On arterial anterior ischemic optic neuropathy (NAION) is the leading cause of sudden optic nerve–related vision loss in individuals over 50 years old and is caused by inadequate blood supply to the optic nerve head (1). In the United States, it affects 2.3 to 10.2 per 100,000 people over 50 years, resulting in 10,000 to 12,000 new cases per year (2,3). Little is understood concerning the pathophysiology of the disease, and there currently is no medical or surgical treatment that has been proven to be consistently beneficial (4). The QRK207 NAION study, sponsored by Quark Pharmaceuticals, Inc. in collaboration with the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC), is the first clinical trial designed to test therapy with potential to provide neuroprotection for acute optic nerve injury due to NAION. In addition, this is the first major collaboration with industry involving neuro-ophthalmologists, who are integrated into the study design, conduct, performance, analysis, and reporting of the trial.

A recent review details the many reports of attempted therapies (5). These previous studies reported treatment successes and failures. Some of the possible pathophysiological mechanisms considered by the interventions include 1) blocking sodium channels, which have been shown to be neuroprotective in in vitro hypoxic injury to the optic nerve; 2) vasodilation, hemodilution, anticoagulation, and increasing blood pressure to increase presumed arterial or capillary perfusion of the optic nerve head; and 3) reduction of compression of optic nerve axons in the neural canal by reducing swelling or enlarging the scleral opening or decompressing the optic nerve sheath. Other procedures seem to have no scientific basis for the treatment of an acute ischemic white matter pathway injury; including intravitreal (IVT) antivascular endothelial growth factor agents and oral L-Dopa. In addition, only 1 study, the Ischemic Optic Neuropathy Decompression Trial (IONDT), was designed, powered, and conducted in a manner appropriate to collect Class I evidence (6). As if clinical research design challenges were not enough, most of the interventions in these studies have been initiated well beyond the time point where permanent axon injury and retinal ganglion cell (RGC) loss or atrophy have occurred (7).

**Experimental Data**

Although NAION clearly begins as a vascular event, several studies from the Bernstein laboratory have confirmed the recruitment of inflammatory cells in the ischemic region shortly after induction of experimental NAION in mice, rats, and nonhuman primates (8–12), as well as in a single clinical specimen from a patient who died shortly after experiencing an episode of acute NAION (13). The earliest inflammatory responses seem to be acellular and based on cytokine and inflammatory protein release from the affected tissues. This suggests additional treatment approaches might first reduce the release of acellular inflammatory cytokines and secondarily address the late inflammatory cellular response.

**QPI-1007 Background, Pilot Safety, and Efficacy Data**

The active study agent, QPI-1007, is a small interfering ribonucleic acid that is designed to temporarily block cells from making caspase 2, which has promotes apoptosis. Caspase 2 is an important enzyme...
that is upregulated when cells are injured or deprived of oxygen. QPI-1007 has been shown to reduce the increase in caspase 2 and to preserve RGCs in several animal models of optic nerve injury (14). The hypothesis for this clinical trial is that the NAION injury to the axons of the optic nerve and their RGCs resulting from increased caspase 2 will be reduced by one or more IVT injections of QPI-1007. An important factor will be how many axons and RGCs are irreversibly injured at presentation. In most studies, the RGC/inner plexiform layers seem intact at presentation as assessed by optical coherence tomography (OCT), but thinning is evident within 2 weeks (7), leading us to propose a maximum window of enrollment of 14 days from the onset of vision loss.

Quark conducted an open-label Phase I trial in the United States and Israel ending in 2010 to test the safety of intravitreally injected QPI-1007 in 48 eyes. All subjects in this trial received a single IVT injection of QPI-1007 at doses ranging from 0.2 to 6.0 mg. Eighteen had permanent injury of the retina or optic nerve mostly due to ischemia and visual acuity 20/200 or worse, whereas 30 had acute NAION and were enrolled within 28 days of vision loss. The results have not yet been published, but no major eye or systemic adverse events were noted. The number of eyes with visual acuity that improved and deteriorated by ≥3 lines for 29 eyes with acute NAION treated with QPI-1007 and follow-up evaluations were compared with the results from the IONDT control arm (Table 1).

The most frequently reported adverse events were conjunctival hemorrhage (48% subjects), conjunctival edema (19% subjects), eye irritation (17% subjects), eye pain (17% subjects), corneal erosion (15% subjects), foreign body sensation in eyes (15% subjects), punctate keratitis (10% subjects), and headache (10% subjects).

Study Design

QRK207 is a double-masked, randomized, sham-controlled efficacy and safety study involving sites in the United States, Israel, India, China, and possibly some European countries and Australia. Randomization will be stratified by country/region. Subjects will be randomized into one of 5 groups in a 1:1:1:1:1 ratio using a centralized randomization system. The 5 treatment groups will be divided into 3 treatment regimens; single dose, multiple dose, and sham control (Table 2).

Sample Size

It has been determined after adjusting for multiple comparisons (4 dose levels vs the sham control) that a sample size of about 106 per group will provide 90% power at an alpha level of 0.05 (2-sided) to detect a 15% absolute improvement in the primary endpoint, assuming that the percentage of subjects who experience at least a 15-letter loss is 1% for each of the QPI-1007 treatment groups and 16% for the control group.

Inclusion/Exclusion Criteria

Major inclusion criteria (complete list on www.clinicaltrials.gov) are:

1. Diagnosis of first episode of NAION in study eye with symptom onset within 14 days before Study Day 1.
2. Clinical sites evaluate NAION diagnosis with Central Reading Center confirmation (using visual field [VF] and OCT criteria).
3. Subjects 50–80 years.
4. Best-corrected visual acuity (BCVA) in the study eye is ≥15-letter score, using the ETDRS chart at presentation examination.
5. NAION diagnosis requires:
   Disc swelling (seen and documented by site PI), VF defects in the study eye consistent with optic neuropathy and mean deviation worse than −3.0 dB on automated perimetry using the SITA standard 24-2 testing protocol. Relative afferent pupillary defect (unless the fellow eye has had previous NAION or other optic nerve or retinal disease that is not exclusionary). Peripapillary retinal nerve fiber layer thickness >95th percentile by OCT and VF pattern compatible with the diagnosis of NAION as determined by a Central Reading Center at Duke University.

Major exclusion criteria (complete list on www.clinicaltrials.gov) are:

1. Present use or history of any treatment for the current episode of NAION, including systemic steroids, brimonidine, or continued use of traditional Chinese herbal medicine.

### TABLE 1. Comparison of visual acuity data for acute nonarteritic anterior ischemic optic neuropathy from nonrandomized open-label use of QPI-1007 compared with the IONDT

<table>
<thead>
<tr>
<th>Time Point</th>
<th>QPI-1007 Patients Improving by ≥3 Lines</th>
<th>IONDT Patients Improving by ≥3 Lines</th>
<th>QPI-1007 Patients Losing ≥3 Lines</th>
<th>IONDT Patients Losing ≥3 Lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 3, %</td>
<td>51.7 (15/29)</td>
<td>39.7 (48/121)</td>
<td>0 (0/29)</td>
<td>9.1 (11/121)</td>
</tr>
<tr>
<td>Month 6, %</td>
<td>44.8 (13/29)</td>
<td>42.6 (52/122)</td>
<td>0 (0/29)</td>
<td>14.8 (18/122)</td>
</tr>
<tr>
<td>Month 12, %</td>
<td>28.6 (8/28)*</td>
<td>41.2 (47/114)</td>
<td>3.6 (1/28)</td>
<td>15.8 (118/114)</td>
</tr>
</tbody>
</table>

*Suggests that more than 1 IVT of QPI-1007 may be needed to maintain improvement.

IONDT, Ischemic Optic Neuropathy Decompression Trial.
2. Previous episode of NAION in the study eye only.
3. Bilateral acute NAION with bilateral disc swelling at presentation.
4. Clinical evidence of temporal arteritis based on: symptoms or signs, or C-reactive protein, or abnormal Westergren sedimentation rate.

**Primary Endpoints**

1. The primary efficacy endpoint is the proportion of subjects who lose 15 letters or more in BCVA score from baseline (Day 1/randomization) to Month 12, as measured by ETDRS visual acuity protocol in the study eye.
2. The primary safety endpoint is the safety and tolerability of QPI-1007 in recent-onset NAION.

**Major Secondary Efficacy Endpoints**

1. Mean change from Day 1 to Month 12 in BCVA score, as measured by ETDRS visual acuity protocol in the study eye.
2. Mean change of VFs; mean deviation from Day 1 to Month 12 as assessed by Humphrey standard automated perimetry using the SITA standard 24-2 testing protocol in the study eye.

**Time Line**

The study started in late 2015 and is expected to continue for about 3 years.

**SUMMARY**

QRK207 will be the first trial to use a potential neuroprotective therapy delivered early to reduce the permanent injury and lessen the vision loss from acute NAION. We do not know if the 14-day window for enrollment will be too long to see an effect, but the length of time NAION-associated optic disc swelling typically lasts, as well as the need to recruit sufficient number of subjects for the study, justify this time window, particularly given the low frequency of NAION and the common several-day delay in seeking medical attention by patients who experience the disorder. Except for thrombolysis in ischemic stroke studies, previous treatment of ischemic injury of the central nervous system including neuroprotective agents, has not been effective. None of these failed treatments worked through mechanisms that decreased apoptosis. Furthermore, oral administration of an agent intended to reduce excitatory neurotoxins hypothesized to worsen neuronal injury in glaucoma has also failed. Thus, this treatment trial, which assesses the efficacy and safety of IVT administration of QPI-1007 to avoid the potential complications of systemically administered therapy, could be the first to show optic nerve protection in patients with NAION. Finally, this study is the first clinical trial that effectively partners the NORDIC with industry. We are truly excited to be a part of this clinical trial.

**REFERENCES**
