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Quick Pulse

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INSPIRE PHARMACEUTICALS' DIQUAFOSOL FOR DRY EYE: FAILS PHASE III TRIAL

A January 2005 issue of *Trends-in-Medicine* warned that Inspire's dry eye treatment, diquafosol (INS365) was likely to fail in its latest Phase III trial, and the company announced on February 9, 2005, that, as expected, the trial did not meet its primary endpoint. This makes it unlikely that diquafosol will be approved for dry eye by the FDA – or European regulators – without an additional trial.

Study 109, which began in June 2004, was a randomized, placebo-controlled safety and efficacy study comparing diquafosol 2% four times daily to placebo in 640 dry eye patients at 34 U.S. sites with a six-week treatment period, followed by a one-week discontinuation period.

Diquafosol Study 109 Results

Measurement	Diquafosol n=318	Placebo n=322	p-value
Demographics			
Dropouts	6%		---
Female	81%		---
Caucasians	81%		---
Mean age	61		---
Results			
Primary endpoint: Clearing of corneal staining	N/A	N/A	Nss
Symptom improvement	N/A	N/A	Nss
Secondary endpoint #1: Mean corneal staining	N/A	N/A	<.001
Secondary endpoint #2: Mean conjunctival staining	N/A	N/A	.002
Secondary endpoint #3: Conjunctival clearing	N/A	N/A	.019
Clearance of central region	N/A	N/A	<.0001

Corneal clearance was chosen as the primary endpoint because that's what the FDA wants to see. The FDA advised Inspire that it is difficult to determine the clinical relevance of a percent change in mean corneal staining, that the Agency is insisting on corneal clearance. CEO Christy Shaffer said, "What the FDA said clearly is that clearance of the central cornea or clearance of the entire cornea would significantly reduce a patient's possible risk of infection…They stated that clearance is pretty unequivocal in demonstrating benefit resulting in not needing any symptomatic benefit to go along with that." Another official said, "It is difficult to show improvement in symptoms because there are so many…So, we need to focus on more clinically-significant measures of corneal staining, which in

the Agency's eyes is clearing of corneal staining…We had been looking at mean corneal staining, and…In our discussions about Study 105, they (FDA) indicated you have corneal clearing...and this is what we (FDA) want replicated because it is more clear without symptomatic benefit as well."

Alternatively, Inspire could have used improvement in mean corneal staining – if it also could show symptom improvement, which it didn't do in this and some other trials. An official said, "If you can show mean corneal staining and a single symptom improvement, they (FDA) would consider that for review. In the absence of demonstrating symptomatic relief, which we said is difficult, their second approach is statistical significance in corneal clearing."

Inspire now plans to submit a comprehensive, meta-analysis of all the diquafosol trials. The FDA requires a "fully integrated safety package" and it appears Inspire also plans to give the Agency an integrated efficacy package.

The trials that Inspire has conducted with diquafosol – a $P2Y_2$ receptor agonist that stimulates fluid and mucin secretion and possibly lipid production – were discordant in that the company didn't show both symptom relief and improvement in corneal staining in the same trial. These trials (all of which except Study 03-108 were submitted to the FDA in support of the NDA) included:

a. **Study 03-103.** In this Phase II trial, there was only a "strong trend" toward symptom improvement.

b. **Study 03-104.** This first Phase III trial did not meet its primary endpoint, and diquafosol was "no more effective than placebo." The trial showed safety but did not show efficacy in reducing symptoms. An Inspire official said, "The FDA doesn't allow adjusting for baseline, but if you adjusted for baseline in this trial, we would meet the endpoint."

c. **Study 03-105.** This second Phase III trial, conducted after the results of Study 104 were known, was a double-masked comparison of the safety and efficacy of diquafosol 1% and 2% to placebo in 527 patients at 34 U.S. sites. The trial missed its primary ***subjective endpoint:*** clearing of the ocular symptom for foreign body sensation at six weeks. However, the trial met the primary ***objective endpoint:*** corneal staining.

d. **Meta-analysis.** A pooled analysis of Study 03-104 and Study 03-105 showed statistically significant results for corneal staining.

e. **Study 03-108.** This was a Phase IIIb trial that included assessments from both a conventional environmental component and an experimental Controlled Adverse Environment (CAE) chamber designed to exacerbate dry eye. This study was a four-week, placebo-controlled, double-masked comparison of the safety and efficacy of 2% diquafosol vs. placebo in 222 patients. Endpoints included corneal staining and patient-reported ocular discomfort measured in both the environmental and the CAE chamber portions of the study.

Inspire Comments on Study 109 Results

In a conference call on the results, Inspire officials complained about a lack of clear guidance from the FDA on dry eye products. Shaffer said, "It has proven very difficult for sponsors of dry eye products to show improvement in both signs and symptoms of dry eye…There is no formal, written guidance by the FDA and their position has continued to evolve as more dry eye trials are conducted."

Inspire is hoping that the FDA will consider all of the data on diquafosol and find it compelling enough to give approval. The company also plans to put new emphasis on Study 108, which was not a part of the original NDA filing. Study 108 failed to meet its primary endpoint, but among the Study 108 findings that Inspire hopes will be persuasive was ocular clearing. At Week 4 in Study 108, ocular clearing (the combination of corneal clearance and clearance of a portion of the conjunctiva) was statistically significant. An official said, "We haven't focused as much on that trial, but we are going to go back, after the Study 109 results, and those (Study 109 and Study 108) may be the two trials (required for approval). Obviously, there was conjunctival clearing in Study 109, so we are trying to put together a cumulative body of evidence for a significant endpoint that other products have not met." Another official said, "We are also doing a meta-analysis from a variety of other studies – Study 105 and 108. Clearance was a primary endpoint in Study 105 and a secondary endpoint in Study 108." Another official said, "The Study 108 data were not included in original NDA. During the process we did have discussions with them on top line data on 108, and that was not particularly focused on corneal clearing. They (FDA) were aware of the data, but in the context of 109, I think this changes how you look at the 108 data – because we continue to show improvement in a variety of measures."

The European regulatory situation for diquafosol also is up in the air. European approval may require an additional trial. Shaffer said, "We have met with Allergan and a few European regulatory agencies, and they were aware Study 109 was coming. We discussed the Study 109 design and got mixed responses on whether 109 would suffice even if it were positive, based on what they want to see…We will meet with Allergan very soon, share the totality of the data, and decide if we can put together a European package or if we need another study – a longer trial looking at symptoms, particularly focused on Europe." Another official said, "There is no consensus in the European community on what would be sufficient for approval for a dry eye product. They lag a little behind the U.S. on the consensus of the nature of supportive evidence needed, and we will continue to discuss this with them and work with Allergan."

Other points Inspire officials made in the conference call included:

- Following the December 2003 approvable letter from the FDA, Inspire met with the FDA and "consulted extensively with Allergan" to design Study 109, which "hinged on replicating important findings from Study 105 on corneal staining." Shaffer said, "We observed a number of positive findings in Study 105 – mean corneal staining, mean conjunctival staining, and complete clearance of cornea vs. placebo…Study 109 was designed to show the corneal clearing shown in Study 105."
- Study 109 had some positive secondary results and was consistent with previous trials of diquafosol.
- There are no confounding factors that explain the poor performance of diquafosol in Study 109.
  - There was a higher placebo response in Study 109, but there was also a lower active response.
  - Study 109 was run at the same time of the year as Study 105, so there were no confounding environmental factors.
  - The patient population in Study 109 was well matched to Study 108 and Study 105. Though patients in Study 109 had slightly milder corneal staining scores at baseline, officials did not think this was a confounding factor in the Study 109 results. Shaffer said, "In order to clear the cornea, there are five regions. If there is a single dot on one region, then it hasn't cleared. This is why we chose a milder population (for Study 109). Looking at Study 105 patients who cleared, we thought it was more likely we would see clearing (with a milder population)."
- Study 109 showed no benefit on symptoms. Shaffer said, "There appears to be a lag in time in staining scores and symptom relief. So, a longer study is needed for symptom relief, and that is difficult for all dry eye products today."
- Officials claimed they only got the results of Study 109 a few days before February 9, 2005. On February 9th, Shaffer said, "I learned of the data this week. We were fortunate to have a call with the FDA soon thereafter. I've had the data a very short period of time."
- Allergan has been briefed on the Study 109 results and is "supportive." Inspire officials plan to meet with Allergan "in the near future" to discuss the details and strategies.
- Inspire is on track to initiate a pilot trial of diquafosol in refractive surgery patients "for a different and specific indication for corneal wound healing." This was originally planned as a label expansion study. The results will be available before the end of 2005.
- A six-month review of the sNDA is still expected.
- Officials avoided comparisons with the package Allergan submitted to the FDA for approval of Restasis (cyclosporine), saying not all of that data is publicly available yet. An official said, "Restasis faced similar challenges in demonstrating improvement in benefit to patients and had to do a number of trials to put together a body of evidence, and that is the direction we are going – putting together a body of evidence." Another official said, "Allergan had problems meeting the primary endpoint as well. Their approach was similar to us – putting together a body of evidence from a variety of different studies which collectively demonstrated the benefit of the drug."

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