IVERIC BIO

DEVELOPING TRANSFORMATIVE THERAPIES
FOR RETINAL DISEASES

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NASDAQ: ISEE

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In this presentation, the Company's forward-looking statements include statements about the significance and implications of the Company's GATHER2 clinical trial evaluating avacincaptad pegol (ACP or Zimura) for the treatment of geographic atrophy, and the potential utility of ACP. Such forward-looking statements involve substantial risks and uncertainties that could cause the Company's research and development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the progress and results of clinical trials and other research and development programs, developments from the scientific and medical community and from the Company's competitors, and other factors discussed in the "Risk Factors" section contained in the quarterly and annual reports that the Company files with the Securities and Exchange Commission.

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GATHER 2
Geographic Atrophy Therapy Trial

GATHER2 Pivotal Phase 3 Study Results:
Safety of Intravitreal Avacincaptad Pegol in Geographic Atrophy

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Avacincaptad Pegol is an investigational product that has not been evaluated for safety and efficacy by the FDA

Disclosures

Dr. Heier

- **Consultant:**
  Abpro, Adverum, Aerie, AffaMed, Allegro, Allergan, Allgenesis Biotherapeutics, Annexon Biosciences, Apellis Pharmaceuticals, Aprea Therapeutics, AsclepiX Therapeutics, Aviceda Therapeutics, Bionic Vision Technologies, Chengdu Kanghong Biotechnology, DTx Pharma, Eloxx Pharmaceuticals, 4D Molecular Therapeutics, Galimedix Therapeutics, Genentech/Roche, Graybug Vision, Gyroscope, Horizon Therapeutics, **Iveric Bio**, LensGen, NGM Biopharmaceuticals, Novartis, Ocular Therapeutix, Oriole, Oxurion, Palatin Technologies, Regeneron Pharmaceuticals, REGENXBIO, Roche, Santen Pharmaceutical, SciFluor Life Sciences, Stealth BioTherapeutics, Surrozen, Laboratoires Théa, Verseon, Vinci

- **Research:**
  Apellis Pharmaceuticals, AsclepiX Therapeutics, Aviceda Therapeutics, Bayer, Chengdu Kanghong Biotechnology, Genentech/Roche, Gyroscope, Hemera Biosciences, **Iveric Bio**, Kodiak, NGM Biopharmaceuticals, Notal Vision, Novartis, Regeneron Pharmaceuticals, REGENXBIO, Stealth BioTherapeutics

- **Financial:**
  Adverum, Aldeyra Therapeutics, Allegro, Aviceda Therapeutics, Digital Surgery Systems, DTx Pharma, jCyte, Ocular Therapeutix, Vinci

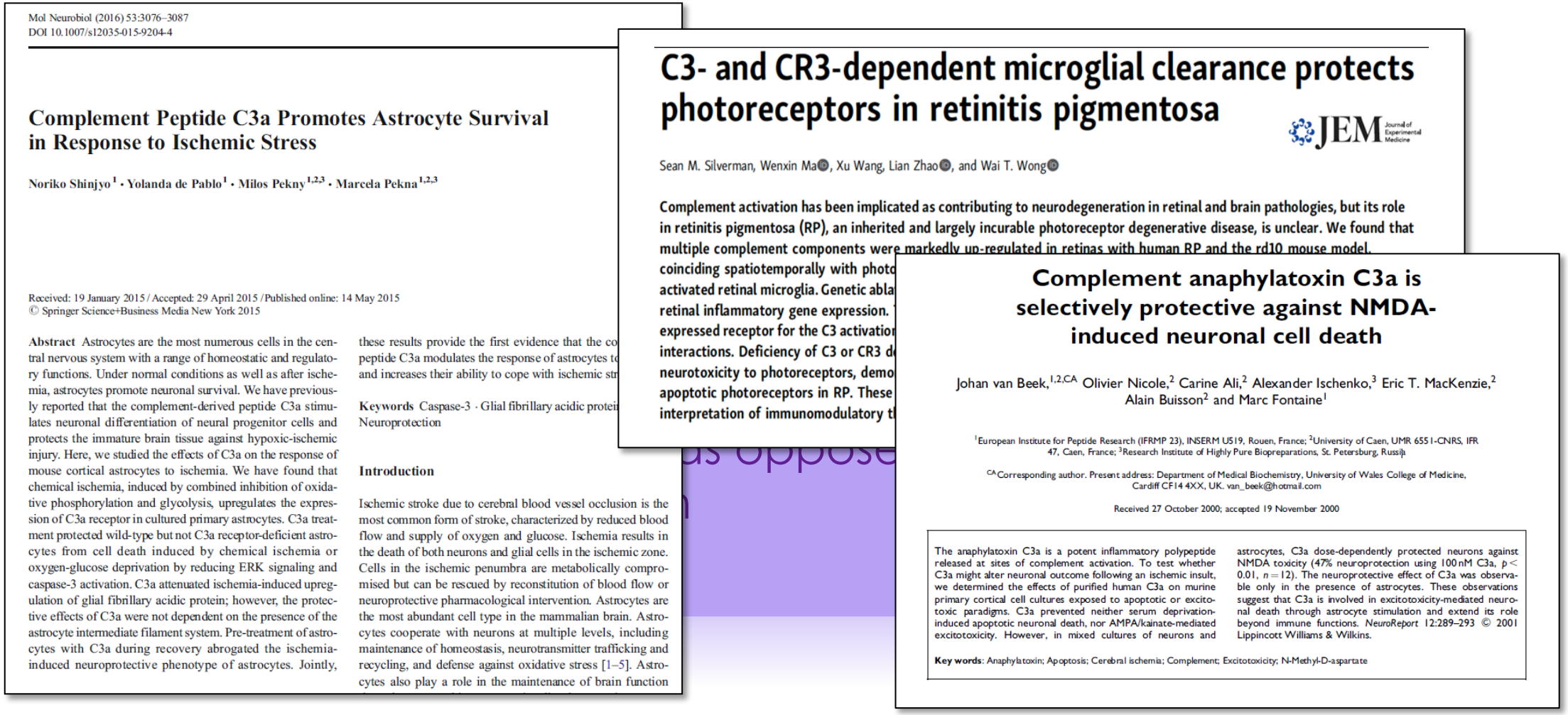
Avacincaptad pegol: An aptamer which inhibits C5

AVACINCAPTAD PEGOL

- **A pegylated RNA aptamer**
  - Relatively small physical size
  - Synthetic, as opposed to biological, production

RNA, ribonucleic acid.

Avacincaptad pegol: An aptamer which inhibits C5, leaves the other beneficial parts of the complement system intact



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Complement Peptide C3a Promotes Astrocyte Survival in Response to Ischemic Stress

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Abstract Astrocytes are the most numerous cells in the central nervous system with a range of homeostatic and regulatory functions. Under normal conditions as well as after ischemia, astrocytes promote neuronal survival. We have previously reported that the complement-derived peptide C3a stimulates neuronal differentiation of neural progenitor cells and protects the immature brain tissue against hypoxic-ischemic injury. Here, we studied the effects of C3a on the response of mouse cortical astrocytes to ischemia. We have found that chemical ischemia, induced by combined inhibition of oxidative phosphorylation and glycolysis, upregulates the expression of C3a receptor in cultured primary astrocytes. C3a treatment protected wild-type but not C3a receptor-deficient astrocytes from cell death induced by chemical ischemia or oxygen-glucose deprivation by reducing ERK signaling and caspase-3 activation. C3a attenuated ischemia-induced upregulation of glial fibrillary acidic protein; however, the protective effects of C3a were not dependent on the presence of the astrocyte intermediate filament system. Pre-treatment of astrocytes with C3a during recovery abrogated the ischemia-induced neuroprotective phenotype of astrocytes. Jointly, these results provide the first evidence that the co
peptide C3a modulates the response of astrocytes t
and increases their ability to cope with ischemic str

Keywords Caspase-3 · Glial fibrillary acidic protei
Neuroprotection

Introduction

Ischemic stroke due to cerebral blood vessel occlusion is the most common form of stroke, characterized by reduced blood flow and supply of oxygen and glucose. Ischemia results in the death of both neurons and glial cells in the ischemic zone. Cells in the ischemic penumbra are metabolically compromised but can be rescued by reconstitution of blood flow or neuroprotective pharmacological intervention. Astrocytes are the most abundant cell type in the mammalian brain. Astrocytes cooperate with neurons at multiple levels, including maintenance of homeostasis, neurotransmitter trafficking and recycling, and defense against oxidative stress [1–5]. Astrocytes also play a role in the maintenance of brain function

C3- and CR3-dependent microglial clearance protects photoreceptors in retinitis pigmentosa

JEM Journal of Experimental Medicine

Sean M. Silverman, Wenxin Ma, Xu Wang, Lian Zhao, and Wai T. Wong

Complement activation has been implicated as contributing to neurodegeneration in retinal and brain pathologies, but its role in retinitis pigmentosa (RP), an inherited and largely incurable photoreceptor degenerative disease, is unclear. We found that multiple complement components were markedly up-regulated in retinas with human RP and the rd10 mouse model, coinciding spatiotemporally with photo
activated retinal microglia. Genetic abla
retinal inflammatory gene expression.
expressed receptor for the C3 activatio
interactions. Deficiency of C3 or CR3 d
neurotoxicity to photoreceptors, demo
apoptotic photoreceptors in RP. These
interpretation of immunomodulatory t

Complement anaphylatoxin C3a is selectively protective against NMDA-induced neuronal cell death

Johan van Beek,[1,2,CA] Olivier Nicole,[2] Carine Ali,[2] Alexander Ischenko,[3] Eric T. MacKenzie,[2] Alain Buisson[2] and Marc Fontaine[1]

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The anaphylatoxin C3a is a potent inflammatory polypeptide released at sites of complement activation. To test whether C3a might alter neuronal outcome following an ischemic insult, we determined the effects of purified human C3a on murine primary cortical cell cultures exposed to apoptotic or excitotoxic paradigms. C3a prevented neither serum deprivation-induced apoptotic neuronal death, nor AMPA/kainate-mediated excitotoxicity. However, in mixed cultures of neurons and astrocytes, C3a dose-dependently protected neurons against NMDA toxicity (47% neuroprotection using 100 nM C3a, $p < 0.01$, $n = 12$). The neuroprotective effect of C3a was observable only in the presence of astrocytes. These observations suggest that C3a is involved in excitotoxicity-mediated neuronal death through astrocyte stimulation and extend its role beyond immune functions. *NeuroReport* 12:289–293 © 2001 Lippincott Williams & Wilkins.

Key words: Anaphylatoxin; Apoptosis; Cerebral ischemia; Complement; Excitotoxicity; N-Methyl-D-aspartate

RNA, ribonucleic acid.

Patient disposition: Low study discontinuation

Randomized and Treated
(N=447)

ACP 2 mg (N=225)		**Sham** (N=222)	
Discontinued study during Year 1	**25**	**Discontinued study during Year 1**	**17**
Adverse event	3	Adverse event	2
Protocol violation	0	Protocol violation	0
Investigator decision	0	Investigator decision	0
Sponsor decision	0	Sponsor decision	0
Subject request	17	Subject request	13
Loss to follow-up	2	Loss to follow-up	1
Subject noncompliance	1	Subject noncompliance	0
Death	2	Death	1

ACP, avacincaptad pegol.

Treatment emergent adverse events (TEAEs)

	ACP 2 mg (N=225)	Sham (N=222)
TEAEs, n (%)	**178 (79.1)**	**157 (70.7)**
Ocular in study eye	110 (48.9)	83 (37.4)
Non-ocular	125 (55.6)	127 (57.2)
Serious TEAEs, n (%)	**30 (13.3)**	**37 (16.7)**
Ocular in study eye	2 (0.9)	2 (0.9)
Non-ocular	29 (12.9)	35 (15.8)
TEAEs leading to study drug discontinuation, n (%)	**6 (2.7)**	**2 (0.9)**
Ocular in study eye	2 (0.9)	0
Non-ocular	4 (1.8)	2 (0.9)

ACP, avacincaptad pegol.
n = study eyes with events. A patient with multiple occurrences of an AE under one treatment is counted only once.

Ocular TEAEs ≥2% in study eye

Ocular TEAEs, n (%)	ACP 2 mg (N=225)	Sham (N=222)
Conjunctival hemorrhage	27 (12.0)	17 (7.7)
Punctate keratitis	11 (4.9)	14 (6.3)
Conjunctival hyperemia	12 (5.3)	13 (5.9)
Choroidal neovascularization	**15 (6.7)**	**9 (4.1)**
Dry eye	8 (3.6)	8 (3.6)
Eye pain	9 (4.0)	6 (2.7)
Vitreous detachment	7 (3.1)	6 (2.7)
Visual acuity reduced	3 (1.3)	5 (2.3)
Vision blurred	6 (2.7)	2 (0.9)
Visual impairment	6 (2.7)	2 (0.9)
Intraocular pressure increased	**21 (9.3)**	**2 (0.9)**
Vitreous floaters	6 (2.7)	1 (0.5)
Visual acuity reduced transiently	6 (2.7)	1 (0.5)
Blepharitis	6 (2.7)	0
Ocular hypertension	5 (2.2)	0

ACP, avacincaptad pegol; TEAE, treatment-emergent adverse event.
n = study eyes with events. A patient with multiple occurrences of an AE under one treatment is counted only once.

Serious Ocular TEAEs

	ACP 2 mg (N=225)	Sham (N=222)
Ocular serious TEAEs in study eye, n (%)	**2 (0.9)**	**2 (0.9)**
Choroidal neovascularization	2 (0.9)	1 (0.5)
Visual acuity reduced	0	1 (0.5)[a]
Visual acuity reduced transiently	0	1 (0.5)[a]

[a]Occurred in the same patient.
ACP, avacincaptad pegol; TEAE, treatment-emergent adverse event.
n = study eyes with events. A patient with multiple occurrences of an AE under one treatment is counted only once.

Study eye cases of intraocular inflammation, endophthalmitis, or ischemic optic neuropathy

	ACP 2 mg (N=225)	Sham (N=222)
Intraocular inflammation, n	0	0
Endophthalmitis, n	0	0
Ischemic optic neuropathy, n	0	0

ACP, avacincaptad pegol.

Comprehensive CNV surveillance program

	ACP 2 mg (N=225)	Sham (N=222)
Total CNV, n (%)	15 (6.7)	9 (4.1)

- Suspected development of CNV in the study eye by the principal investigator triggered full imaging workup assessed with FP, FA, and OCT and confirmed by the Duke Reading Center within 1 hour of submission
- If the diagnosis was confirmed, the patient continued receiving the study treatment in the trial, and the study eye was also treated with ranibizumab or aflibercept according to the country label
  - No patients in GATHER2 received anti-VEGF therapy without a Duke-confirmed CNV diagnosis
- All Month 12 imaging (FA, FP and OCT) was evaluated by the Duke Reading Center for CNV, irrespective of suspicion by the principal investigator

ACP, avacincaptad pegol; CNV, choroidal neovascularization; FA, fluorescein angiography; FP, fundus photography; OCT, optical coherence tomography.

Exudative MNV in the study eye[a]

	ACP 2 mg (N=225)	Sham (N=222)
Total CNV, n (%)	**15 (6.7)**	**9 (4.1)**
eMNV, n (%)	11 (4.9)	7 (3.2)
neMNV, n (%)	1 (0.4)	0
Peripapillary NV, n (%)	3 (1.3)	2 (0.9)

- Exudation status was read by the CORE Reading Center at Cole Eye Institute of the Cleveland Clinic
- OCT images were read to determine the number of CNV cases that were (1) macular neovascularization (MNV), versus peripapillary neovascularization and (2) exudative vs. non-exudative

The Reading Center classifies cases of MNV as exudative or non-exudative based on the following OCT criteria:

- **"eMNV"** is MNV that presents with new onset fluid in either the subretinal space or the intraretinal space
- **"neMNV"** is MNV which does not present with new onset fluid in the subretinal or intraretinal spaces. In some cases, isolated fluid may be present in the sub-RPE space. A case is considered to be neMNV when the MNV may not be visible but both a double-layer sign and sub-RPE fluid are present

[a]Post hoc analysis
ACP, avacincaptad pegol; CNV, choroidal neovascularization; CORE, Center for Ocular Research and Evaluation; eMNV, exudative MNV; neMNV, non-exudative MNV; NV, neovascularization; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

Conclusions

At Month 12, there were no cases of intraocular inflammation, endophthalmitis and ischemic optic neuropathy in study eyes treated with avacincaptad pegol 2 mg

CNV rates were 6.7% in the avacincaptad pegol 2 mg group and 4.1% in the sham group; eMNV rates were 4.9% in the avacincaptad pegol 2 mg group and 3.2% in the sham group

Avacincaptad pegol is the first investigational therapy in GA to achieve the 12-month, prespecified, primary endpoint vs. sham, coupled with a consistent safety profile, in two pivotal, phase 3 studies

CNV, choroidal neovascularization; eMNV, exudative MNV; GA, geographic atrophy.

Thank you to the GATHER program investigators, research staff, and patients