A Phase 1, Open-Label, Dose-Escalation Trial to Investigate Safety and Tolerability of Single Intravitreous Injections of ICON-1 Targeting Tissue Factor in Wet AMD

John A. Wells, MD; Christine R. Gonzales, MD; Brian B. Berger, MD; Victor H. Gonzalez, MD; Brian D. Sippy, MD, PhD; Gabriela Burian, MD, MPH

BACKGROUND AND OBJECTIVE: This phase 1 study evaluated the safety and tolerability of single intravitreous injections (IVIs) of ICON-1 (Iconic Therapeutics, South San Francisco, CA) in patients with neovascular age-related macular degeneration (nAMD). ICON-1 is a modified factor VIIa protein linked with the Fc portion of a human immunoglobulin G1. The molecule binds tissue factor overexpressed on choroidal neovascularization (CNV) in AMD.

PATIENTS AND METHODS: Open-label, interventional, dose-escalation trial in 18 patients with CNV due to AMD, with six patients per dose cohort. Patients received a single IVI of ICON-1 at baseline in one of three escalating doses: 60 µg, 150 µg, or 300 µg. Standard anti-vascular endothelial growth factor treatment was allowed at the investigator’s discretion at least 2 weeks after the ICON-1 injection; patients were followed up to 24 weeks. Dose escalation was based on the absence of significant safety events. At each study visit, best-corrected visual acuity (BCVA), ophthalmic examination (intraocular pressure, slit-lamp, and dilated fundus examination), and ophthalmic imaging (color fundus photography, fluorescein angiography, and optical coherence tomography) assessments were performed. The systemic pharmacokinetics of ICON-1 and presence of anti-ICON-1 antibodies were also assessed.

RESULTS: ICON-1 was safe and well-tolerated up to the highest dose administered, which was 300 µg. Commonly reported adverse events were considered related to the IVI procedure or to the underlying nAMD. No significant systemic levels of ICON-1 or anti-ICON-1 antibodies were detected. Preliminary evidence of biological activity (improved BCVA, reduced central retinal thickness, decreased CNV size, and leakage) was most evident with the 300 µg dose at 1 to 2 weeks after the single ICON-1 injection.

CONCLUSION: Intravitreous administration of ICON-1 in single doses up to 300 µg in eyes with neovascular AMD was safe and well-tolerated.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD), which is characterized by choroidal neovascularization (CNV), affects 10% to 15% of patients with AMD but accounts for 90% of the severe vision loss caused by AMD.1 It is expected that with the aging population, there will be a significant increase in the number of cases of AMD in the United States. The abnormal blood vessels in CNV grow, leak fluid, and bleed, thus damaging the structure and function of the retina layers and leading to loss of central vision. To reduce this visual loss, current clinical practice for pharmacological treatment of nAMD relies on drugs with anti-angiogenic activity, including ranibizumab (Lucentis; Genentech, South San Francisco, CA), bevacizumab (Avastin; Genentech, South San Francisco, CA), and aflibercept (Eylea; Regeneron, Tarrytown, NY). These agents function by binding and blocking the activity of vascular endothelial growth factor (VEGF). With ongoing repeated anti-VEGF injections, patients typically require frequent injections and often fail on ‘maximal medical therapy’ with an increasing risk of visual loss.

To reduce the frequency of injections, new treatments are being investigated. Clinical trials with investigational agents are ongoing, including those that target proteins in the VEGF pathway. The activity of VEGF is mediated by specific receptors on the surface of vascular endothelial cells. Antagonists of the VEGF receptor are currently available, including ranibizumab, aflibercept, and bevacizumab, but do not target proteins other than VEGF. A recent study evaluated the role of factors other than VEGF in angiogenesis in neovascular AMD.2 Multiple studies have shown that tissue factor (TF) is expressed on choroidal neovascularization membranes.3,4 Recent preclinical studies showed that the TF pathway is involved in tumorigenesis and inflammation and that it promotes angiogenesis.5,6 Tissue factor is a plasma protein that is overexpressed on endothelial cells and is involved in blood coagulation and inflammation.7,8 Amino acids near the active site of TF binds factor VIIa, which is involved in fibrinolytic activity.9,10 The TF-fibrinolytic axis is important in the development of choroidal neovascularization and poor visual outcomes in AMD.11,12 The TF pathway is a potential target for pharmacological therapy in nAMD.

ICON-1 is a modified recombinant human factor VIIa (rFVIIa) linked with the Fc portion of a human IgG1 antibody. The molecule binds tissue factor overexpressed on choroidal neovascularization membranes. Clinical studies showed that ICON-1 decreased CNV size and leakage (improved BCVA, reduced central retinal thickness, decreased CNV size, and leakage) was most evident with the 300 µg dose at 1 to 2 weeks after the single ICON-1 injection; patients were followed up to 24 weeks. Dose escalation was based on the absence of significant safety events. At each study visit, best-corrected visual acuity (BCVA), ophthalmic examination (intraocular pressure, slit-lamp, and dilated fundus examination), and ophthalmic imaging (color fundus photography, fluorescein angiography, and optical coherence tomography) assessments were performed. The systemic pharmacokinetics of ICON-1 and presence of anti-ICON-1 antibodies were also assessed.

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Partial results of this study were previously presented at the ARVO Annual Meeting and Retina Society Meeting 2012, the BPEI Angiogenesis Meeting, AAO Retina Subspeciality Day 2013, and at the EURETINA 2014 Congress. Iconic Therapeutics, South San Francisco, CA, sponsored the study. The sponsor participated in study design and conduct, data collection, data management, data analysis and interpretation, and preparation and reviews of manuscript.

Drs. Wells, Gonzales, Berger, Gonzalez, and Sippy participated each as clinical study investigators and received institutional financial support to conduct the study. Drs. Wells and Gonzales received advisory board consulting fees from Iconic Therapeutics. Dr. Burian received consultant and financial support from Iconic Therapeutics.

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we can see reduced exudation from the CNV, stabilization of visual acuity (VA) in most cases, and visual improvement in some cases. Although these agents suppress leakage from the neovascular tissue, they do not have a lasting effect on the underlying choroidal neovasculature that is present at the time of diagnosis and continues to progress and grow in the majority of patients.

An immunoconjugate protein known as ICON-1 (Iconic Therapeutics, South San Francisco, CA) has been developed as a therapeutic candidate (Figure 1) for treating neovascular AMD. The effector domain of ICON-1 is a fully functional Fc region of human immunoglobulin G1 (IgG1), which can bind Fc receptor bearing cells such as the natural killer cells that mediate antibody-dependent cellular cytotoxicity.\(^2\) The targeting domain is a modified (proteolytically inactive) version of activated plasma coagulation factor VIIa (FVIIa), which binds with high affinity to the tissue factor (TF) that is overexpressed on the choroidal neovascularization of AMD but does not interfere with normal blood coagulation.\(^3,4\)

TF is a 46 kD transmembrane cell-surface receptor for plasma coagulation factor VII (FVII) and its activated form FVIIa that is constitutively expressed on vascular subendothelial cells (pericytes).\(^5\) Upon vascular injury, TF binds FVII to form the TF/FVIIa complex, which initiates the extrinsic coagulation cascade by activating downstream coagulation factors (X, V, II, I). The TF/FVIIa complex also mediates intracellular signaling through protease-activated receptors, and promotes inflammation mediated by TNF-\(\alpha\), IL-1, IL-6, IL-8, MIP-2a/CXCL2a, C5a, and other proinflammatory and proangiogenic cytokines.\(^6-12\)

TF is undetectable on normal ocular blood vessels, but its enhanced expression in nAMD has been reported by Cho et al.\(^6\) These findings implicate TF as a key molecular contributor of the inflammatory and angiogenic processes underlying nAMD. Prior findings suggest that proinflammatory cytokines and VEGF in turn stimulate expression of TF on the choroidal neovascularization, and that such reciprocal, stimulatory molecular interactions perpetuate the neovascular pathology of AMD and contribute to the continuous progression of the disease.\(^7\) Interfering with TF-mediated signaling pathways may therefore provide a novel therapeutic approach for the treatment of nAMD, and potential to differentiate from the anti-VEGF agents by affecting the underlying CNV lesion progression.

Through its targeting domain, ICON-1 may interfere with the TF-mediated stimulation of both angiogenesis and inflammation in nAMD. In addition, ICON-1, by binding TF present on CNV, may direct the cytolytic response that its effector domain can elicit and reduce or remove the pathologic neovascularization in the same manner other Fc-fusion proteins have been shown to be capable of doing in solid tumors.\(^13\) In two different animal models of CNV, ICON molecules have been shown to be effective in additionally removing pathological new vessels.\(^3,4\)

Figure 1. Structure of ICON-1. An immunoconjugate fusion protein with a targeting region that is a modified (proteolytically inactive) version composed of two activated plasma coagulation factor VIIa (FVIIa) domains, which binds with very high affinity to tissue factor (TF), joined via a linker to a fully functional Fc region of human immunoglobulin G1 (IgG1). mutFVIIa = mutated coagulation factor VIIa; IgG1 Fc = Fc region of human IgG1.
This article reports the 6-month results of a phase 1 study that evaluated the safety and tolerability of single intravitreal injections (IVIs) of ICON-1, followed by treatment as needed with anti-VEGF drugs according to standard clinical care in patients with nAMD.

PATIENTS AND METHODS

Study Design

The primary objective of this study was to evaluate the safety and tolerability of single IVIs of three different doses of ICON-1 in patients with CNV due to AMD. Secondary objectives included the assessment of biological activity (change from baseline in best-corrected VA [BCVA], fluorescein leakage, central retinal thickness [CRT]) through fundus examination, fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT); determination of the systemic pharmacokinetic levels of ICON-1 after IVT administration; and detection of systemic anti-ICON-1 protein antibodies.

The trial was a prospective, open-label, dose escalation, multicenter, nonrandomized study conducted in the United States with sequential cohort enrollment. Safety and biological activity of ICON-1 in nAMD were evaluated in subjects previously treated with anti-VEGF or who were treatment-naïve. A medical review committee monitored patient safety throughout the study. Dosing and escalation to the next dose level occurred in a sequential manner (Figure 2), based on medical review of the clinical safety data from each dose cohort. The study was initiated in October 2010, and the last patient completed the study in July 2012.

Selection of Doses for the Study

The efficacy of ICON-1 in a CNV animal model, and the safety of a single IVI of up to 600 µg in minipigs or 150 µg of ICON-1 in rabbits for a period of 28
days or 15 days, respectively, supported the proposed single injection, escalating dose design of this phase 1 study, with an initial dose of 60 µg per injection.

**Patient Selection**

Patients were eligible to participate in the study if they were men or women older than 50 years of age and able to provide written informed consent. Patients were ineligible if they had ever been treated with any investigational agent or had an anti-VEGF treatment in the study eye within 60 days of baseline, were allergic to or had prior significant adverse reaction to fluorescein dye, or had a blood pressure of greater than 160/90 mm Hg. There were no additional restrictions regarding the systemic medications for concomitant diseases in patients with wet AMD.

Key ocular inclusion criteria in the study eye were: active CNV due to AMD, as evidenced on FA and OCT, with subretinal hemorrhage (if present) smaller than 50% of the total lesion size. In the first three patients (first, second, and third) enrolled in each cohort, there was no restriction in CNV lesion size and number of prior treatments; in the second three patients (fourth, fifth, and sixth) enrolled in each cohort, a total CNV lesion area less than 6 disc areas, of which at least 50% was actively leaking and at least 30% of the CNV was determined to be classic on the FA, was required. In each dose cohort, the first three patients enrolled had more advanced CNV and any number of previous anti-VEGF treatments, whereas the second three patients enrolled were treatment-naïve. BCVA eligibility criteria were 20/80 Snellen equivalent to Count Fingers. Only one eye of each patient was treated; if VA was the same in both eyes, the eye with the most active CNV was selected to be the study eye. Clear ocular media and adequate pupillary dilation in the study eye were required to permit retina photography.

Key ocular exclusion criteria in the study eye included: any retinal vascular disease or retinal degeneration other than AMD, serous pigment epithelial detachment without the presence of CNV, pigment detachment, glaucoma, or previous laser photocoagulation or a vitreous hemorrhage.

![Graph of the mean change in best-corrected visual acuity (BCVA). Data are shown for the low-dose cohort (60 µg), mid-dose cohort (150 µg), and high-dose cohort (300 µg) from weeks 2 through 24. BCVA was measured by ETDRS letter score. Results at week 2 (in some patients up to week 4) are before any standard therapy with anti-vascular endothelial growth factor agents could be administered.](image-url)
epithelial tears or rips, previous posterior vitrectomy or retinal surgery, any periocular infection in the past 4 weeks, use of IVT or periocular steroids within 90 days of baseline, current or prior use of extended-release steroid implants (eg, fluocinolone acetonide intravitreal implant or dexamethasone intravitreal implant [Ozurdex; Allergan, Dublin, Ireland]).

Study Drug and Doses

The study drug was supplied in single-use glass vials, each containing 0.28 mL of a sterile solution of ICON-1 at a concentration of 3 mg/mL. The drug is a clear, colorless aqueous solution of ICON-1 with a pH of 7.4. The vials were manufactured by Laureate Pharma (Princeton, NJ), shipped by the distributor (Almac Clinical Services, Durham, NC), and stored frozen at the clinical sites at -60°C until just prior to administration. Patients received at baseline (day 1) a single IVI of one of three volumes from the ICON-1 solution, equivalent to 60 µg (0.02 mL) in Cohort 1, 150 µg (0.05 mL) in Cohort 2, or 300 µg (0.1 mL) in Cohort 3 ICON-1 per injection (Figure 2).

Study Procedures

If no more than one of six patients in a dose cohort experienced a significant safety event (SSE), dose escalation would occur to the next dose level cohort. If two of six patients experienced a SSE at any dose, no additional patients would be enrolled. The maximum tolerated dose of ICON-1 was defined as the maximum dose at which no more than one of six subjects had a confirmed SSE in each cohort. Therapy with standard anti-VEGF was allowed starting at the earliest 2 weeks after the single injection of ICON-1, at the investigators’ discretion. By protocol, rescue therapy with ranibizumab was available starting at week 2 in patients who experienced a BCVA loss of 10 letters or more from baseline.

The study assessments for safety and biological activity (adverse events [AEs], VA, ophthalmic examinations, intraocular pressure [IOP], OCT, FA, and concomitant medications) were performed on the follow-up visits on days 2, 8, 15, 29, and 57. Additional follow-up visits occurred at weeks 12 and

**Figure 4.** Graph of mean change in central subfield retina thickness (CRT). Data are shown for the low-dose cohort (60 µg), mid-dose cohort (150 µg), and high-dose cohort (300 µg) from weeks 2 through 24. Mean CRT in µm was determined by optical coherence tomography. Results at week 2 (in some patients up to week 4) are before any standard therapy with anti-vascular endothelial growth factor agents could be administered.
24, when patients were again assessed for safety and biological activity. Heparinized blood (2 mL) for measurement of levels of ICON-1 was drawn at baseline (day 1) pre-dose and at 2, 4, and 24 hours post-dose. Heparinized blood (2 mL) for measurement of levels of anti-ICON-1 antibodies was drawn on day 1 pre-dose; on days 8, 15, 29, 57; and at week 12.

Statistical Methods

This was an open-label phase 1 study and no formal statistical power calculation was performed. All study data were summarized using descriptive statistics. Efficacy parameters were described using mean, standard deviation, minimum, maximum, and sample size. Safety data were summarized for all patients who received one dose of ICON-1. Missing visits data were handled by the last-observation-carried-forward method. All patients completed the 6-month study follow-up.

RESULTS

A total of 18 patients were enrolled in the study, and all completed the study as planned; none with-
drew prematurely. Demographics and study eye ocular characteristics of the 18 subjects are presented in Table 1. The patients had a mean age of 76, 82, and 79 years in Cohorts 1, 2, and 3, respectively, and 10 of the 18 patients were male. Nine patients (50%) had received prior treatment for CNV due to AMD in the study eye, and nine were treatment-naive. Five study eyes were pseudophakic. The most common concomitant medical problems at baseline were vascular disorders (13 patients, 72%) and metabolism and nutrition disorders (13 patients).

The mean BCVA score in the study eye at baseline was 55, 48, and 57 letters in Cohorts 1, 2, and 3, respectively. The first three subjects enrolled in each cohort had worse BCVA levels compared to the fourth, fifth, and sixth subjects enrolled in each cohort. The mean CRT (center subfield) in the study eye at baseline was 426.3 µm, 316.8 µm, and 496.3 µm in Cohorts 1, 2, and 3, respectively. The mean area of the CNV lesion at baseline was higher in Cohort 1, with 28.0 mm², and lower in Cohorts 2 and 3, with 19.8 mm² and 16.5 mm², respectively (Table 1). All IOP measurements were within normal range at baseline.

**Safety and Tolerability Analysis**

Table 2 presents the types and frequencies of reported adverse events (AEs) in the study eye. All subjects had at least one AE reported. There were no deaths in the study, and no AE led to premature discontinuation from the study. One serious adverse event (SAE) was reported in a 75-year-old male patient who received study drug at a dose of 300 µg: 23 days after the single IVT with ICON-1, the subject was hospitalized with flu-like symptoms, sore throat, and vague chest symptoms; premature atrial contractions were noted. The investigator considered and reported the SAE as not related to study drug. No other significant or unexpected AEs were reported. Thirteen subjects had at least one ocular AE in the study eye. One AE, a case of mild vitritis in Cohort 3, was considered by the investigator to be related to the study drug. Overall, the most frequently reported AEs were eye disorders, and they were mostly related to the injection procedure: conjunctival hemorrhage, conjunctival edema, vitreous floaters, anterior chamber cell, and eye pain. All ocular AEs were graded “mild” or “moderate.”

Reported non-ocular AEs were gingival, upper respiratory, sinus, and urinary tract infections. Routine hematology and chemistry laboratory tests were not performed in this study.

During the study, no subject experienced a significant safety event (SSE), and ICON-1 was well-tolerated for the highest dose of 300 µg tested. The maximum tolerated dose as defined in this study was therefore not reached and will be further explored in future studies.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>Cohort 1 (60 µg) n = 6</th>
<th>Cohort 2 (150 µg) n = 6</th>
<th>Cohort 3 (300 µg) n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>Mean</td>
<td>76.2</td>
<td>82.0</td>
<td>78.8</td>
</tr>
<tr>
<td>Prior Wet AMD Treatments</td>
<td>Treatment-naive</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Any prior treatments</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>BCVA Study Eye (ETDRS Letters)</td>
<td>Mean</td>
<td>55.2</td>
<td>47.8</td>
<td>56.7</td>
</tr>
<tr>
<td></td>
<td>All patients</td>
<td>44.0</td>
<td>50.0</td>
<td>37.3</td>
</tr>
<tr>
<td></td>
<td>Patients 1, 2, and 3</td>
<td>56.0</td>
<td>46.3</td>
<td>68.3</td>
</tr>
<tr>
<td>CRT (µm)</td>
<td>Mean</td>
<td>426.3</td>
<td>316.8</td>
<td>496.3</td>
</tr>
<tr>
<td>CNV Size (FA, mm²)</td>
<td>Mean</td>
<td>28.0</td>
<td>19.8</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>Area of lesion</td>
<td>19.9</td>
<td>5.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

n = number of patients; BCVA = best-corrected visual acuity; CRT = central retinal thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study letter score; CNV = choroidal neovascularization; FA = fluorescein angiography
Pharmacokinetics and Immunogenicity

In the majority of the plasma samples assayed (88%), the levels of ICON-1 were below the lower limit of quantification of 20 ng/mL. None of the subjects in this study developed detectable antibodies to ICON-1 up to 12 weeks after receiving an IVT injection of up to 300 µg of ICON-1.

Biological Activity

The most evident changes from baseline were observed in the highest, 300 µg dose group (Cohort 3). In this cohort, a mean BCVA change of +8 letters was observed 2 weeks after the single injection of ICON-1 (Figure 3). Similarly, a reduction in the mean CRT from baseline was most apparent in the same Cohort 3 patients starting at week 2 after the study treatment (Figure 4). These findings continued to be observed at week 4 and were maintained throughout the 24 weeks of the study. Many of these patients did receive anti-VEGF injections as allowed in the protocol after the single dose of ICON-1. Figure 5 shows the outcome for an 83-year-old white female patient with treatment-naïve CNV at baseline who was treated with a single IVI dose of 300 µg of ICON-1. At baseline, this patient presented with a BCVA of 58 letters, and a CRT of 467 µm. Two weeks after the single IVI of ICON-1, the patient gained +16 letters compared to baseline, and her CRT was reduced by -148 µm. These effects continued to be observed at week 4, with +11 letters in BCVA and -175 µm compared to baseline, together with a reduction in the CNV leakage and lesion area. After the week 4 visit, this patient initiated standard of care CNV treatment with ranibizumab until the completion of the 24-weeks follow-up in the study.

### TABLE 2
Ophthalmic Adverse Events in Study Eye

<table>
<thead>
<tr>
<th>Cohort 1 (60 µg)</th>
<th>Cohort 2 (150 µg)</th>
<th>Cohort 3 (300 µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Events</td>
<td>Patients</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Anterior Chamber Cell</td>
<td>2</td>
<td>33.3</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctival Hemorrhage</td>
<td>1</td>
<td>16.7</td>
</tr>
<tr>
<td>Conjunctival Hyperemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctival Edema</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Corneal Epithelium Defect</td>
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<td>0</td>
</tr>
<tr>
<td>Detachment of Retinal Pigment Epithelium</td>
<td>1</td>
<td>16.7</td>
</tr>
<tr>
<td>Eye Irritation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye Pain</td>
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</tr>
<tr>
<td>Eye Pruritus</td>
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<td>0</td>
</tr>
<tr>
<td>Macular Degeneration</td>
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<tr>
<td>Retinal Dystrophy</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Retinal Hemorrhage</td>
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<td>0</td>
</tr>
<tr>
<td>Retinal Pigment Epithelial Tear</td>
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<td>0</td>
</tr>
<tr>
<td>Subretinal Fibrosis</td>
<td>1</td>
<td>16.7</td>
</tr>
<tr>
<td>Vision Blurred</td>
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<td>0</td>
</tr>
<tr>
<td>Visual Acuity Reduced</td>
<td>1</td>
<td>16.7</td>
</tr>
<tr>
<td>Vitreous Floaters</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vitritis</td>
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</tr>
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</table>

n = number of patients
**DISCUSSION**

Angiogenesis and inflammation are the key pathogenic processes that underlie nAMD. By binding to TF expressed on the choroidal neovasculature through its modified FVIIa domain, ICON-1 has the potential to interfere with these intracellular signaling processes responsible for inflammatory cytokines and VEGF release and thus to potentially impact the course of this blinding macular disease. Preclinical data show that via its Fc domain, ICON-1 can recruit and activate the innate immune system (via natural killer cell-mediated cytotoxicity) to reduce or remove pathologic neovascular cells, providing an additional mechanism for slowing or halting disease progression.1,4

In the study reported here, a single IVI dose of ICON-1 was found to be safe and well-tolerated at all doses tested (60 µg, 150 µg, and 300 µg). There were no dose-limiting toxicities identified in the study population, and the maximum tolerated dose was not reached in this study.

AEs were experienced by all patients. The most frequently observed included conjunctival hemorrhage, vitreous floaters, conjunctival edema, and signs of macular degeneration progression. No unexpected or significant safety concerns were observed in patients who were treatment-naïve for their CNV, in patients who previously received anti-VEGF treatment, or in patients who continued with anti-VEGF treatment after the single dose of ICON-1. The patients enrolled in the study presented with a medical history representative of nAMD patients. One patient was reported with a SAE due to a preexisting and concomitant medical condition. Systemic concentrations of ICON-1 were not detected after IVT administration. None of the study patients developed anti-ICON-1 antibodies up to 12 weeks after receiving an IVI.

Following a single IVI dose of ICON-1, mean BCVA improved by +8 letters by week 2 compared to baseline in subjects treated with the highest dose of 300 µg ICON-1. Reductions in mean CRT were also observed early after the single dose, and, consistent with the improvements in BCVA, this decrease was most evident for subjects receiving the 300-µg dose of ICON-1. Furthermore, the CNV lesion size and leakage were reduced in some patients. These biological effects of a single dose of ICON-1 in monotherapy can be best appreciated at 2 weeks and up to 4 weeks following treatment, prior to continuing or initiating treatment with an anti-VEGF agent, as the design of the trial allowed investigators to treat with anti-VEGF therapy as their standard of care after week 2 if desired, or if the rescue criterion was met. As a phase 1 clinical trial, the number of patients was small and many patients had prior or subsequent anti-VEGF injections; therefore, no efficacy conclusions can be drawn. However, evidence of biologic activity was demonstrated anatomically and visually in both treatment-naïve patients after receiving only study drug and in patients who had received multiple prior anti-VEGF injections who had persistent fluid and were no longer improving visually.

The clinical observations in this study are consistent with the preclinical findings of CNV size and exudation reduction in eyes treated with the ICON molecule. Taken together, the data support the novel therapeutic potential of ICON-1 to halt CNV activity and lesion progression by interfering with the underlying CNV pathological process. The absence of dose related toxicities and the signs of biological effect most evident with the 300-µg dose tested in this study support further clinical exploration of intravitreal ICON-1 with higher doses and in multiple IVI administration. The novel mechanism of action of ICON-1, distinct from anti-VEGF agents, on CNV lesion progression has the potential to add to our abilities to halt or reverse the disease and lead to long term benefits in patients with CNV due to AMD.

In conclusion, this first-in-human trial of a single intravitreous injection of ICON-1, a modified FVIIa-IgG1 Fc immunoconjugate fusion protein, administered at three dose levels, demonstrated that ICON-1 was safe and well-tolerated. During the study, no subjects experienced a significant safety event, even at the maximum planned dose of 300 µg; thus, dose-related toxicities and a maximum tolerated dose were not established. No quantifiable systemic levels of study drug or antibodies to study drug were detected. Preliminary signs of biological activity were seen with the 300 µg dose (highest dose tested) as early as 2 weeks after the single IVI, with improvement in mean BCVA, reduction in mean CRT, and a decrease in CNV lesion and leakage in some patients.

The aberrant expression of TF in CNV makes this protein a new target for nAMD. ICON-1 through its interaction with TF may bring a novel mechanism of action into the clinical arena. Blockade of TF pathologic signaling, along with activation of an immune response against the abnormal choroidal neovascular cells, has the potential to provide a differentiat-ed, new biological outcome with improved clinical benefits to patients compared to current standard of clinical care. This therapy has the potential to particularly address the clinical need in patients for whom, despite ongoing treatment with anti-VEGF, the CNV
Lesion continues to be active, progress to advanced stages, and lead to visual loss. Therefore, these initial results support and warrant further evaluation of the possible biological and clinical activity observed with ICON-1.

REFERENCES