Combining ISTH0036, an antisense oligonucleotide targeting Transforming Growth Factor beta 2 (TGF-β2) mRNA, with aflibercept as novel treatment strategy for neovascular retinal diseases

Presentation No.: 236
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Abstract

Purpose: Anti-VEGF agents represent the current main option for treatment of neovascular eye diseases. However, antiplatelet response and emerging resistance represent a significant clinical challenge. ISTH0036 is a 14-mer phosphorodiamidate locked nucleic acid-modified antisense oligodeoxynucleotide (gapmer) targeting TGF-β2 mRNA, and was shown to have potent anti-angiogenic, anti-proliferative, and anti-inflammatory effects in vitro studies. In vivo, with the function of its target, a decrease of epithelial to mesenchymal transition is suspected for ISTH0036, a process involved in retinal pigment epithelial (RPE) cell detachment during choroidal neovascularization (CNV). The aim of the study was to evaluate the anti-CNV efficacy and safety of ISTH0036, and to identify the potential of a combination in a murine model of laser-induced CNV following intravitreal (IVT) administration.

Methods: The effect of ISTH0036 was studied in a murine CNV model by performing 3 laser-induced burns on the choriocapillaris of C57Bl/6J mouse eyes. ISTH0036 and aflibercept were administered IVT gapmers (1.5 µM) via a single eye injection using a fluorescence angiography and spectral domain optical coherence tomography (SD-OCT).

Results: Mice treated with ISTH0036, aflibercept, or a combination of aflibercept and ISTH0036 had a significantly lower mean of CNV area compared to the vehicle group as measured between days 4 and 14. During this time, ISTH0036 showed a similar potency as aflibercept. The lowest percentage of CNV lesions on days 5 and 14 was found in the group treated with a combination of aflibercept and ISTH0036. In addition, alternative approach, CNV lesions in the combination group were not significantly lower compared with the vehicle group. The results indicated that the combination group had the highest number of grade 1 lesions, showing the most favorable shift away from grade 2 or higher CNV lesions.

Conclusions: Combining aflibercept with ISTH0036 resulted in significantly reduced CNV induction and severity in this mouse model. In head-to-head comparison, ISTH0036 was equivalent to aflibercept, when used as single agent. ISTH0036, with its novel mechanism of action and preclinical potency represents a promising new combination treatment strategy with aflibercept. Clinical evaluation of this approach is in planning.

ISTH0036 is a fully phosphorodiamidate 14-mer oligodeoxynucleotide (with a 3x3 LNA™ gapmer pattern) selectively targeting TGF-β2 mRNA.

Efficacy of ISTH0036 and/or Eylea on CNV formation

Figure 1: Effect of ISTH0036 and/or Eylea (atfibreceptor) on CNV formation

- Age-related Macular Degeneration (AMD)
- Diabetic Macular Edema (DME)
- Glaucoma
- Diabetic Retinopathy (DR)
- Proliferative Vitreoretinopathy (PVR)

• Uregulates VEGF-secretion by retinal pigment epithelial cells (RPE) and endothelial cells inducing neangiogenesis
• Drives Epithelial-to-mesenchymal degeneration of retinal pigment epithelial cells (RPE) and other retinal components, which are key to initiation of photoreceptor degeneration
• Promotes Fibrosis as terminal step of retinal degeneration

Efficacy of ISTH0036 and/or Eylea in Murine CNV Model

Figure 3: Time-dependent effect of ISTH0036 and/or Eylea (atfibreceptor) on CNV formation

Method: CNV was induced in male 7-8 week old C57Bl/6J mice (n=8-10). Animals were treated with ISTH0036 (5 µg) or Eylea (50 µg) at day 1, and followed for 14 days. Animals were euthanatized at day 14.

Results: Time-dependent decrease of CNV area was found for ISTH0036 in comparison to vehicle or control groups. In the Eylea group, a similar reduction of CNV area was observed. However, the combination of ISTH0036 and Eylea significantly reduced CNV area compared to the vehicle group.

Efficacy of ISTH0036 and/or Eylea in Murine CNV Model

Figure 4: Efficacy of ISTH0036 and/or Eylea (atfibreceptor) on CNV formation

Method: CNV was induced in male 7-8 week old C57Bl/6J mice (n=8-10). Animals were treated with ISTH0036 (5 µg) or Eylea (50 µg) at day 1, and followed for 14 days. Animals were euthanatized at day 14.

Results: In the ISTH0036 group, a significant reduction of CNV area was observed compared to the vehicle group. In the Eylea group, a similar reduction of CNV area was observed. However, the combination of ISTH0036 and Eylea significantly reduced CNV area compared to the vehicle group.

Efficacy of ISTH0036 and/or Eylea combination treatment

Method: CNV was induced in male 7-8 week old C57Bl/6J mice (n=8-10). Animals were treated with ISTH0036 (5 µg) or Eylea (50 µg) at day 1, and followed for 14 days. Animals were euthanatized at day 14.

Results: In the ISTH0036 group, a significant reduction of CNV area was observed compared to the vehicle group. In the Eylea group, a similar reduction of CNV area was observed. However, the combination of ISTH0036 and Eylea significantly reduced CNV area compared to the vehicle group.

Conclusions

- Time-dependent inhibition induced by single IVT administration of ISTH0036 (sequence-specific and dose-dependent effects) on CNV formation and vascular leakage, similar to that observed with aflibercept/Eylea
- Trend (non-statistically significant) for improved effect in the ISTH0036/aflibercept-treated combination group

ARTIK Annual Meeting
Helsinki, 24th May - 2nd June, 2018