New Therapies in wet AMD

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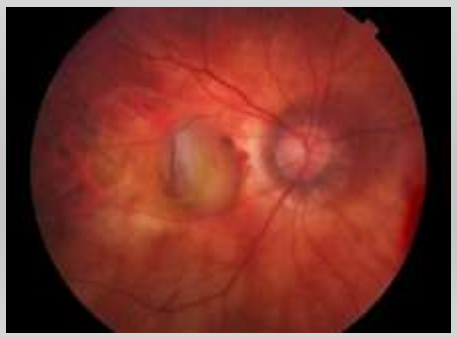
Approximately 20 to 25 million people are affected by nAMD, a leading cause of blindness worldwide



- ***Current anti-VEGF monotherapies for neovascular AMD are burdensome,***

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- ***Current anti-VEGF monotherapies for neovascular AMD are burdensome, requiring frequent clinic visits for eye injections,***

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- ***Current anti-VEGF monotherapies for neovascular AMD are burdensome, requiring frequent clinic visits for eye injections, some people are under-treated and experience subsequent declining vision over time***

5

Unmet medical need

Areas of unmet need

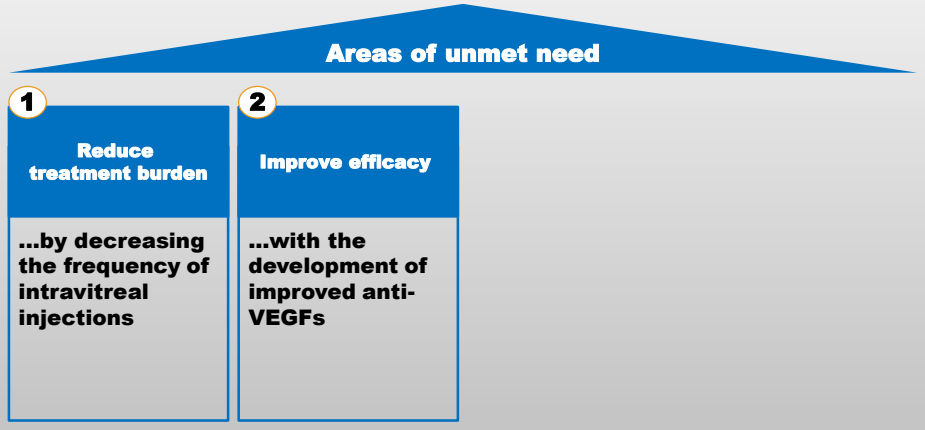
1

Reduce treatment burden

...by decreasing the frequency of intravitreal injections

6

Unmet medical need



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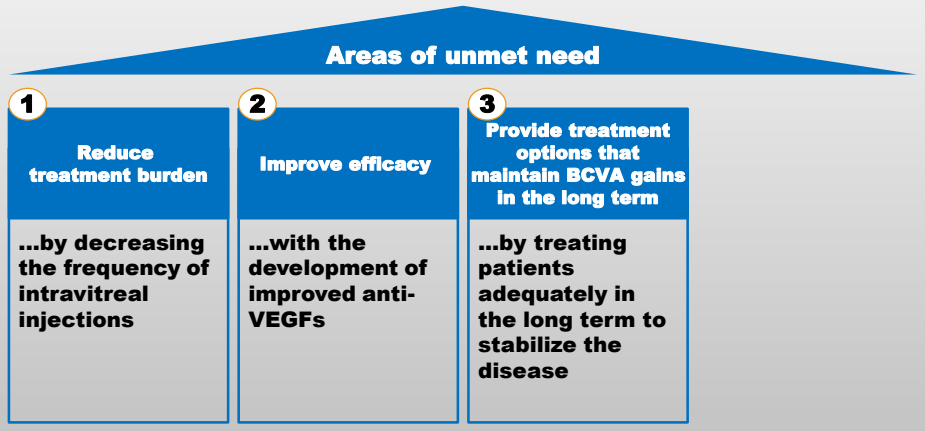
Unmet medical needs



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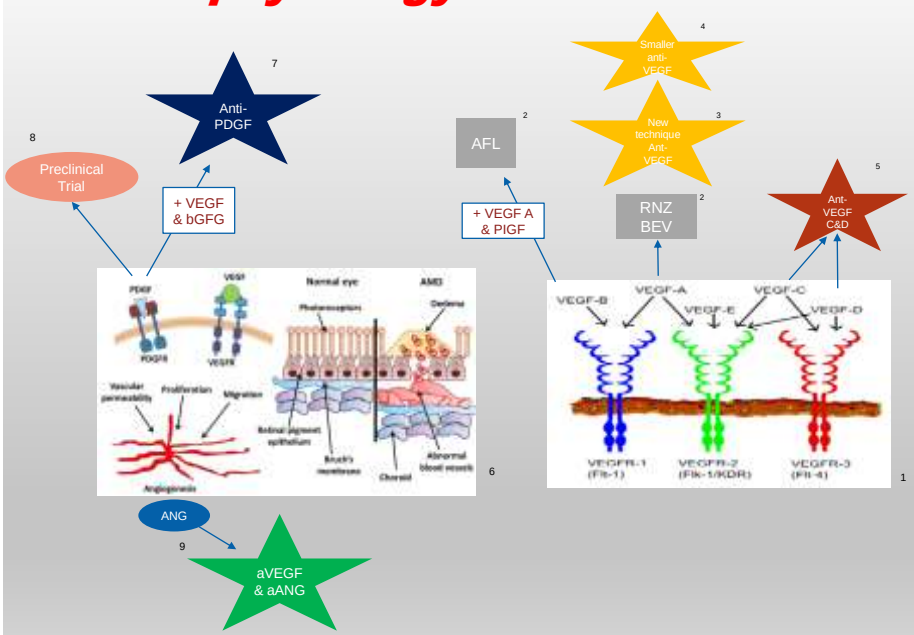
Unmet medical need

Areas of unmet need

1	2	3	4
Reduce treatment burden	**Improve efficacy**	**Provide treatment options that maintain BCVA gains in the long term**	**Improve quality of life**
...by decreasing the frequency of intravitreal injections	**...with the development of improved anti-VEGFs**	**...by treating patients adequately in the long term to stabilize the disease**	**...by optimizing personalized medical treatment approaches**

9

Pathophysiology of wAMD



10

Upcoming Therapies

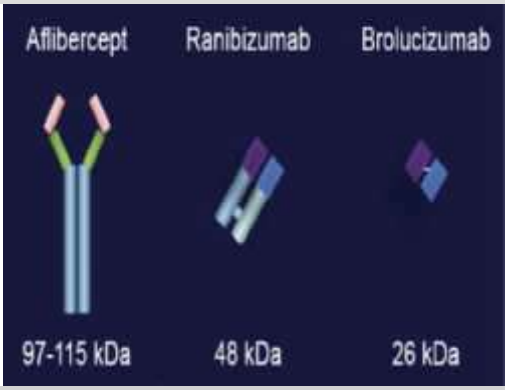
Brolucizumab

Brolucizumab (RTH258)

- ***Brolucizumab (RTH258) is the most clinically advanced, humanized single-chain antibody fragment (scFv) .***
- ***It has the advantages of small size, enhanced tissue penetration & rapid clearance from systemic circulation .***

13

- **It has small molecular weight (26 kDa) with potent inhibition of, and high affinity to, *all VEGF-A isoforms.***



14

HAWK & HARRIER

Study Overview

HAWK and HARRIER are prospective, randomized, double-masked, 2-year ongoing studies to evaluate the efficacy and safety of brolucizumab for the treatment of nAMD:

HAWK
(NCT02307682)
Began in December 2014
in study sites in North, Central, and South America, Israel, Australia, New Zealand and Japan.[7]

HARRIER
(NCT02434328)
Began in July 2015
across Europe and Asia.[8]

BOTH STUDIES
have completed patient recruitment, enrolling

>1800 PATIENTS
over
400 STUDY SITES
in total[9]

https://novartis.gcs-web.com/static-files/ad93faf6-c1a9-47a1-899a-547a1b1c66f9. last accessed on 13th of February, 2018.

15

- ***The studies were designed to compare the efficacy and safety of intravitreal injections of brolucizumab 6 mg (HAWK and HARRIER) and 3 mg (HAWK only) versus aflibercept 2 mg in patients with nAMD.***

16

Brolucizumab (RTH258)

Two parallel Phase III registration studies

	C001[1]	C002[2]
Drug	Brolucizumab (RTH258)	Brolucizumab (RTH258)
Study	Phase III, 2-year, randomized, double-masked, multi-center, three-arm study comparing the efficacy and safety of RTH258 vs. aflibercept in subjects with nAMD	Phase III, 2-year, randomized, double-masked, multi-center, two-arm study comparing the efficacy and safety of RTH258 6 mg vs. aflibercept in subjects with nAMD
Primary objective	Non-inferiority of mean BCVA change at year 1	Non-inferiority of mean BCVA change at year 1
Indication	nAMD	nAMD
Dosing schedule	Brolucizumab 3 mg and 6 mg vs. aflibercept 2 mg	Brolucizumab 6 mg vs. aflibercept 2 mg
Planned no. of patients	990	660
Study milestones	• **Study start**: Dec 2014 • **Study completion**: Q2 2018	• **Study start**: Jul 2015 • **Study completion**: Q2 2018
Publication	www.clinicaltrials.gov (NCT02307682)	www.clinicaltrials.gov (NCT02434328)

BCVA, best corrected visual acuity;
nAMD, neovascular age-related macular degeneration

[1] https://clinicaltrials.gov/ct2/show/NCT02307682
[2] https://clinicaltrials.gov/ct2/show/NCT02434328

17

STUDY DESIGN

- *Initial 3-month loading phase.*
- *Patients in the brolucizumab arms received a q12w dosing interval with an option to adjust to a q8w dosing interval based on masked disease activity assessments at defined visits.*
- *Aflibercept was dosed bi-monthly according to its label at the time of study initiation*

18

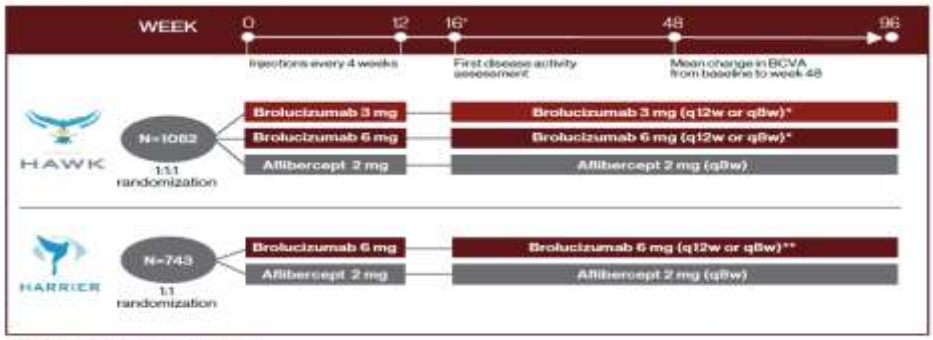
HAWK & HARRIER

Study Design

What?

Two pivotal trials to test the efficacy and safety of intravitreal injections of brolucizumab 6 mg (HAWK and HARRIER) and brolucizumab 3 mg (HAWK only) versus aflibercept 2 mg in patients with nAMD

How?



+ Matched regimen head-to-head assessment

* Disease activity assessments were conducted at prespecified visits by the masked investigator supported by protocol guidance based on dynamic functional and anatomical characteristics at weeks 20, 32, 44, 56, 68, 80 and 92

** Additional assessments and potential dosing interval adjustments occurred at weeks 28, 40, 52, 64, 76 and 88 in HARRIER only

Primary End Point

Change in Best Corrected Visual Acuity (BCVA) from Baseline at Week 48

20

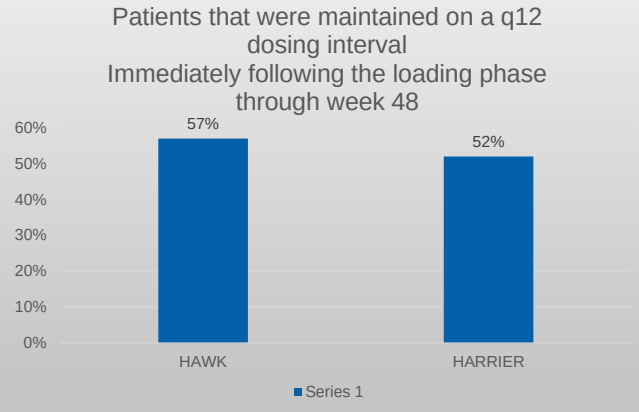
Secondary endpoints

- *Central subfield retinal thickness.*
- *Retinal fluid (intraretinal fluid and/or subretinal fluid) .*
- *Disease activity .*

21

RESULTS

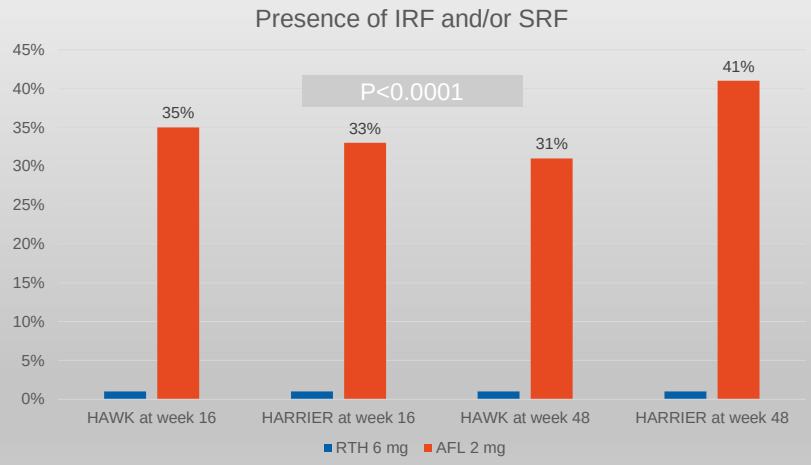
Study results
Majority of patients maintained on a q12 dosing regimen



https://novartis.gcs-web.com/Novartis-brolucizumab-RTH258-demonstrates-superiority-versus-aflibercept-in-key-secondary-endpoint-measures-of-disease-activity-in-nAMD-a-leading-cause-of-blindness. Last accessed on 13th of |February, 2018

23

Study results
Presence of IRF/SRF were significantly lower with Brolucizumab



https://novartis.gcs-web.com/Novartis-brolucizumab-RTH258-demonstrates-superiority-versus-aflibercept-in-key-secondary-endpoint-measures-of-disease-activity-in-nAMD-a-leading-cause-of-blindness. Last accessed on 13th of |February, 2018

24

Study results met the primary end point

Brolucizumab (6 mg) met the primary efficacy endpoint of *non-inferiority to aflibercept* in mean change in BCVA from baseline to week 48 in both trials with high statistical significance.

25

Brolucizumab demonstrated superiority in three secondary endpoints considered key parameters of nAMD:

- **Central subfield retinal thickness.**
- **Retinal fluid (intraretinal fluid and/or subretinal fluid) .**
- **Disease activity .**

Year two results

- *Secondary endpoints at year two reaffirmed superiority of brolucizumab 6 mg in reduction of retinal fluid in patients with neovascular age-related macular degeneration (nAMD).*

27

These consistent results continue to support Brolucizumab as a potential new treatment for patients with nAMD.

28

Abicipar pegol

29

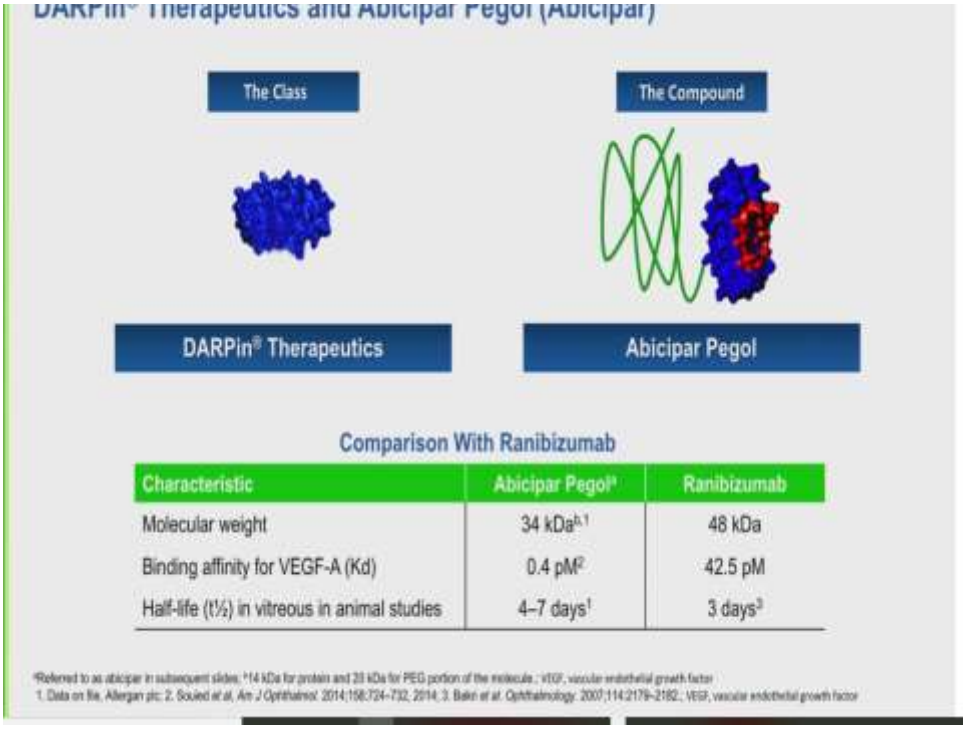
Class of Drug

- Abicipar is Anti-VEGF that inhibits all relevant subtypes of VEGF-A with very high potency.

Advantages

- Small size.
- High potency .
- long intra-vitreal half-life.

***It offers the potential for less frequent injections and higher gains in visual acuity*.**



1. CEDAR study

A Safety and Efficacy Study of Abicipar Pegol in Patients With Neovascular Age-related Macular Degeneration.

Phase III

Arms: abicipar pegol, ranibizumab, sham.

2. SEQUOIA study

Safety and Efficacy of Abicipar Pegol in Patients With Neovascular Age-related Macular Degeneration.

Phase III

Arms: abicipar pegol, ranibizumab, sham.

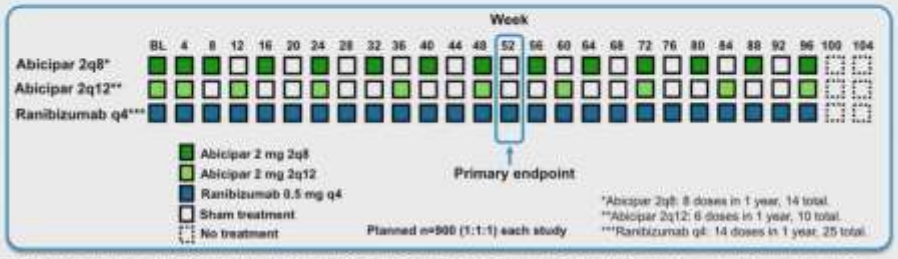
Phase 3 Study Design

Two randomized, double-masked, parallel-group, clinical trials with identical protocols

Objective: To assess the safety and efficacy of abicipar compared with ranibizumab in treatment-naïve patients with nAMD

Primary endpoint: Proportion of patients with stable vision (loss of <15 ETDRS letters compared with baseline) at Week 52

Secondary endpoints: Mean change from baseline in ETDRS BCVA, mean change from baseline in CRT, and proportion of patients with ≥15-letter gain at Week 52

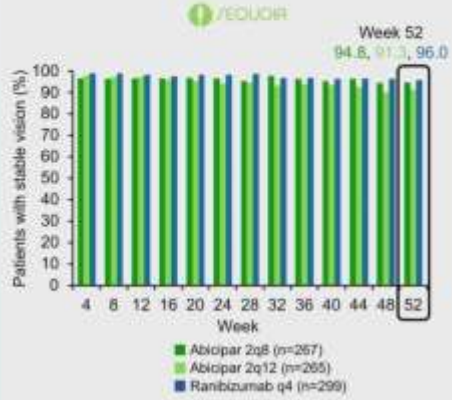


BCVA, best-corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration. ClinicalTrials.gov Identifiers: NCT02462928 and NCT02462486

33

Results

Abicipar 2q8 and 2q12 Noninferior to Ranibizumab for Primary Endpoint of Stable Vision



34

- ***Abicipar pegol hits the primary end point, matching the efficacy of Lucentis at one year with a more-convenient dosing profile every 12 W after two loading doses. (Allergan on July 19th, 2018)***

35

Adverse events

the rate of ocular inflammation with Abicipar pegol reached 15-16% over one year, compared with less than 1% with Lucentis. .

Most of the inflammations were moderate to mild and were treated with topical steroids.

36

Optimization of the drug formulation was continuing and a new formulation is being evaluated in the ongoing Phase II MAPLE trial.

Faricimab

38

Angiopoietin-2 (ANG-2)

- **In nAMD, Ang-2 works synergistically with VEGF to drive pathologic blood vessel permeability and destabilisation, abnormal blood vessel growth and fluid leakage .**

Mechanism of Action

- **Faricimab is the first bispecific antibody designed for intravitreal use to simultaneously bind to and neutralize both *angiopoietin-2 (ANG-2),* and *VEGF-A* with high potency and specificity.**

STAIRWAY STUDY

STAIRWAY is a 52 week , phase II, multicentre, randomised, controlled, parallel group clinical trial study that assessed two extended dosing regimens of faricimab 6.0mg given every 16 weeks or every 12 weeks, compared to ranibizumab 0.5 mg every four weeks.

41

STUDY DESIGN

- ***Four loading monthly doses.***
- ***Patients then randomised to Faricimab every 16 weeks switched to 12-week dosing if they were shown to have active disease, per pre-defined criteria.***

42

RESULTS

AAO 2018

- ***At 52 weeks, Faricimab patients dosed either every 16 weeks or every 12 weeks demonstrated sustained vision outcomes comparable to ranibizumab dosed every four weeks.***

- **The rates of ocular and systemic adverse events observed with Faricimab were similar to the rates observed with ranibizumab.**

- **The STAIRWAY data show the potential of Faricimab to allow fewer injections while achieving and sustaining the same visual gains seen with a current standard of care.**

- **Based on these data, a global phase III program for Faricimab in neovascular AMD will be initiated .”**

46

Squalamine

Class of Drug

- An anti-angiogenic small molecule with a novel intracellular mechanism of action, which counteracts multiple growth factors and pathways implicated in the angiogenic process, including VEGF, PDGF, and basic fibroblast growth factor (bFGF).

➢ *Eye drops*

➢ *MAKO (Phase III)*

Efficacy and Safety Study of Squalamine Ophthalmic Solution in Subjects With Neovascular AMD.

Arms:

- **Topical squalamine twice daily (“BID”) and monthly Lucentis® injections (“squalamine combination”)**
- **Topical placebo BID and monthly Lucentis® injections (“Lucentis monotherapy”).**

Primary End Point

The primary efficacy endpoint was the mean visual acuity gain at nine months .

51

RESULTS

Subjects receiving squalamine combination therapy (n=119) achieved a mean gain of 8.33 letters from baseline versus 10.58 letters from baseline with Lucentis® monotherapy (n=118).

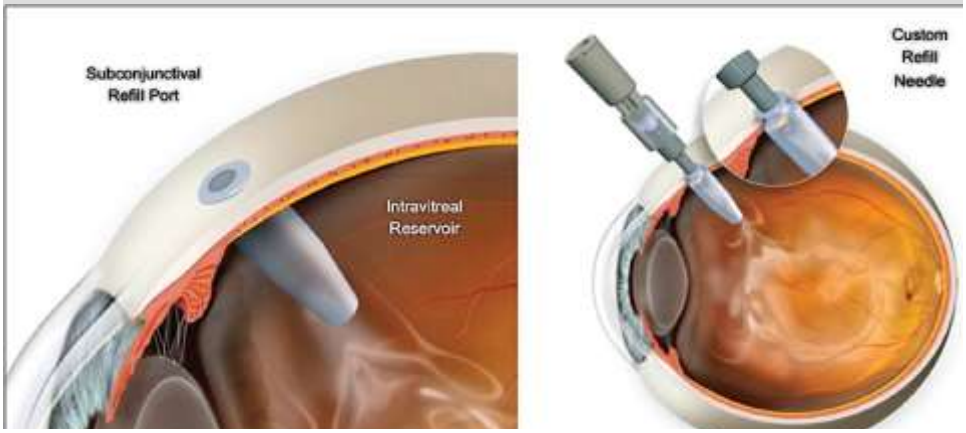
There were no differences in the safety profile between the two treatment groups

52

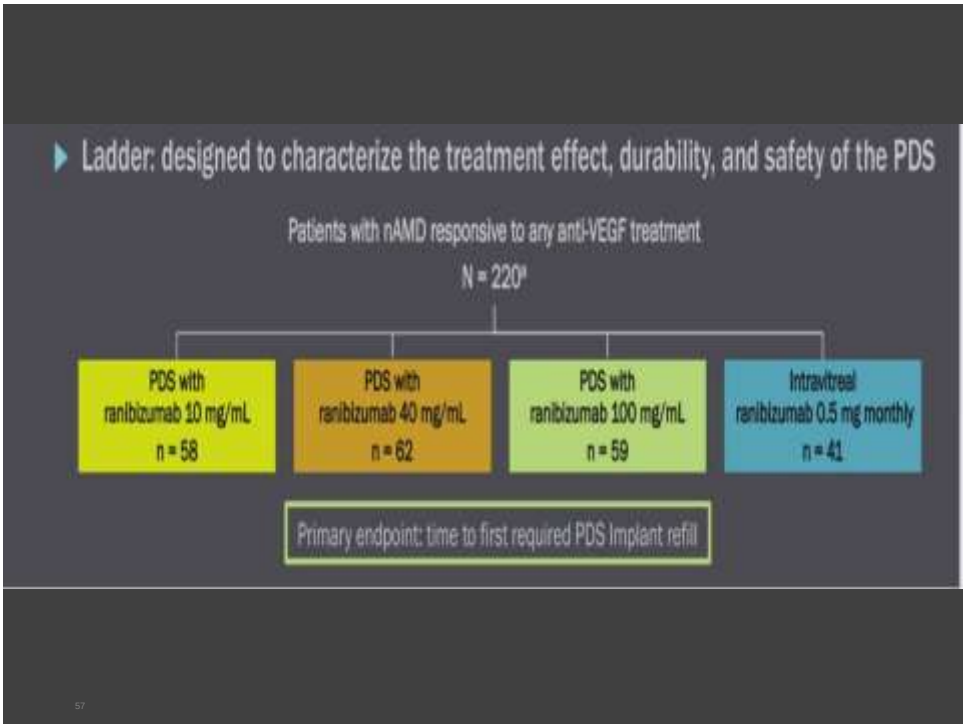
- **MAKO**
  - **Did not meet its primary efficacy endpoint.**

Port Delivery System with ranibizumab (PDS)

A small, refillable eye implant, which is slightly longer than a grain of rice, is designed to allow most people with nAMD to go six months without needing a refill.



LADDER STUDY



- ***Topline results showed the majority of PDS patients – including approximately 80% of patients in the high-dose PDS group – went six months or longer between the implantation and the first required refill of the device.***

- ***Importantly, patients in the high-dose PDS group achieved similar visual outcomes as 0.5 mg ranibizumab dosed every four weeks***

58

- ***Based on data from the phase II Ladder program, the pivotal phase III Archway clinical trial and the Portal open label extension study were initiated in September 2018.***

- ***These studies will evaluate the efficacy and safety of PDS with ranibizumab 100 mg/ml concentration in patients with nAMD at a fixed dosing interval of 24 weeks.***

59


THANK YOU!