Effect of Dual Angiopoietin-2/VEGF-A Inhibition With Faricimab on Macular Anatomy in the STAIRWAY Phase 2 Study of Neovascular Age-Related Macular Degeneration

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- DS: Employee: Roche Products Ltd., UK
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- This study includes research conducted on human subjects
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Faricimab is a bispecific antibody that independently binds and neutralizes Ang-2 and VEGF-A, the key drivers of retinal and choroidal diseases, with high specificity and potency and without steric hindrance.

In preclinical in vivo models, compared with the inhibition of either Ang-2 or VEGF-A alone, dual inhibition showed synergistic benefits, reducing:
- Vascular leakage
- CNV lesion activity
- Microvascular inflammation

Dual Ang-2 and VEGF-A inhibition using faricimab may lead to a more sustained vessel stabilization compared with VEGF-A inhibition alone.

STAIRWAY, a phase 2 trial, showed the potential for extended durability for faricimab in nAMD.
- BCVA gains and anatomic improvements observed in patients treated with faricimab Q12W/Q16W were comparable with ranibizumab Q4W
- 2/3 (65%) of faricimab-treated patients had no active disease 12 weeks after the last initiation dose

Phase 3 trials investigating faricimab in nAMD are currently underway.
Ang-2 and VEGF-A Are Key Drivers of Vascular Instability: Vascular Leakage, Neovascularization, and Inflammation

- **Ang-1** binds to Tie2 on endothelial cells, leading to Tie2 activation and vascular stability
- **Ang-2** levels are increased in the vitreous of patients with nAMD, DR, and RVO1
- **Ang-2** competes with Ang-1 for binding to Tie2 and inactivates the Tie2 receptor
- **Ang-2** and VEGF synergistically drive vascular instability, characterized by:
  - Vascular leakage
  - Neovascularization
  - Inflammation

Preclinical Evidence Suggests a Role for Ang-2 in Vascular Instability

Vascular Leakage

- Dual Ang-2/VEGF-A inhibition significantly reduced the severity of vessel leakage

Neovascularization

- Dual Ang-2/VEGF-A inhibition promoted vessel stability by synergistically reducing angiogenesis and enhancing pericyte coverage

Inflammation

- Dual Ang-2/VEGF-A inhibition synergistically reduced leukocyte transmigration in the retina


Ang-2, angiopoietin-2; CNV, choroidal neovascularization; Fab, fragment antigen binding; IgG, immunoglobulin G; VEGF-A, vascular endothelial growth factor-A.
Faricimab: First Bispecific Antibody Designed for Intraocular Use

Engineered for efficacy, duration within the eye, and fast systemic clearance

1 molecule, 2 targets

Anti–Ang-2 Fab
Enhances vessel stabilization

Anti–VEGF-A Fab
Inhibits vascular leakage and neovascularization

Modified Fc
• Reduced systemic exposure
• Reduced inflammatory potential

CrossMAb molecule representative of faricimab.
Ang-2, angiopoietin-2; Fab, fragment antigen binding; Fc, fragment crystallizable; VEGF-A, vascular endothelial growth factor-A.
Primary Efficacy Objective:

• To evaluate the efficacy of faricimab administered at 16- and 12-week intervals, as assessed by BCVA

Key Inclusion Criteria:

• Treatment-naïve nAMD
• Subfoveal CNV
• Age ≥ 50 years
• BCVA 20/40–20/320 (73–24 ETDRS letters)
At 12 Weeks After Last Faricimab Loading Dose, 65% of Patients Had No Disease Activity, and Could Potentially Benefit From Q16W Dosing

Disease Activity Was Assessed Using 6 Strict Protocol-Defined Criteria

<table>
<thead>
<tr>
<th>Disease Activity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>&gt; 50 μm vs average CST over last 2 visits on SD-OCT</td>
</tr>
<tr>
<td>CST</td>
<td>≥ 75 μm over lowest CST over last 2 visits on SD-OCT</td>
</tr>
<tr>
<td>BCVA</td>
<td>≥ 5 letters of BCVA vs average BCVA over last 2 visits</td>
</tr>
<tr>
<td>BCVA</td>
<td>≥ 10 letters of BCVA vs highest BCVA over last 2 visits, due to nAMD</td>
</tr>
<tr>
<td>Fundus Exam</td>
<td>Presence of new macular hemorrhage</td>
</tr>
<tr>
<td>Other Disease Activity</td>
<td>Investigator opinion of significant nAMD disease activity at week 24 that requires immediate treatment</td>
</tr>
</tbody>
</table>

~2/3 could be suitable for Q16W dosing

% of faricimab-treated patients free from disease activity 12 weeks after the last initiation dose (36/55 patients)

65%

Maintenance of BCVA Gains With Faricimab Q16W Flex and Q12W Comparable With Ranibizumab Q4W

Vision gains and maintenance with faricimab Q16W flex and Q12W were comparable with ranibizumab Q4W at week 52

Least squares means from linear model analysis of study eye BCVA change from baseline. Model includes categorical covariates of treatment group, visit, visit by treatment group interaction, and the continuous covariate of baseline BCVA. Error bars represent 80% Cls. STAIRWAY clinical trial (NCT03038880). Baseline BCVA, mean (SD): ETDRS letters: ranibizumab Q4W: 55.3 (12.1); faricimab Q12W: 57.8 (10.5); faricimab Q16W flex: 60.4 (10.8). BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; SD-OCT, spectral-domain optical coherence tomography.
Faricimab Dosed at Extended Q16W Intervals Showed Sustained Anatomic and Visual Improvements

Case Images of Patients From Q16W Flex Arm With No Active Disease at Week 24; Treated With Q16W Dosing Through Study End

Least squares means from linear model analysis of study eye change from baseline. Model includes categorical covariates of treatment group, visit, visit by treatment group interaction, and the continuous covariate of baseline * BCVA or * CST. STAIRWAY clinical trial (NCT03038880).

BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Q16W, every 16 weeks.
Least squares means from linear model analysis of study eye change from baseline. Model includes categorical covariates of treatment group, visit, visit by treatment group interaction, and the continuous covariate of baseline BCVA or CST. STAIRWAY clinical trial (NCT03038880).

BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Q12W, every 12 weeks; Q16W, every 16 weeks.
Anatomic Outcomes With Faricimab Q16W Flex and Q12W Were Comparable With Ranibizumab Q4W

CST (SD-OCT): least squares means from linear model analysis of study eye CST change from baseline. Model includes categorical covariates of treatment group, visit, visit by treatment group interaction, and the continuous covariate of baseline CST. Error bars represent 80% CIs. STAIRWAY clinical trial (NCT03038880). Lesion area and area of leakage (FFA). Error bars represent SE. Baseline sample size: ranibizumab Q4W: 16; faricimab Q12W: 24; faricimab Q16W flex: 31. Baseline CST, mean (SD), µm: ranibizumab Q4W: 443.1 (125.0); faricimab Q12W: 417.9 (84.3); faricimab Q16W flex: 382.2 (80.9). Baseline area of chorioidal neovascularization, mean (SD), mm²: ranibizumab Q4W: 7.3 (2.9); faricimab Q12W: 7.1 (3.9); faricimab Q16W flex: 5.9 (3.8). CST, central subfield thickness; CNV, chorioidal neovascularization; FFA, fundus fluorescein angiography; Q4W, every 4 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; SD-OCT, spectral-domain optical coherence tomography.
**Primary Study Objective:** Mean BCVA change from baseline at Week 48 as an average of Weeks 40, 44 and 48

**Key Secondary Objective:** Proportion of patients on a Q8W, Q12W, or Q16W treatment interval
In preclinical in vivo models, compared with the inhibition of either Ang-2 or VEGF-A alone, dual inhibition showed synergistic benefits, reducing:

- Vascular leakage
- CNV lesion activity
- Microvascular inflammation

STAIRWAY, a phase 2 trial, showed the potential for extended durability of faricimab in nAMD

- BCVA gains and anatomic improvements observed in patients treated with faricimab Q12W/Q16W were comparable with ranibizumab Q4W
- 2/3 (65%) of faricimab-treated patients had no active disease 12 weeks after the last initiation dose
- Faricimab was well tolerated, with no new safety signals identified

2 large global phase 3 trials, TENAYA and LUCERNE, are investigating the efficacy, safety, and durability of faricimab in patients with nAMD.