INTRODUCTION
Pathologic neovascularization and vessel leakage are key drivers for vision loss in several back-of-the-eye diseases, such as diabetic retinopathy and wet age-related macular degeneration. In the eye, integrin receptors play an important role in (pathological) angiogenesis and vascular leakage. Blocking integrin receptors has the potential to inhibit these processes, different from the current anti-VEGF therapy. In this study, we evaluated the integrin-blocking and anti-angiogenic properties, as well as the safety profile, of THR-687, a novel small molecule integrin receptor antagonist.

METHODS
Integrin profiling: The ability of THR-687 to antagonize various integrin receptors was studied via competition ELISA. 96-well plates were coated with an integrin receptor antagonist. Mouse choroidal explant model: Human umbilical vein endothelial cells (HUVEC) were seeded onto fibronectin-coated Oris™ 96-well plates. After adherence, the stoppers were removed, creating circular cell-free areas, and cells were treated with various concentrations of THR-687. 24h after incubation, CellT ox assay was performed.

RESULTS & DISCUSSION
1. THR-687 potently inhibits integrin receptors involved in angiogenesis and permeability
The ability of THR-687 to bind to various integrins of human origin, and to compete with the binding of their natural ligands, was assessed via competition ELISA. THR-687 inhibited multiple integrin receptors belonging to the RGD class within the nanomolar range, as shown in the table below (average ± SD, n=3).

<table>
<thead>
<tr>
<th>Integrin</th>
<th>IC50 (nM)</th>
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<tbody>
<tr>
<td>αVβ3</td>
<td>4.4 ± 2.7</td>
</tr>
<tr>
<td>α5β1</td>
<td>4.2 ± 1.5</td>
</tr>
<tr>
<td>α6β1</td>
<td>6.8 ± 3.2</td>
</tr>
<tr>
<td>α7β1</td>
<td>121 ± 25</td>
</tr>
<tr>
<td>α6β4</td>
<td>&gt; 5,000</td>
</tr>
</tbody>
</table>

2. THR-687 potently inhibits endothelial cell migration
Integrins play a crucial role in endothelial cell migration and adhesion (Avraadimes et al, 2008). The inhibitory effect of THR-687 on HUVEC migration was investigated in the Oris™ cell migration assay. THR-687 potently inhibited HUVEC migration with an IC50 of 82 ± 11nM. Data shown below are average values ± SEM of at least 3 independent experiments.

3. THR-687 inhibits blood vessel outgrowth from ex vivo murine choroidal explants
As integrins are highly involved in (pathologic) angiogenesis, the anti-angiogenic potential of THR-687 was evaluated in a mouse microvascular explant model, which closely mimics in vivo choroidal angiogenesis (Rezzola et al, 2013; Shao et al, 2013). As shown in the representative graph below, THR-687 dose-dependently inhibited choroidal vessel outgrowth ex vivo with an IC50 of 1504 ± 270nM. Representative pictures of all concentrations are shown below. Data are average values ± SEM of at least 3 independent experiments.

CONCLUSION
THR-687 is a potent and safe drug candidate for the treatment of back-of-the-eye vascular diseases.

REFERENCES