Multikinase Inhibitor compound key points:

Therapeutic Areas: **Age Related Macular Degeneration (Wet)**

- **Mechanism of Action:** A potent and reversible multikinase inhibitor targeting a wide spectrum of tyrosine kinases involved in angiogenic and inflammatory related events. It shows activity on a number of kinases, including Yes, Src and KDR.
- **Patent protection:** 2020 and limited coverage until 2027.
- **Route of administration:** Topical (eyedrop)
- **Development Phase:** Preclinical. Time to IND: 1 year.
1. RATIONALE AND BACKGROUND

Age-related Macular Degeneration (AMD) is the leading cause of blindness among people over 50 years of age in developed countries. In the United States alone, 15 million people have AMD, with 2 million new cases each year (Sherris 2007). AMD is a slow degenerative disease resulting in destruction of the central retina, the macula, which leads to loss of central vision. AMD can be classified as either dry or wet. The majority of AMD is dry or non-neovascular and is characterized by macular drusen, geographic atrophy of RPE cells, and loss of photoreceptor cells. The hallmark of wet AMD, also known as exudative or neovascular, is choroidal neovascularization (CNV), a process by which abnormal new blood vessels from the choroid breach Bruch's membrane and spread under the retina, resulting in hemorrhage, scarring, or retinal detachment. AMD has a multifactorial pathogenesis and oxidative stress and immune alterations appear to contribute to the pathology of AMD.

AMD has emerged as a significant health problem among elderly individuals and has a major impact on their quality of life. Disease incidence is rising sharply and with the rapidly aging population, AMD is predicted to increase by 50% in 2020 (Rattner and Nathans 2006; Yeoh, Sims et al. 2006; Lottery and Trump 2007). The current standard of care for wet AMD is intravitreal injection with anti-VEGF agents to control CNV. Such agents include Macugen® (pegaptanib) and Lucentis® (ranibizumab). Although a significant amount of patients experience improvement and stabilization of vision, these agents have major limitations (Yeoh, Sims et al. 2006). Frequent dosing via intravitreal injection is required, thus there is an inherent risk of intraocular infection and trauma to ocular structures. These risks could potentially cause more loss of vision. Given these concerns, injections are only administered a certain number of times, but this is not ideal since AMD is a chronic disease. Accordingly, the window of opportunity remains open for the development of new drugs, especially in regards to route of administration, different mechanisms, and efficacy. Understanding the underlying pathogenesis and root cause of CNV is crucial in searching for a suitable treatment.

2. MARKET

In a recent report by AMD alliance, the global prevalence of vision impairment due to AMD was projected to increase from 33 million persons in 2010 to 40 million persons in 2020. It is also reported to be associated with direct health care system expenditure of $255 billion in 2010, increasing to $294 billion in 2020 and a health burden of 6 million Disability Adjusted Life Years (DALYs) in 2010, increasing to 7 million DALYS in 2020.

Current treatment options are both invasive and expensive. An eye drop formulation could offer cost, convenience, and patient adherence advantage. The key target population for which SAR397769 eyedrop formulation could be developed is adult patients with moderate-to-severe wet AMD who are either candidates for anti-VEGF treatment or are already on anti-VEGF treatment.

3. COMPOUND PROFILE

SAR397769 is a potent, competitive, and reversible multikinase inhibitor showing biochemical activity on a number of kinases involved in angiogenesis, vascular leakage, and inflammation. Relevant kinases targeted by SAR397769 include Yes and c-Raf (IC50=30 nM against both), which are downstream mediators of pathways coupled to angiogenesis and leakage. In summary, SAR397769 has the potential to impact the pathogenesis of a number of pro-inflammatory indications, in particular, age-related macular degeneration (AMD).
OCULAR FORMULATION DEVELOPMENT

Although topical administration (eye drops) is the most common delivery method for anterior eye diseases (e.g. dry eye syndrome), there are currently no marketed topical products for posterior eye diseases, with only few compounds in clinical trials.

Our topical formulation development focused on 2 goals simultaneously: Increasing drug solubility & increasing residence time.

Promising prototypes following detailed in vitro studies, were then screened in vivo for bioavailability and eye tissue distribution in Dutch-Belted rabbits in an iterative process where the main goal was to progressively increase the levels of SAR39776 reaching the posterior eye.

SUMMARY OF OCULAR PK SCREENING IN DUTCH BELTED RABBITS USING PROTOTYPE FORMULATIONS

A total of 5 different ocular formulations were developed for screening in PK studies. All formulations were dosed at 30 µL eye drop in each rabbit’s eye (Dutch-Belted) as a single administration except for formulation #3 that was tested as QD (formulation #3) and BID (referred to as formulation #4 in the figure below).

A comparison of the exposure in the posterior eye cup with the various ocular formulations tested is provided in Figure 1. Formulation #5 demonstrated the highest exposure in all ocular tissues followed by the formulation #3. No major differences were observed between a single administration of #3 (Formulation #3 line) and two administrations, 12 hours apart (Formulation #4 line).

In vivo study observations showed that drug reached all posterior eye tissues from all formulations and that sustained drug levels were observed in some tissues up to the last time point assessed (48 hours or 144 hours). Furthermore, no signs of redness, itching, excessive blinking, or irritation in any of the rabbits noted.
Detailed analysis of PK data comparing all prototype formulations demonstrated that plasma levels were low from all prototypes and hence systemic (pulmonary) toxicity was not a concern.

**INVIVO PHARMACOLOGY**

The pre-clinical efficacy of topical SAR397769 in an eye drop formulation (Formulation #3) was assessed in a laser-induced model of macular degeneration (LIMD) in the pigmented rat.

The results showed that topical SAR397769 significantly reduced the development of CNV volume in the rat LIMD model similarly at all three doses (see Table 1). Oral SAR397769 dosed BID was used as a positive control/ comparator and reduced CNV by 66.3% (p<0.0001).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Median (µm³)</th>
<th>Interquartile Range</th>
<th>p value</th>
<th>% Inhibition of CNV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>23</td>
<td>160073.63</td>
<td>118865.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.1% QD SAR397769</td>
<td>21</td>
<td>69291.22</td>
<td>64157.64</td>
<td>0.0039</td>
<td>56.7</td>
</tr>
<tr>
<td>0.1% BID SAR397769</td>
<td>22</td>
<td>50746</td>
<td>84524.43</td>
<td>&lt;0.0001</td>
<td>68.3</td>
</tr>
<tr>
<td>0.1% TID SAR397769</td>
<td>25</td>
<td>58008.63</td>
<td>53090.75</td>
<td>&lt;0.0001</td>
<td>63.7</td>
</tr>
<tr>
<td>10 mg/kg SAR397769 p.o. BID</td>
<td>26</td>
<td>53959.14</td>
<td>43940.72</td>
<td>&lt;0.0001</td>
<td>66.3</td>
</tr>
</tbody>
</table>

The pharmacokinetic results obtained in parallel of the efficacy study in the plasma, anterior segment and posterior segment showed high drug exposure in the target tissue, the posterior eye cup, after multi-day dosing with minimal systemic exposure.

SAR397769 levels in the anterior eye cup were also detected, but decreased rapidly within an hour. The exposure levels of compound in the posterior segment at 30 minutes at the topical administration and at oral administration were very similar. This may explain the similar efficacy shown by all the doses/frequencies administered. After 4 hrs, SAR397769 levels decrease, but still remain relatively high in the posterior eye cup.

This study (presented at Association of Research in Vision and Ophthalmology conference in 2011) provided the first non-clinical proof of principle for future studies to evaluate the topical formulation of SAR397769 in other animal models and subsequently humans. It is speculated the SAR397769 could target the VEGF-related angiogenic and leakage effects that occur in the posterior segment of the eye after CNV.

**5. PRELIMINARY OCULAR SAFETY PROFILE**

A specific ocular tolerance study was performed to evaluate the tolerance SAR397769, when administered up to 5 times daily for 5 days via topical instillation to rabbits. Assessment of ocular tolerance was based on ocular irritation scoring, clinical ophthalmic examinations, esthesiometry, and anatomic pathology. Assessment of general animal health was assessed based on mortality, clinical signs, body weights, and qualitative food consumption. In conclusion, no compound-related changes were observed following topical ocular administration of the vehicle control article or SAR397769 up to 5 times daily for 5 days to Dutch Belted rabbits.
6. VALUE PROPOSITION

SAR397769 has the potential to revolutionize treatment of AMD by utilizing a convenient route of delivery (ocular) approach to be used in adjunction to injections of anti-VEGF and leading to a clinically significant synergistic effect in improving visual acuity, colour perception, contrast sensitivity or visual fields. It allows a significant incremental proportion of patients over anti-VEGF to avoid legal blindness and to recover independence by restoring ability to perform activities of daily living such as reading or driving.

7. REFERENCES


8. CONTACTS

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