligible for Exemptions for Compounded Drugs Under Sections 503A and 503B of the FD&C Act<sup>1</sup>

### All Compounded Biologic Products are Unlicensed Biologics Under the PHSA<sup>2,3,4,5</sup>

- 503A and 503B exemptions only apply to drug approvals under Section 505 under the FD&CA
- The BPCIA requires biologics to be licensed under Section 351 of the PHSA, with certain exception before March 23, 2020 for biologics in a product class for which a biological product in such product class is the subject of an approval under Section 505 under the FD&C Act, as was the case for bevacizumab

### Compounded Biologics are Not FDA-Approved / Licensed and Have Not Undergone Review for Safety, Purity or Potency

- FDA permits certain mixing, diluting, and repackaging of biologics through enforcement discretion policy, requiring pharmacies to comply with certain requirements before they can lawfully compound a biologic<sup>3</sup>
- Practice could create significant risks to patients as these biologics have not been shown to be safe, pure or potent and may have been prepared under substandard manufacturing conditions, particularly in state-licensed facilities that are not required to comply with current Good Manufacturing Practice<sup>6</sup>

# ONS-5010

The Form of Bevacizumab the  
Market Wants

# ONS-5010 Ophthalmic Bevacizumab Target Product Profile

## ONS-5010 (bevacizumab-vikg) Investigational Therapy

### Patient Population

- Patients diagnosed with **wet AMD, DME, or BRVO**

### Description

- Anti-VEGF **bevacizumab designed for ophthalmic indications** wet AMD, DME, and BRVO
- Demonstrated high affinity to bind to all isoforms of VEGF A

### Dosing and Administration

- Supplied either as **pre-filled ophthalmic syringe for intravitreal 1.25 mg injection** administered once monthly, **or in a glass vial**

### Efficacy, Safety, and AEs

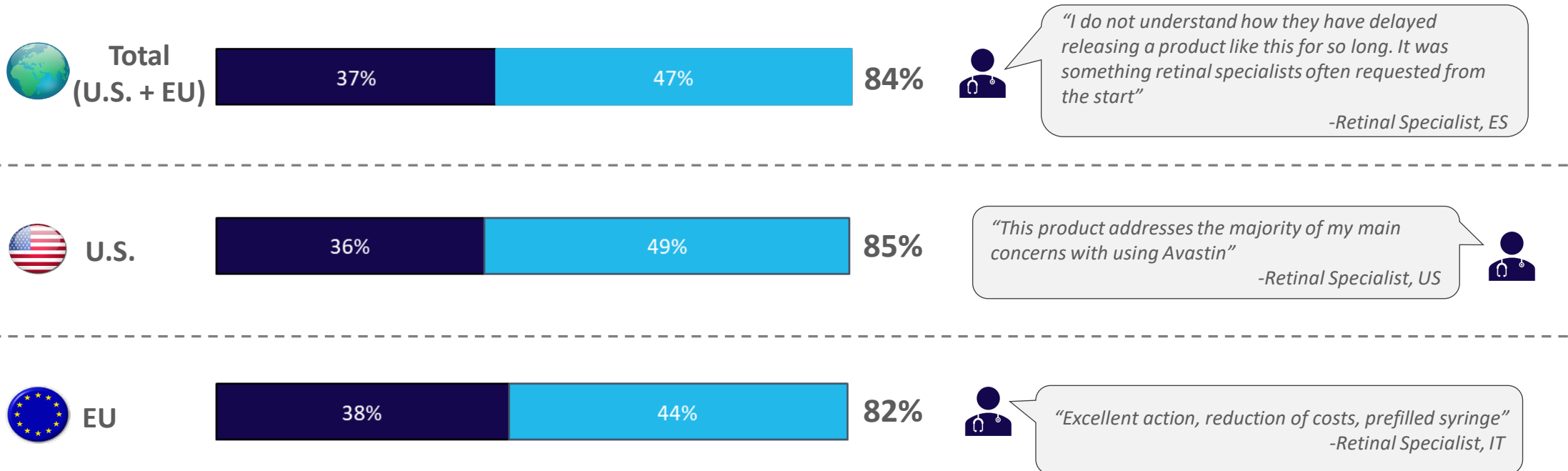
- NORSE TWO demonstrated significant efficacy and safety, and when combined with NORSE ONE and NORSE THREE provides the necessary registration database. These ONS-5010 data when taken as a whole continue to be consistent with previously published results for bevacizumab

# FDA Approval Requirements vs Compounded Bevacizumab

Ophthalmic Solution Requirement	Off-Label Compounded Repackaged IV Solution	FDA Approved Ophthalmic Solution for Intravitreal Injection
Sterile USP <71> <sup>1</sup>	?	Yes
Particulates per USP <789> for ophthalmic solutions <sup>1</sup>	?	Yes
Bacterial endotoxins USP <85> <sup>1</sup>	?	Yes
GMP <sup>2,3</sup>	?	Yes
FDA approved ophthalmic package consistent with USP <771> <sup>1</sup>	No	Yes
FDA reviewed stability data supporting shelf life <sup>2,3</sup>	No	Yes
pH FDA approved and consistent with USP <771> <sup>1,2,3</sup>	No	Yes
Potency FDA approved specifications for shelf life <sup>2,3</sup>	No	Yes
Osmolarity specification for ophthalmic solution <sup>2,3</sup>	No	Yes

# Do Physicians Want an Ophthalmic Approved Bevacizumab?

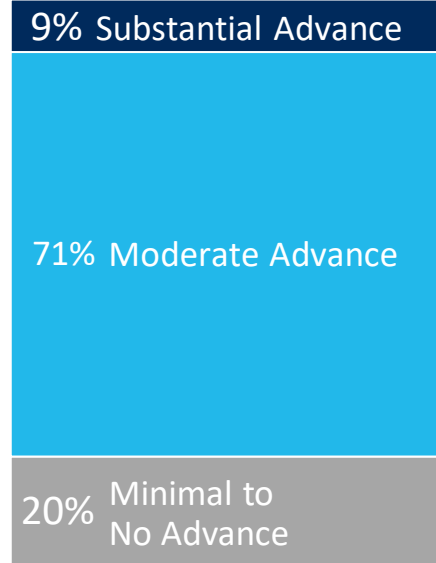
**>80% of Retinal Specialists Express Interest/High Interest in an FDA-Approved Ophthalmic Bevacizumab to Treat Wet AMD, DME and BRVO**



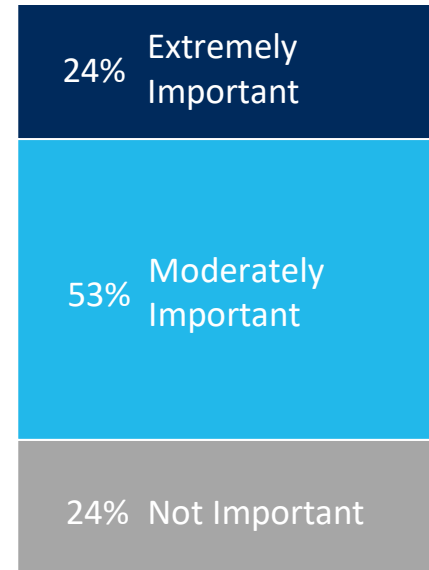


# Investigational Therapy ONS-5010 Ophthalmologists Survey

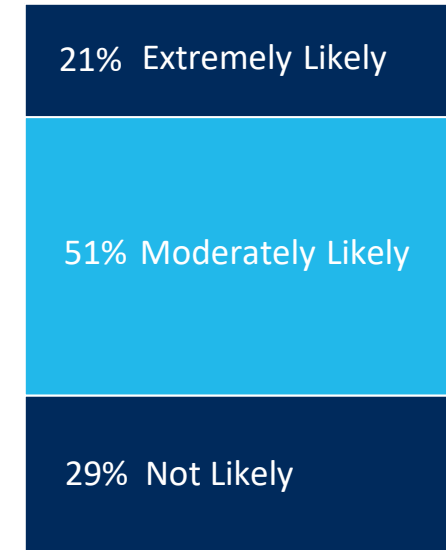
**80% of Surveyed Perceive ONS-5010 as an Advancement**



**77% of Surveyed Believe an FDA Approved Bevacizumab for Wet AMD is Important**



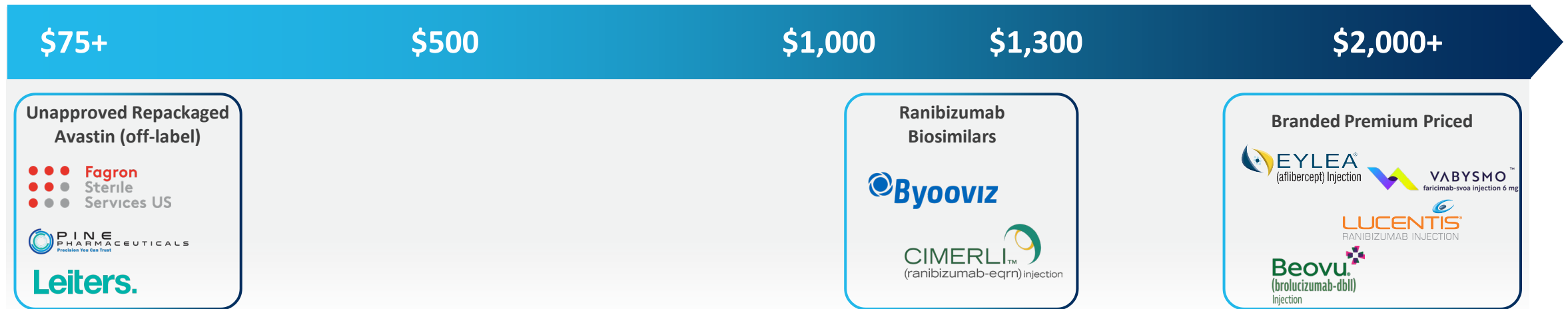
**71% of Surveyed are Likely to Prescribe ONS-5010 if Approved**



# LYTENAVA™ Pricing Opportunity



Pricing spectrum of anti-VEGFs per dose



## LYTENAVA™ Pricing Strategy

Price low enough to move off-label users to branded LYTENAVA™, while still creating significant margin and value compared to any biosimilar and significantly less than the premium branded products

# ONS-5010

## Commercial Activities

# Strategic Commercialization Partnership in U.S. with Preeminent Leader in Specialty Pharma Distribution

## AmerisourceBergen

**Establishes Commercial Depth in Advance of Potential ONS-5010 Commercial Launch**

✓ Third-Party Logistics  
Services and Distribution

✓ Medical Information and  
Pharmacovigilance Services

**Besse Medical is One of the Largest Specialty  
Pharmaceutical Distributors to Retina Specialists**

# ONS-5010

Clinical Data



# Compelling Clinical Data Support Potential FDA Approval in Wet AMD

- ✓ U.S. FDA BLA Accepted with Target PDUFA of August 29, 2023
- ✓ Received Validation of Marketing Authorization Application by European Medical Agency

## ✓ Positive Signals



Clinical Experience Trial

## ✓ Positive Top-Line Data



Pivotal Trial

## ✓ Completed



Open-Label Safety Study

# NORSE ONE and NORSE THREE Results



## Clinical Experience Trial

Demonstrated anticipated safety and efficacy signals consistent with previously published results for ophthalmic use of bevacizumab

### Trial Highlights:

- Desired proportion of 3-line visual acuity gainers achieved
- Desired mean gain in visual acuity achieved
- Zero ocular inflammation observed
- Safety was comparable to published bevacizumab studies, such as CATT



## Open-Label Safety Study

Positive safety profile reinforces previously reported safety data for ONS-5010 (bevacizumab-vikg)

### Trial Highlights:

- Provided adequate number of patient exposure required for BLA submission
- No unexpected safety trends
- Zero cases of ocular inflammation



## Pivotal Trial

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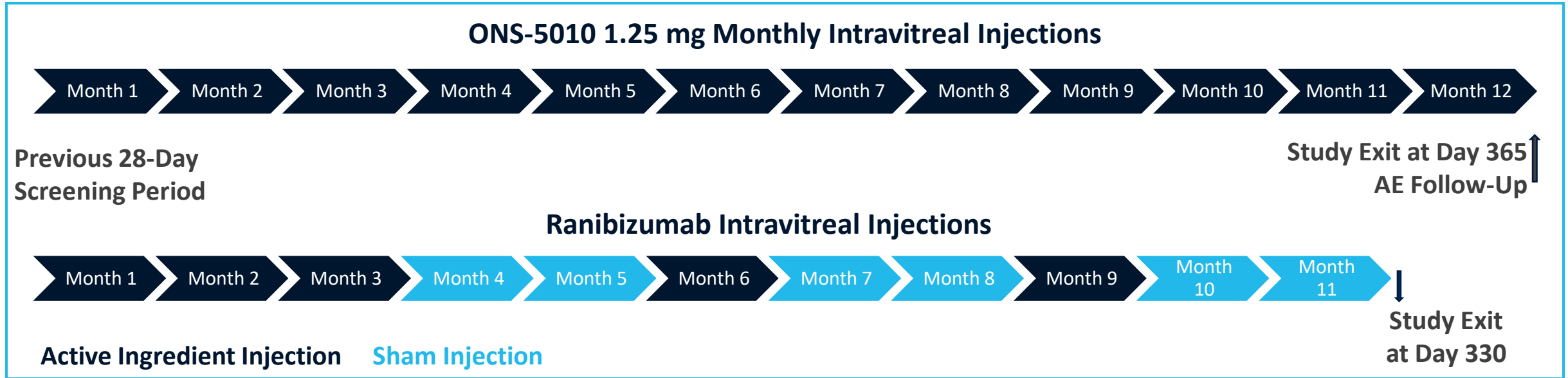


### Trial Highlights:

- Randomized masked controlled trial
- ONS-5010 (bevacizumab-vikg) vs LUCENTIS® (ranibizumab)
- 228 patients enrolled
- Trial conducted in the United States
- Trial arms included >95% treatment-naïve patients

# Phase 3 Pivotal Study Design – Registration Strategy

## 12-Month Study of Safety and Efficacy of ONS-5010 in Subjects with Wet AMD Study Design and Statistical Analysis Plan Agreed to by U.S. FDA



### Study Eye Characteristics

- Active, primary CNV due to wet AMD
- Treatment-naïve
- BCVA: 20/50 – 20/320

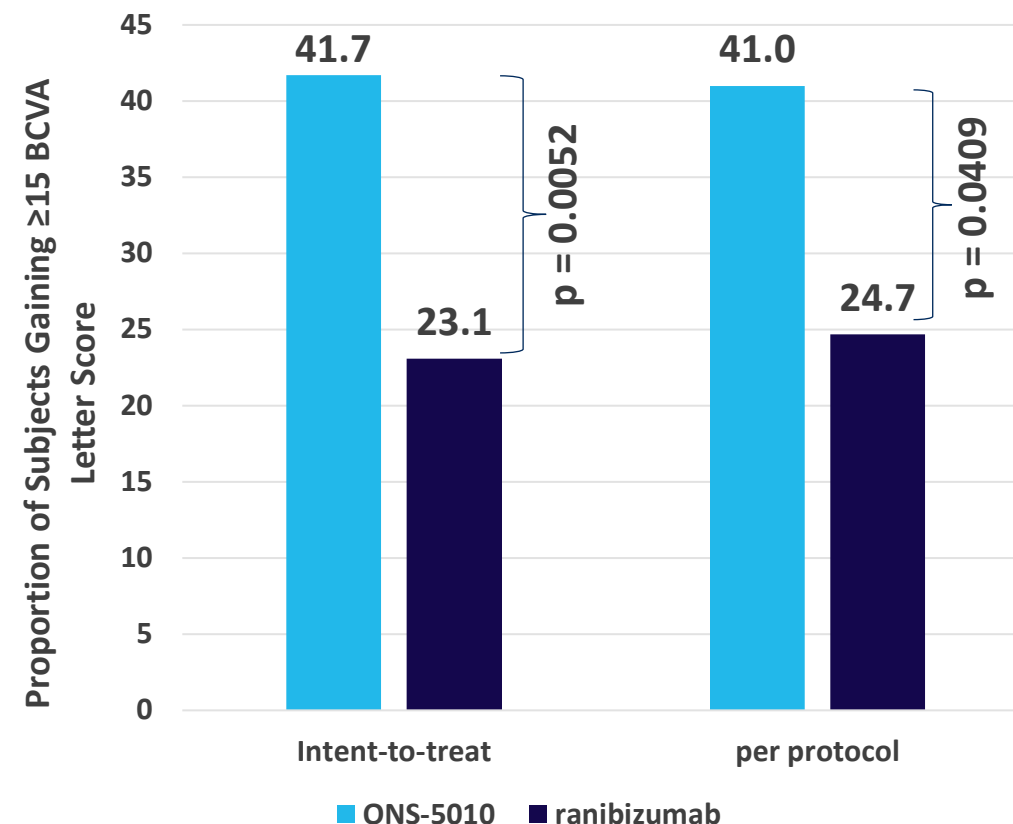
### Key Study Outcomes

- Proportion of subjects who gain  $\geq 15$  letters in BCVA
- Mean change in BCVA from baseline to Month 11
- Frequency and incidence of AEs

# Primary Endpoint Met with Statistically Significant, Clinically Relevant Results<sup>1</sup>

Characteristic	Statistic	ONS-5010 (n=113)	Ranibizumab (n=115)
Intent-to-Treat Pop.			
Number of Subjects	n/N (%)	45/108 (41.7)	24/104 (23.1)
Risk Difference		0.1859	
95% CI		(0.0442,0.3086)	
p-value		0.0052	
Per Protocol Pop.			
Number of Subjects	n/N (%)	34/83 (41.0)	18/73 (24.7)
Risk Difference		0.1631	
95% CI		(0.0120, 0.3083)	
p-value		0.0409	

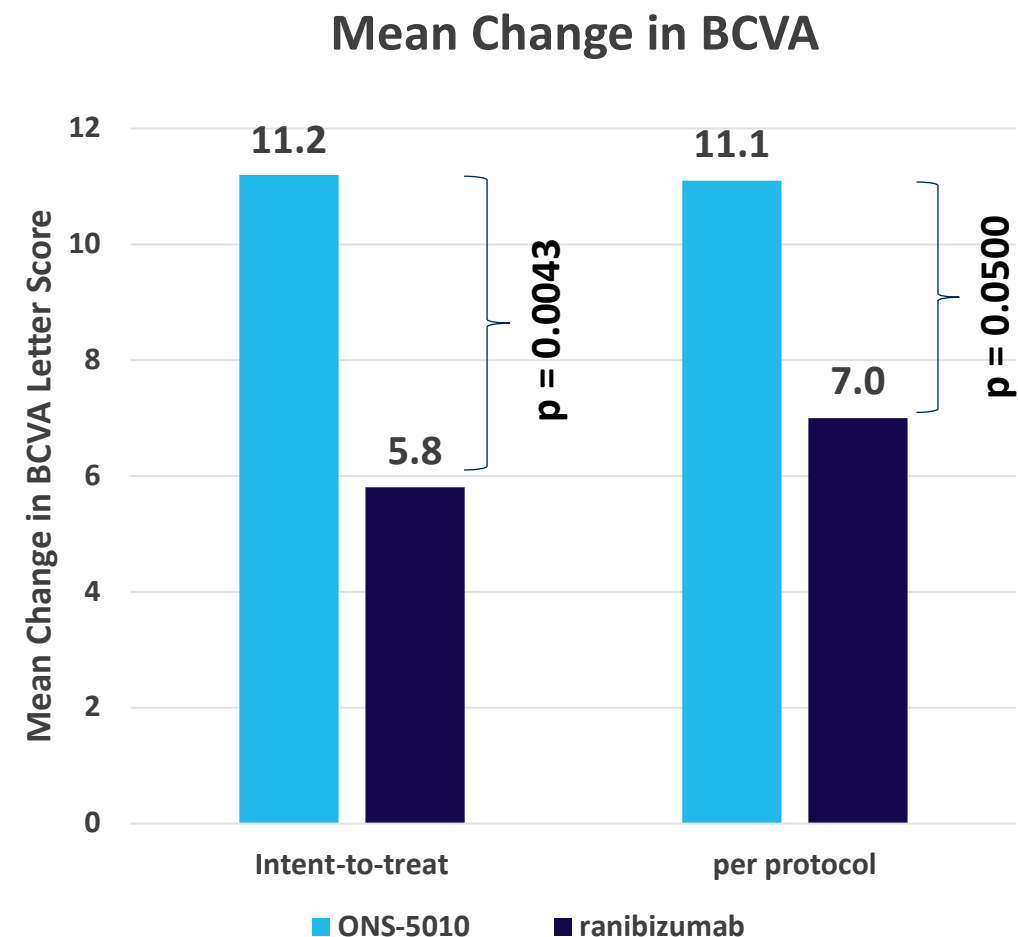
**Difference in % Subjects Gaining 3 Lines Vision**





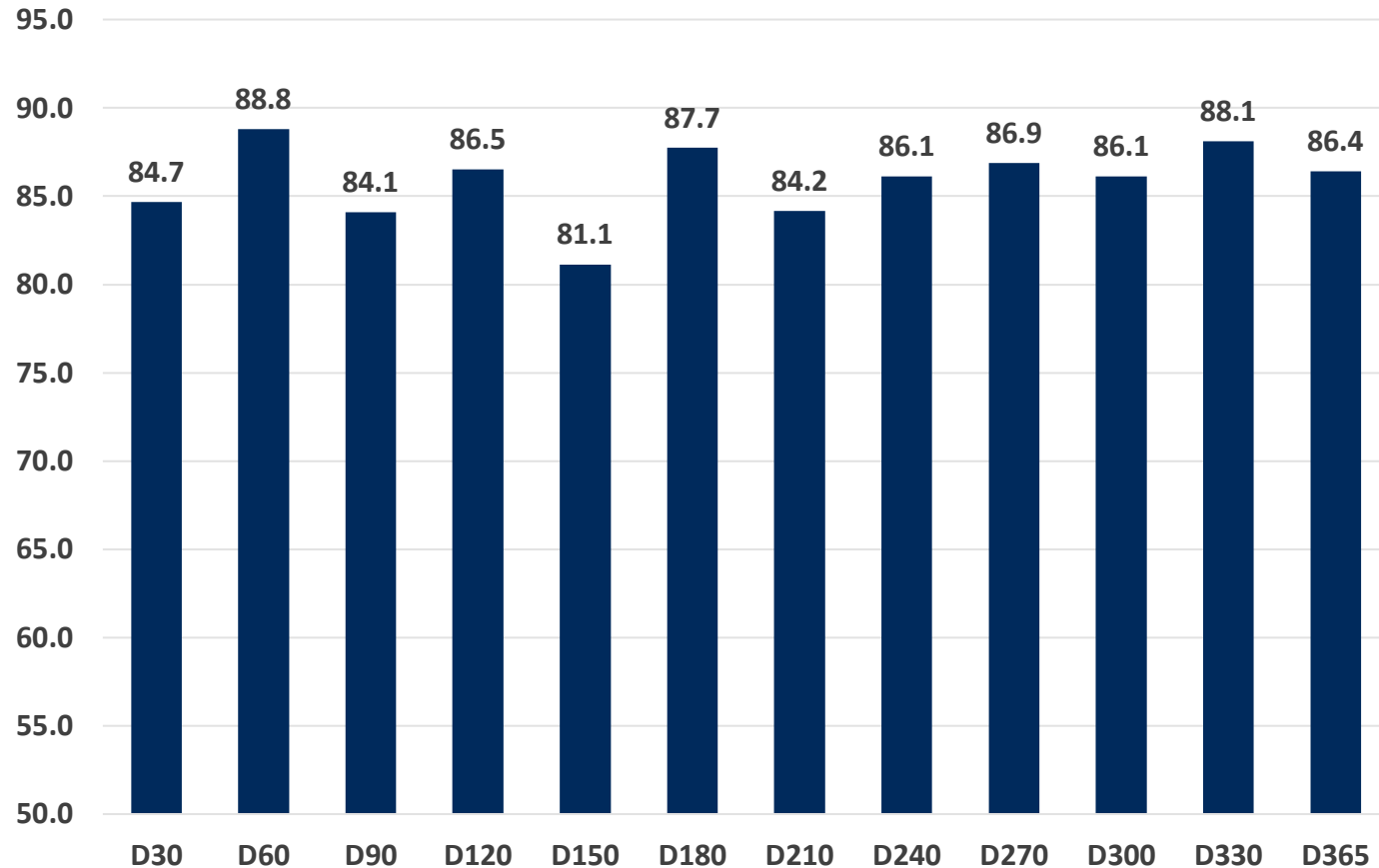
# Key Secondary Endpoints Met with Highly Statistically Significant, Clinically Relevant Results

Characteristic	Statistic	ONS-5010 (n=113)	Ranibizumab (n=115)
BCVA Score Change from Baseline to Month 11 (ITT)	n	104	96
	Mean (SD)	<b>11.2 (12.19)</b>	5.8 (14.80)
p-value		<b>0.0043</b>	
BCVA Score Change from Baseline to Month 11 (PP)	n	80	68
	Mean (SD)	11.1 (12.77)	7.0 (14.56)
p-value		0.0500	



# NORSE TWO - BCVA

## Proportion of Subjects Who Maintained or Gained BCVA by Visit



The **majority** of subjects maintained or gained BCVA during the study (defined as change from baseline in BCVA  $\geq 0$ )

- $\geq 80\%$  of subjects maintained BCVA each month
- At 1 year, **86.4%** of subjects had maintained or gained BCVA, supporting the sustained positive effect of ONS-5010

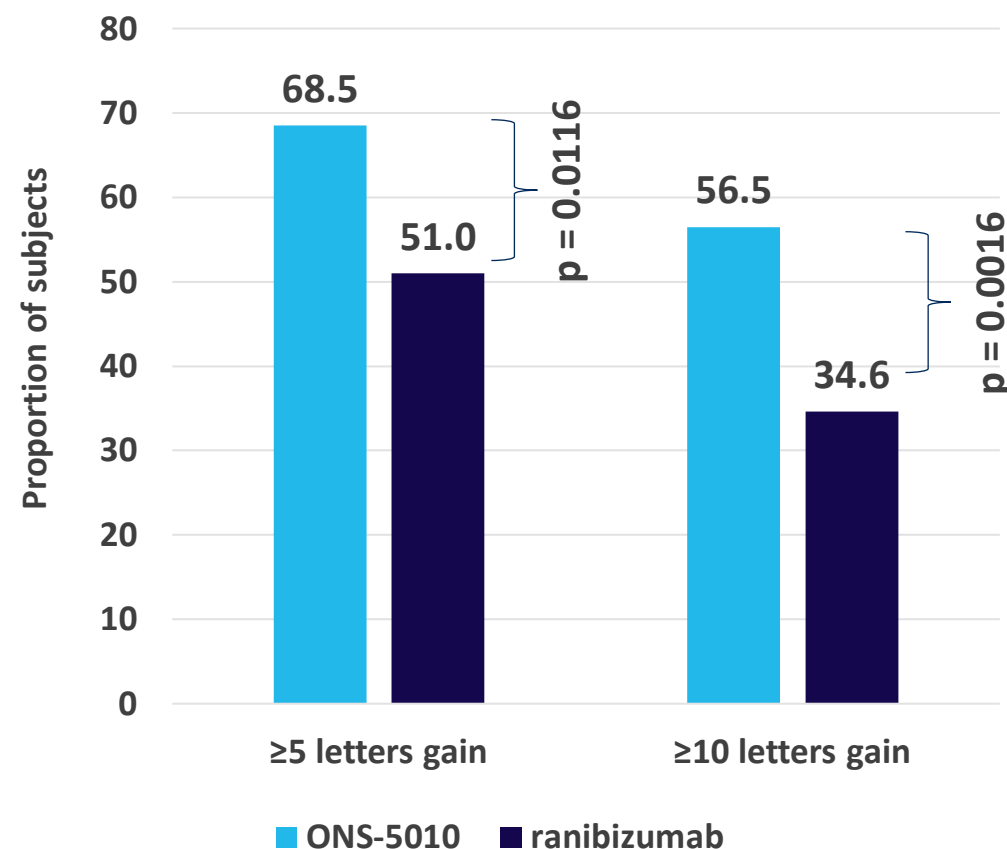


# Statistically Significant, Clinically Relevant Secondary Endpoints

Characteristic	Statistic	ONS-5010 (n=113)	Ranibizumab (n=115)
Subjects Gaining ≥5 letters			
Number of Subjects	n/N (%)	74/108 (68.5)	53/104 (51.0)
Risk Difference		0.1756	
95% CI		(0.0315,0.3052)	
p-value		0.0116	
Subjects Gaining ≥10 letters			
Number of Subjects	n/N (%)	61/108 (56.5)	36/104 (34.6)
Risk Difference		0.2187	
95% CI		(0.0726,0.3487)	
p-value		0.0016	

68.5% (p = 0.0116) ONS-5010 subjects gained ≥ 5 letters of vision  
 56.5% (p = 0.0016) ONS-5010 subjects gained ≥ 10 letters of vision  
 41.7% (p = 0.0052) ONS-5010 subjects gained ≥ 15 letters of vision

## Responder Analysis



# Safety Results: Consistent with Previously Reported Results from NORSE ONE and NORSE THREE

## Only One ONS-5010 Ocular Inflammation AE Reported in NORSE TWO (Iritis)

Characteristic	Statistic	ONS-5010 (n=113)	Ranibizumab (n=115)	Overall (n=228)
<b>≥ 1 Adverse Event</b>	<b>n (%)</b>	<b>85 (75.2)</b>	<b>85 (73.9)</b>	<b>170 (74.6)</b>
≥ 1 ocular Adverse Event	n (%)	59 (52.2)	61 (53.0)	120 (52.6)
≥ 1 non-ocular Adverse Event	n (%)	56 (49.6)	52 (45.2)	108 (47.4)
<b>≥ 1 Serious Adverse Event</b>	<b>n (%)</b>	<b>14 (12.4)</b>	<b>16 (13.9)</b>	<b>30 (13.2)</b>
≥ 1 ocular Serious Adverse Event	n (%)	1 (0.9)	0	1 (0.4)
≥ 1 non-ocular Serious Adverse Event	n (%)	13 (11.5)	16 (13.9)	29 (12.7)

# Financial Highlights

NASDAQ: OTLK

**Sufficient to Fund Operations Through the Anticipated Approval  
of the BLA for ONS-5010 in the 3<sup>rd</sup> Calendar Quarter of 2023,  
and Potentially Through the 4<sup>th</sup> Calendar Quarter of 2023<sup>4</sup>**

**\$43.7M**

Cash Balance<sup>1</sup>

**~\$308M**

Market Cap<sup>2</sup>

**~257M**

Shares Outstanding<sup>3</sup>

**~584K**

Average Volume<sup>2</sup>



## Company Summary

- **Targeting \$13.1 billion global ophthalmic anti-VEGF market<sup>1</sup>**
  - *Initial U.S. target segment worth up to billions in potential yearly revenue served by compounding pharmacies which by law should be converted to Outlook Therapeutics' LYTENAVA, if FDA approved*
- **Potential FDA approval August 29, 2023 as the first FDA approved ophthalmic formulation of bevacizumab**
- **Received validation of Marketing Authorization Application by European Medical Agency**
- **Current capital expected to fund operations through anticipated FDA approval of ONS-5010 in the third calendar quarter of 2023<sup>2</sup>**
- **Management team with proven ophthalmic commercial launch expertise**
  - *Leveraging strategic commercialization agreement with AmerisourceBergen to preserve capital and enhance commercial reach*