Clinical Evaluation of Belzupacap Sarotalocan (AU-011), a First-in-Class Targeted Therapy for Choroidal Melanoma with Intravitreal or Suprachoroidal Route of Administration

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Leiden University
Targeted Oncology Platform - Virus-Like Drug Conjugates (VDCs)

Virus-Like Particles Conjugated to a Cytotoxic Payload to form the VDC

VDCs can Recognize Tumor Associated HSPGs*

Technology Platform Designed to Target a Broad Range of Solid Tumors Based on Virus-Like Particles with Multiple Options for Cytotoxic Payloads

Kines et al; International Journal of Cancer, 138;901–911, February 2016; Kines et al; Molecular Cancer Therapeutics, 17(2) February 2018; Kines et al; Cancer Immunology Research, May 2021

* HSPGs: Heparan Sulphate Proteoglycans
Belzupacap Sarotalocan (AU-011) is a VDC with a Novel Dual Mechanism of Action

Belzupacap Sarotalocan
Belzupacap sarotalocan is a novel VDC that consists of a VLP conjugated to ~200 molecules of phthalocyanine dye

Potential Key Differentiation: Physical Ablation May Reduce Risk to Develop Resistance and is Genetic Mutation Agnostic

Kines et al; Cancer Immunology Research, May 2021
Completed Phase 1b/2* – Key Patient Populations and Objectives

**Primary Objective: Safety**
- Drug or treatment related adverse events (AEs) / serious adverse events (SAEs)

**Secondary Objective: Efficacy**
- Tumor thickness growth rate before and after treatment
- Local tumor control
- Visual acuity preservation
- ≥ 0.3mm tumors thickness within 2 years of screening

All Subjects Evaluated for Safety and Efficacy
Subjects with Small Tumors with Active Growth Treated with Two Cycles Evaluated for Efficacy

All Patients Enrolled with Clinical Diagnosis of Choroidal Melanoma or Indeterminate Lesions

- Safety Evaluation (All Treated)
- Efficacy Evaluation
  - Therapeutic Regimen (2 Cycles)

All Treated Patients

- All Patients Treated with 2 Cycles
- All Patients with Small Tumors with Active Growth Treated with 2 Cycles

n=56

n=20

n=14

AU-011-101 *NCT03052127
Phase 1b/2 – Tumor Control Achieved with Therapeutic Regimen

Completed Ph1b/2 IVT trial (AU011-0101), post-SOC data not included

Progression Definition:
- Tumor Height Increase >0.5mm
- LBD >1.0mm due to definitive Tumor Growth (i.e., not judged by the Investigator to be due to inflammation/swelling, hemorrhage or pigmentary changes) and not treated with standard of care

<table>
<thead>
<tr>
<th>Populations</th>
<th>Total Patients (n)</th>
<th>Tumor Control Rate (at 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Doses/Regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Treated Patients</td>
<td>56</td>
<td>54% (30/56)</td>
</tr>
</tbody>
</table>

| **Lower Doses/Regimens** | | |
| All Treated Patients up to 1 Cycle (Cohorts 1-9) | 36 | 44% (16/36) |

| **Therapeutic Dose/Regimen - 2 Cycles** | | |
| All Patients | 20 | 70% (14/20) |
| All Patients with Small Tumors with Active Growth | 14 | 64% (9/14) |

**Results Support the Potential Use of Belzupacap Sarotocalan as First Line Treatment for Choroidal Melanoma, Potentially Avoiding the Need for Radiotherapy in Many Patients**
Phase 1b/2 – Statistically Significant Growth Rate Reduction

Reduction in Tumor Growth Rate is Statistically Significant and Supports Planned Pivotal Key Endpoint

### Change in Tumor Growth (mm/yr)
**Small Tumors with Active Growth (n=14)**

<table>
<thead>
<tr>
<th>Historical Growth Rate (mm/yr)</th>
<th>AU-011 Growth Rate over 12 months (mm/yr)</th>
<th>Growth Rate Reduction (mm/yr)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.555</td>
<td>0.072</td>
<td>-0.483</td>
<td>0.018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with Small Tumors with Active Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
</tr>
</tbody>
</table>

- Many patients had a zero or negative growth rate after treatment with belzupacap sarotalocan
- Disease-modifying effect supports tumor is inactive and malignant cells have been targeted by belzupacap sarotalocan

### Change in Tumor Growth
Follow up 12 months

- p=0.018, n=14
- Completed Ph1b/2 IVT trial (AU-011-101)

Tumor thickness growth rates/ slopes estimated using MMRM
**Phase 1b/2 – Visual Acuity was Preserved in Majority of Patients**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Total Patients (n)</th>
<th>Vision Preservation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Dose Cohorts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Treated Patients</td>
<td>56</td>
<td>86% (48/56)</td>
</tr>
<tr>
<td>Patients with Active Growth - High Risk for Vision Loss</td>
<td>17</td>
<td>76% (13/17)</td>
</tr>
<tr>
<td><strong>Therapeutic Regimen (2 cycles)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Treated Patients</td>
<td>20</td>
<td>75% (15/20)</td>
</tr>
<tr>
<td>Patients with Active Growth</td>
<td>14</td>
<td>71% (10/14)</td>
</tr>
</tbody>
</table>

1 patient had loss ≥15 letters at Week 52 visit which recovered within 15 letters at the next visit which was ~3 weeks after standard of care (SOC); all other post-SOC data excluded for all subjects. Completed Ph1b/2 IVT trial (AU-011-101).

- Vision loss was transient but recovered in most patients after inflammation or transient AEs resolved.
- Vision was preserved in most patients with tumors near the fovea or optic nerve that had a high risk for vision loss.

Vision Loss was Transient but Recovered in Most Patients after AE Resolution
Vision was Preserved in a Majority of Patients.
Ph 1b/2 Safety: Belzupacap Sarotalocan was Well Tolerated
Majority of Adverse Events (AEs) were Transient and Managed with Standard of Care Treatment

<table>
<thead>
<tr>
<th>All Treated Subjects (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Treatment Related Adverse Events (≥10% Subjects)</td>
</tr>
<tr>
<td>Vitreous Inflammation</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
</tr>
<tr>
<td>Increase in Intraocular Pressure</td>
</tr>
<tr>
<td>Peritumoral RPE/ Pigmentary Changes</td>
</tr>
<tr>
<td>Keratic Precipitates</td>
</tr>
<tr>
<td>Floaters/ Vitreous Opacity</td>
</tr>
<tr>
<td>Decreased Visual Acuity/ Vision Loss</td>
</tr>
<tr>
<td>Eye Pain/ Soreness</td>
</tr>
<tr>
<td>Corneal Abrasion/ Epithelial Defect</td>
</tr>
<tr>
<td>Corneal Edema</td>
</tr>
</tbody>
</table>

Treatment Related Serious Adverse Events (n=56)

| Vision Loss (juxtafoveal tumor) | 3.6% | 3.6% |

Table presents percentage of subjects with AEs related to AU-011 or laser by severity and overall; subjects with more than 1 AE are counted in the highest severity group.

Anterior inflammation, keratic precipitates treated with topical steroid drops; vitreous inflammation treated with topical, oral or peri- or intraocular steroids; IOP treated with topical anti-hypertensives

*2 subjects treated with vitrectomy – 1 with vitreous opacity and another with persistent vitreous inflammation

*SAEs are listed separately.
Suprachoroidal Administration Optimizes Delivery to the Posterior Segment – More Targeted Delivery to the Tumor

Optimize therapeutic index
- 5x higher tumor exposure with SC versus IVT observed in pre-clinical model
- Lower levels in the vitreous translates into lower risk of Intraocular Inflammation and vitreous floaters

Optimize treatment parameters
- Shorter time to laser activation

May increase potential patient population
- Medium choroidal tumors
- Choroidal Metastases

PK studies in rabbit tumor model demonstrate higher tumor bioavailability with SC administration

Evaluating Suprachoroidal Administration to Determine Optimal Administration Route for Pivotal Trial

**Single Dose Cohorts – Completed**

- **Cohort 1 (n=1)**: 20 μg x 1 Laser
- **Cohort 2 (n=3*)**: 40 μg x 1 Laser
- **Cohort 3 (n=2)**: 40 μg x 2 Lasers

**Multiple Dose Cohorts**

- **Cohort 4 (n=3)**: 40 μg x 2 Lasers QWx2
- **Cohort 5 (n=3)**: 40 μg x 2 Lasers QWx3 Up to 3 cycles
- **Cohort 6 (n=10)**: 80 μg x 2 Lasers QWx3 Up to 3 cycles

**Objective:**

- Determine the optimal dose and therapeutic regimen with suprachoroidal administration
- Apply route, dose and regimen to pivotal portion of the trial

**18 subjects enrolled**

- Cohort 6 currently enrolling
- 80μg dose and 3 cycles of therapy
  - Tumor thickness ≥0.5 mm and ≤2.5 mm
  - LBD ≤10 mm
  - Tumor growth within 3 mo -2 years of screening
  - Growth rate ≥ 0.2 mm/yr and <1.5 mm/yr
  - 6 subjects

*2 subjects were planned; third subject was additionally enrolled due to dose error in 1 subject*
Phase 2 SC – Demonstrated Favorable Safety Profile To Date

Preliminary results

- Majority of AEs were transient and resolved without clinical sequelae
- No DLTs†, no significant vitritis to date through 3 cycles with 80 µg of belzupacap sarotalocan
- 4 moderate severity events related to injection procedure - scleritis, subconjunctival hemorrhage, conjunctival edema and eye irritation. All other injection related events were mild
- 6 non-treatment related SAEs reported in 3 subjects^  
- No pigmentary changes observed at edge of tumor treatment

### All Treated Subjects (n=18)

<table>
<thead>
<tr>
<th>Treatment Related Adverse Events (&gt;5%)</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior chamber cell/ inflammation</td>
<td>22.2%</td>
<td>0</td>
<td>0</td>
<td>22.2%</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>5.6%</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>16.7%</td>
<td>0</td>
<td>0</td>
<td>16.7%</td>
</tr>
<tr>
<td>Cystoid macular edema</td>
<td>5.6%</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>5.6%</td>
<td>5.6%</td>
<td>0</td>
<td>11.1%</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>5.6%</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
</tr>
<tr>
<td>Ocular discomfort</td>
<td>5.6%</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
</tr>
<tr>
<td>Photophobia</td>
<td>5.6%</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>11.1%</td>
<td>0</td>
<td>0</td>
<td>11.1%</td>
</tr>
<tr>
<td>Pupils unequal</td>
<td>5.6%</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
</tr>
<tr>
<td>Retinal pigment epitheliopathy</td>
<td>5.6%</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
</tr>
<tr>
<td>Salivary gland enlargement*</td>
<td>0</td>
<td>5.6%</td>
<td>0</td>
<td>5.6%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>5.6%</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
</tr>
<tr>
<td>Afferent pupillary defect (term not coded yet)</td>
<td>5.6%</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

Table presents percentage of subjects with AEs related to AU-011 or laser by severity and overall; subjects with more than 1 AE are counted in the highest severity group

Data cutoff Jun 1, 2022

* Likely related to COVID vaccine per investigator

AU-011-202 NCT04417530

Favorable Tolerance in Early Cohorts with no Related SAEs/DLTs Observed to Date

† DLTs: Dose Limiting Toxicities, ^retinal detachment, ischemic CRVO, brain abscess, deep vein thrombosis, sarcoma, seizure
Belzupacap Sarotalocan Ocular Oncology Development Program

**Choroidal Melanoma**

Demonstrated safety and efficacy with IVT and safety with SC supports starting a pivotal trial in primary indeterminate lesions and small choroidal melanoma

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**Choroidal Metastasis (CMets)**

Dose-dependent activity in vivo using syngeneic mouse models for cancer types known to metastasize to the choroid
- Significantly inhibits tumor growth and prolongs survival
- Statistically significant results in multiple tumor models seen in CMets (breast, lung, etc.)

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**In Combination with ICIs***

Belzupacap sarotalocan plus ICIs (anti-PD-L1 & anti-LAG-3) showed potential to induce complete and lasting tumor responses in both primary and distant tumors in murine models – to be presented in detail tomorrow

*ICIs – immune checkpoint inhibitors

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Study Results Support Further Evaluation Of Belzupacap Sarotalocan As a Potential Treatment For Ocular Cancers

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