Corporate Presentation

September 9, 2019
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Overview of Aerpio

• Developing first-in-class treatments for ocular diseases and complications of diabetes
• Lead product candidate: AKB-9778, a Tie2 activator, which is a key regulator of vascular stability and ocular fluid outflow
• Completed TIME-2b Phase 2 clinical trial in patients with non-proliferative diabetic retinopathy and evidence of Tie2 activation based on:
  – Reproduced the statistically significant reduction in intra-ocular pressure (IOP) seen in TIME-2
  – Reproduced evidence of improved kidney function (UACR) in patients early diabetic nephropathy
• Pipeline opportunities
  – Phase 1b of topical ocular AKB-9778 for evaluation in open-angle glaucoma ongoing
  – Seeking a pharma partner to further study slowing diabetic nephropathy of subcutaneous AKB-9778
  – Gossamer partnership on GB004: up to $400M in milestones, tiered royalties to mid-teens, option to participate in sale of GB-004
  – ARP-1536 humanized Mab that activates Tie2:
    • NIH funded for development as an intravitreal adjunct to anti-VEGF therapy in diabetic macular edema
    • Potential for subcutaneous administration for diabetic nephropathy
• Balance sheet of - $48.2mm at end Q2 ‘19 expected to be sufficient to fund planned operations to mid-2021
Tie2 Biology & the Critical Role of VE-PTP in Regulating Tie2 Activation
**Tie2** is a transmembrane receptor found on endothelial cells (EC), the foundation for vascular stability, and for formation and maintenance of Schlemm’s canal (SC) and the conventional outflow tract (CO) in the eye.

**Tie2** activity...
- Maintains integrity of endothelial cell junctions
- Enhances endothelial cell function and viability
- Inhibits vascular inflammation

**Inactive Tie2 = Vascular Destabilization**
- Promotes elevated intra-ocular pressure and pathologic vascular leak, neovascularization
Inhibiting VE-PTP with AKB-9778 restores Tie2 activation and endothelial cell stability even in absence of Ang1

Ang-1 = Angiopoietin 1
Ang-2 = Angiopoietin 2
VE-PTP = Vascular endothelial protein tyrosine phosphatase
AKB-9778: Primary Open-Angle Glaucoma
The ANGPT/Tie2 Pathway Plays a Key Role in Maintenance of Schlemm’s Canal

- In the normal CO pathway, Tie2 is active, and ECs of the inner wall of SC, adjacent to the trabecular meshwork, support the formation of giant vacuoles which provide a conduit for aqueous humor drainage.

- Loss of ANGPT/TIE2 pathway activation leads to loss of SC endothelial cell specialization, ultimately resulting in SC degeneration, increased IOP and glaucomatous retina pathology.

- **Hypothesis:** Restoring Tie2 activation will restore SC integrity and improve conventional outflow facility resulting and decreased IOP and reduced progression of glaucoma.
TIME-2: Three-month Phase 2 study in patients with DME

- **STUDY VISITS**
  - **PLACEBO** subcutaneous BID
    - 3 SHAM injections q4
  - **15 mg AKB-9778** subcutaneous BID
    - 3 doses intravitreal **LUCENTIS** (0.3 mg) q4
  - **9 mg AKB-9778** subcutaneous BID
    - 3 SHAM injections q4

- **N=144**
  - **R 1:1:1**

- **AKB-9778 15mg SC BID**
  - Intravitreal **LUCENTIS** injection
  - Sham injection

- **Placebo SC BID**
  - IOP measured at baseline and monthly during active treatment
TIME-2 Study: AKB-9778 15mg BID Shows Significant IOP Reduction in a Pressure Dependent Manner

Brigell et al. ARVO 2018 Abstract Number 1252
Tie2 Pathway Activation is Critical for Development and Maintenance of Schlemm’s Canal and Conventional Outflow: Mouse and Human Genetic Data

- Tie2 KO or Angpt-1/2 KO in mice results in congenital glaucoma due to Schlemm’s canal development
- Families with Tie2 LOF mutations associated with congenital glaucoma
- Several loci support an important role of Tie2/ANGPT signaling in IOP regulation.

Mice and humans with LOF Angpt-1 mutations associated with congenital glaucoma

Genome-wide analyses identify 68 new loci associated with intraocular pressure and impact risk prediction for primary open-angle glaucoma.
TIME-2b: Clinical Trial Design

- Phase 2b study in pts with moderate to severe non-proliferative diabetic retinopathy (NPDR) without DME
- 1° Endpoint: ≥ 2-step improvement in DRSS at 48 weeks
- Key 2° Endpoints: development of DME/PDR, DR progression, renal function, IOP
- Enrollment commenced June 2017, enrollment closed February 2018 at 167 patients
- Top-line data announced March 18, 2019

**N=150 R 1:1:1**

**STUDY VISITS**

- Day 1
- Week 4
- Week 8
- Week 12
- Week 16
- Week 20
- Week 24
- Week 28
- Week 32
- Week 36
- Week 40
- Week 44
- Week 48

- 15 mg AKB-9778 subcutaneous BID
- Placebo subcutaneous QD + 15 mg AKB-9778 subcutaneous QD
- Placebo subcutaneous BID

**Abbreviations**

- **DME** – Diabetic macular edema
- **DR** – Diabetic retinopathy
- **DRSS** – Diabetic retinopathy severity score
- **PDR** – Proliferative diabetic retinopathy
TIME-2b: Top-Line Results

- Twice daily subcutaneous dose increased improvement in DRSS compared to placebo but not clinically or statistically significant
  - Established need for concomitant anti-VEGF therapy to improve diabetic retinopathy
- Generally well tolerated
- Dizziness AE 10.9% in AKB-9778 BID vs 7.0% in the placebo arm (vast majority rated as mild, and none rated as severe)
- Headache AE of 10.9% in AKB-9778 BID vs 3.5% in the placebo arm (all rated as mild)
- Withdrawals due to AE and SAEs were balanced between AKB-9778 BID and placebo groups
TIME2b: IOP Effects of Subcutaneous AKB-9778 Confirmed and Extended in 48 Week Trial*

- Clear IOP reduction in both QD and BID groups with trend favoring dose dependence
- Week 24 IOP measured **predose** (red ovals) shows a persistent IOP effect that supports QD dosing (BID >12hr since prior dose; QD >24hr since prior dose)

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* MMRM (Mixed-Effect Model Repeated Measures) Analysis LOCF:
  Within Treatment Change from Baseline – AKB-9778 QD $p = 0.04$; AKB-9778 BID $p < 0.0001$
  AKB-9778 Group vs Placebo – AKB-9778 QD $p = 0.0553$; AKB-9778 BID $p < 0.0002$
TIME2b: Effect of AKB-9778 on Systolic BP
Dose Related IOP Decrease Observed After Topical Ocular Administration of AKB-9778

Normotensive New Zealand White Rabbits

- IOP lowering is dose dependent (40 mg/ml > 15 mg/ml) and is persistent 24 hours post-dose (Day 8)
- IOP lowering by topical dosing (40 mg/ml group) was greater than SC dosing (10 mg/kg)
VE-PTP is Co-Expressed with Tie2 in Schlemm’s Canal Endothelium and Topical Ocular Dosing of AKB-9778 Activates Tie2

- VE-PTP (purple color) and Tie2 (red color) are expressed in Schlemm’s canal endothelium (PECAM-1 positive cells; green color)

- Administration of a single topical ocular dose of AKB-9778 activates Tie2 (pTie2; red color) in Schlemm’s canal endothelium

Stamer et al. ARVO 2019 Abstract Number 2186
Topical AKB-9778 Lowers IOP by Increasing Outflow Facility in Ocular Normotensive Mice

- Topical ocular AKB-9778 reduces predose IOP gradually over three days of dosing (Panel A)
- On Day 3 IOP is substantially lower at 2 and 4 hours post-dose (Panel B)
- IOP lowering on Day 3 is associated with increased outflow facility (Panel C)

Stamer et al. ARVO 2019 Abstract Number 2186
Topical AKB-9778 in Primary Open-Angle Glaucoma

Near-Term Development Plan

- Initiate Phase 1b study: Q1 2019
- Top-line results from Phase 1b study: Q3 2019
- Initiate 28-day Phase 2a study: Q1 2020
- ARVO data presentation: Q3 2019

2019
2020
Commercial Opportunity in Glaucoma

- **2018 US Market:** $3B
  - Half of volume is first-line prostaglandins (mostly generics)
  - Half of volume is 2-3X/day adjuncts

- **2017 EU5 Market:** $1B
- **2017 JP Market:** $0.8 B

Sources: Aerie Corporate Presentation – March 2019

- **AKB-9778** could be the first drug targeting the site of pathology – Schlemm’s Canal

CAI: carbonic anhydrase inhibitor; AA: alpha agonist; BB: beta blockers

Source: Cowen and Company 2018 Therapeutics Conference

**Novel, Additive IOP-Lowering Agents For Glaucoma Are Badly Needed**

The vast majority of our surveyed physicians believe that approximately 20-40% of patients are treated with second-line or two concurrent IOP-lowering agents. Yet, physicians are still unsatisfied with available options and are demanding agents with new, safe, mechanisms of action.
• Mouse and human genetic data support a role for the Tie2 pathway in development and maintenance of Schlemm’s canal and conventional outflow facility

• In ocular normotensive patients, subcutaneous AKB-9778, a VE-PTP inhibitor and Tie2 activator, reduces IOP in a pressure dependent manner

• In mice, VE-PTP and Tie2 are co-expressed in SC and topical ocular AKB-9778 increases Tie2 activation in SC resulting in enhanced outflow facility and reduced IOP

• In rabbits, topical ocular AKB-9778 reduces IOP more than subcutaneous dosing, an effect that persists 24 hours post dose

• Data supports pursuing topical ocular AKB-9778 as the first SC targeted OHT/OAG therapy
  – Phase 1b MAD study in normal subjects on-going with results in Q4 2019
AKB-9778: Kidney Function TIME-2 and TIME-2b Data
TIME-2b Data – Prespecified UACR Endpoint

Prespecified Endpoint: Percent Change in UACR for Patients with Baseline Proteinuria (≥ 30 mg/g) – All Patients and Patients On ACEi/ARB Therapy

Change in UACR at Week 48 in Subjects with Baseline Albuminuria (LOCF)

- AKB-9778 QD (n=23)
- AKB-9778 BID (n=29)
- Placebo (n=29)

Change in UACR at Week 48 in Subjects on ACEi/ARBs with Baseline Albuminuria (LOCF)

- AKB-9778 QD (n=11)
- AKB-9778 BID (n=23)
- Placebo (n=18)

% Change in Geometric Mean
UACR – Urine albumin/creatinine ratio
TIME-2 UACR Data: Baseline Proteinuria Subgroup (≥ 30 mg/g)

SC – Subcutaneous
UACR – Urine albumin/creatinine ratio
p = 0.03, unadjusted (All SC AKB-9778 vs. SC placebo)
p = 0.006, adjusted for baseline UACR, HgbA1c, and systolic blood pressure (All SC AKB-9778 vs SC placebo)
VE-PTP Knockout Activates Tie2 and Protects the Hypertensive, Diabetic Kidney

VE-PTP expression (blue) in renal vasculature

- VE-PTP is upregulated by hypoxia and hyperglycemia\(^1,2\)
- VE-PTP is markedly upregulated in diabetic and in hypertensive mice\(^2\)
- Normal mice with VE-PTP knockout have increased Tie2 and eNOS activation, decreased blood pressure, higher glomerular filtration rates, and normal glomeruli\(^2\)
- Hypertensive, diabetic mice have increased VE-PTP, decreased Tie2 activation, glomerular scarring and proteinuria\(^2\)
  - When crossed with VE-PTP knockout mice, glomerular scarring, fibrosis and proteinuria were all significantly decreased with no effects on glucose levels

VE-PTP – Vascular endothelial protein tyrosine phosphatase; Aerpio data on file

\(^1\) Shen et al. Journal of Clinical Investigation, 2014
\(^2\) Carota et al. Journal of Experimental Medicine, 2019
Diabetic Kidney Disease is a Major Healthcare Burden

~30 million diabetics in the United States

- The overall prevalence of CKD in the general population is approximately 14 percent
- More than 661,000 Americans have kidney failure
- 468,000 individuals are on dialysis
  - $89,000 per year
  - $42 billion per year in the US
- 193,000 live with a functioning kidney transplant
- Each year, kidney disease kills more people than breast or prostate cancer

Approximately 40% have kidney disease

https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease
https://pharm.ucsf.edu/kidney/need/statistics
GB004 (formerly AKB-4924): Inflammatory Bowel Disease
GB004 (formerly AKB-4924) Activity Observed in Multiple Models of IBD

- Pre-clinical proof-of-concept across multiple models of IBD in both the induction and maintenance setting
  - TNBS-induced colitis
    - Wild type mice (below)
    - Chronic granulomatous disease mice
  - DSS-induced colitis
  - Genetic TNFα overexpression induced Crohn’s Disease
  - Gut Graft Versus Host Disease

DSS – dextran sodium sulfate
IBD – inflammatory bowel disease
TNBS – trinitrobenzene sulphonic acid
TNFα – tumor necrosis factor alpha
GB004/AKB-4924 in Inflammatory Bowel Disease

- First-in-class, HIF-1α stabilizer for IBD
- Designed to address major unmet needs in IBD
- Profile in preclinical models and early human studies support a preferred profile for moderate/severe and potentially earlier stage disease vs. current standard of care
- Oral, once-daily route of administration
- Per Gossamer:
  - Phase 1 MAD complete, GB004 was generally well tolerated w no SAEs reported
  - Proof-of-concept data anticipated in 1H 2020
  - Plan to initiate Phase 2 trial in UC in 1H 2020

HIF-1α—hypoxia inducible factor-1 alpha
IBD—inflammatory bowel disease
MAD—multiple ascending dose
UC—ulcerative colitis
Partnership with Gossamer Bio

- Gossamer Bio founded by former Receptos team of Faheem Hasnain and Sheila Gujrathi, MD
  - Receptos sold to Celgene in 2015 for $7.2 billion after Phase 2 IBD and MS trials
- $20 million upfront payment for exclusive worldwide rights to AKB-4924 (now named GB004)
- $400 million in potential development and commercial milestones
- Tiered royalties ranging from high single-digit to mid-teens percentages on annual sales
- Potential option to participate in sale of GB004 in exchange for relinquishing existing royalty and milestones
Milestones and Summary
Expected Near-Term Milestones

AKB-9778 in POAG (eye drops)
AKB-4924/GB004 in IBD**

Initiate Phase 1b study
Top-line results from Phase 1b MAD study
Initiate 28-day Phase 2a study

Q1 2019: Top-line results from MAD study
Q2 2019: Initiate Phase 1b study
Q3 2019: Top-line results from Phase 1b MAD study
Q4 2019: Initiate 28-day Phase 2a study
Q1 2020: Top-line results from Phase 1b study 1H 20
Q2 2020: Plan to initiate P2 in UC 1h 20

MAD – Multiple ascending dose
POAG – Primary open angle glaucoma
UC – Ulcerative colitis
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