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Quick Pulse

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INSPIRE PHARMACEUTICALS' DIQUAFOSOL FOR DRY EYE

In December 2003, Inspire received an approvable letter from the FDA for diquafosol (INS365), and the company announced that it had to do another trial to gain approval. That trial, Study 109, got underway in June 2004, and the results could be reported any day.

It came as no surprise that the FDA was requiring an additional trial before approval. The FDA appeared to want diquafosol to show a benefit on objective (sign) and subjective (symptom) measures in the same trial. In one trial, diquafosol showed symptom relief but no statistically significant improvement in an objective measure of dry eye. In the pivotal trial, Study 03-105, diquafosol 2% showed a statistically significant benefit on the primary objective endpoint of mean corneal staining score (ITT with LOCF) at Week 6 but not on the primary subjective endpoint (clearing of foreign body sensation at Week 6).

On June 2, 2004, Inspire announced that it had started a new Phase III trial, Study 109. The delay in getting this trial going reportedly was due to negotiations with the FDA over trial design. Study 109 is a randomized, placebo-controlled safety and efficacy study comparing diquafosol 2% four times daily to placebo in ~500 patients at 36 U.S. sites with a six-week treatment period, followed by a one-week discontinuation period. Study 109 reportedly:

- Must show a statistically significant improvement in corneal staining, the primary endpoint – not in symptom relief, though there is more than one subjective secondary endpoint.
- Must meet a higher hurdle on the primary endpoint p-value than p=.05. The company did not explain what p-value must be reached, but in other cases where the FDA has required a lower p-value than p=.05, it has often been either p≤.025 or p≤.01. In this case, it would not be surprising if the p-value has to be ≤.01.

However, the devil may be in the detail here. There are several points to keep in mind in predicting the outcome of Study 109 or the likelihood for FDA approval of diquafosol based on the results of Study 109. Following is a discussion of some of these issues.

BACKGROUND ON DRY EYE

Dry eye affects approximately 11%-20% of adult Americans, but diagnosing it isn't straightforward. Patient complaints of dry eye symptoms may be more reliable and accurate than many dry eye clinical tests. A study by researchers at Ohio State University, reported in the November 2004 issue of the journal ***Cornea***, found that dry eye symptoms generally are not associated with clinical signs. This was true even when adjustments were made for age and use of artificial tears.

Current treatments for dry eye include:

- Artificial tears.
- Punctal plugs.
- Allergan's Restasis (cyclosporine A), which was approved by the FDA in December 2002. An optometrist said, "Cyclosporine (Restasis) supposedly reduces inflammation and therefore produces better quality and quantity of tears in cases that are aqueous deficient, but in mucin-related dry eye, there is precious little (treatment) out there."
- Topical corticosteroids.

Doctors use a variety of tests to diagnose dry eye, including tear meniscus height (TMH) measurements, meibomian gland assessment (MGD), tear film breakup time (TBUT), Schirmer test, phenol red thread test, and rose bengal staining. Experts disagree on the value of corneal staining as a diagnostic test for dry eye. One expert said, "Corneal staining doesn't say anything at all about symptom relief…Corneal staining suggests epithelial cells have been damaged…In terms of dry eye, one of the ongoing problems routinely has been finding something that correlates tightly with patient symptomatology. That is why, in my view, there is so much opportunity for snake oil out there…I wouldn't be convinced (of the efficacy of a dry eye product) just by corneal staining." Another expert said, "There is little correlation between clinical symptoms and clinical findings. Patients who have dry eye, may not have clinical signs, and vice versa. So, the applicability of the drug is measured in different ways. One is cornel staining, and the other is clinical symptoms…Part of the problem with dry eye is that most patients come in because they are symptomatic, and not all causes of corneal staining are dry eye…But is corneal staining a good measure of dry eye? Absolutely."

BACKGROUND ON DIQUAFOSOL

The trials that Inspire submitted to the FDA in support of 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 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.

Inspire had hoped to use Study 03-108, a Phase IIIb trial, to meet the additional requirement, but the FDA would not accept that. Study 03-108 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.

FDA VIEW OF DRY EYE TRIAL ENDPOINTS

It has been difficult for companies to get dry eye drugs approved. Allergan's Restasis is the only currently approved prescription medication for dry eye, and its approval process took much longer than the company expected.

Schirmer and corneal staining are not considered surrogate markers; they are signs, and a sign alone has not been sufficient in a dry eye trial. Symptom relief also has been required by the FDA. The most common signs in dry eye trials are: Schirmer, corneal staining, tear breakup, and osmolality.

There is no single "best" endpoint for dry eye trial. Dr. Wiley Chambers, Deputy Director of Ophthalmics in the FDA's Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products, Office of Drug Evaluation V, Center for Drug Evaluation and Research (CDER), said, "It depends on what you are trying to accomplish…Dry eye is not a single disease. It can be from (a) a lack of producing enough water component, (b) the individual constituents not having enough lipid, or (c) too quick evaporation."

Yet, endpoints for dry eye trials do not appear to be a concern for the FDA. Dr. Chambers said, "The only endpoint in flux in ophthalmology is in the prevention of myopia…There are no other endpoint issues that we've identified. We have been pretty good at giving people specific endpoints for specific indications."

In an interview in December 2003, Dr. Chambers discussed endpoints in dry eye trials. He was asked what it means for approval of a (dry eye) drug if a sponsor:

➢ ***Proves a primary endpoint "sign" in two trials but does not show symptom benefit?***
"Unless the change in the sign is known to be clinically significant, we would not approve the product for a dry eye indication with a sign only. The only single sign we consider clinically significant is clearing of corneal staining. Otherwise, a clinically significant change in dry eye is, by definition, a change that correlates with a change in symptoms."

➢ ***Proves a primary endpoint "sign" in one trial but not symptom relief, and then in a second trial meets the primary endpoint for symptom relief but does not show a statistically significant improvement in a sign in that same trial?***
"The clinical trials need to show the same sign and symptom in each trial."

➢ ***Shows an effect on a sign in one trial and an effect on symptom relief in another trial?***
"The clinical trials should demonstrate replication of the same results."

WHAT THIS MEANS FOR DIQUAFOSOL

Does this mean Study 109 must show a statistically significant benefit on both the primary (objective) endpoint and on at least one of the secondary (subjective) endpoints?
Not according to the company.

A company official claimed the FDA is requiring only a showing of statistical significance on corneal staining, not symptom relief. A source said, "I would take that (acceptance of only corneal staining) as an indication that (the FDA) would like to approve it, but they want to see more consistency in the data before they do. To ask for that short a trial suggests they really just need a slightly bigger n (more patients) or a p-value just a little better to be comfortable… What is important with dry eye is less a concern with side effects than the need for some demonstration that there is any efficacy at all." Another expert said, "The FDA could be asking only for corneal staining if they already have the other information they need."

If it is the case that Inspire only has to show an effect on corneal staining and not on symptoms, it is likely that this means clearance of corneal staining, not simply improvement in corneal stain score. That could be a difficult hurdle, especially if the p-value must be ≤.01. Consider the results of Study 03-105, which were published in November 2004 in the journal ***Cornea***.

- **Objective results.** Diquafosol 2% easily showed a statistically significant improvement in the mean corneal staining score, but it failed to show a statistically significant improvement in clearing of corneal staining (across all areas) at Week 6. Thus, if clearing corneal staining is a requirement in the absence of a benefit on symptoms, it may be difficult for Inspire to meet this endpoint. If not – if diquafosol merely has to show similar results to Study 03-105, then diquafosol most likely will meet its primary endpoint in Study 109.
- **Subjective results.** Diquafosol 2% failed to show a statistically significant improvement in the key symptom measure (foreign body sensation) at Week 6. It may be that it takes longer for this drug to affect symptoms. An expert said, "Six weeks is a pretty short trial. I don't think it is enough (to show symptom improvement). Usually, you need a longer trial to show an effect…It can take three to six months to show an effect on symptoms."

6-Week Diquafosol Study 03-105 Results *(ITT analysis with LOCF)*

Measurement	Placebo n=176	Diquafosol 1% n=176	Diquafosol 2% n=175
Discontinuations	11%	13%	9%
Objective Results			
Primary endpoint #1: Corneal staining score, averaged across all 5 areas of the cornea	~1.125	~0.85 (p=.002)	~0.8 (p<.001)
Adjusted (ANCOVA) mean corneal staining score	1.03	0.90 p<.05	0.83 (p<.001)
Secondary endpoint #1: Clearing of the cornea across all areas	1%	5% (p<.05)	5% (p<.10)
Secondary endpoint #2: Clearing of the central cornea	39%	50% (p<.05)	54% (p<.01)
Corneal staining score 1 week after drug discontinuation	~0.98	~0.86 (p=0.878)	~0.87 (p=0.959)
Subjective Results			
Primary endpoint #2: Clearing of foreign body sensation (score of 0)	15%	N/A	21% (p=.193)
Adverse Events			
Any adverse event	57%	62%	62%
Any ocular adverse event	27%	22%	30%
Burning/stinging on use	2%	3%	7%

*All p-values vs. placebo.

Would the FDA approve diquafosol if Study 109 misses its primary endpoint? **Probably, because this is an "important" endpoint.**

In some medical specialty areas, missing a pre-defined primary endpoint means almost certain death for a new drug application (NDA), but that is not always true in ophthalmology. Dr. Chambers explained, "It depends on whether the primary endpoint is something we agreed to in advance or not…We care about the endpoints we think are important, whether they are primary or not. But if you pick something important for your endpoint, and you don't meet it, that is a big deal."

Does Inspire have to show improvement in the mean corneal stain score or clearing of corneal staining? **Probably clearing of corneal staining.**

The company has not clarified this, but Dr. Chambers comments above would suggest the FDA will want to see clearing, not just a score improvement.

Is Study 109 likely to show an improvement in the secondary symptomatic endpoint? **Probably not.**

Experts warned that this drug may take longer than six weeks to show a symptomatic effect. An ophthalmologist said, "I probably would still use a drug that didn't show improvement in symptoms (in the clinical trial) because there might be a delay in how long it takes to work.

Is six weeks sufficiently long for Study 109? **Probably.**

Inspire has shown the longer term safety the FDA wants, and efficacy trials in dry eye do not need to be long. Dr. Chambers said, "If you can show an effect in a single day, we will take that as efficacy because dry eye waxes and wanes; it is not a consistent thing…On safety, we would want longer term data, generally a year for safety, but we will accept an application before that; we just want the sponsor to continue the trial until ultimately they have that time."

ANOTHER DIQUAFOSOL TRIAL DELAYED

Inspire plans another large, multicenter, randomized, prospective trial of diquafosol in dry eye, but an investigator said this trial has been delayed, and now will not start until January 2005 or later. There are two possible reasons for this:

1. This is a back-up trial in case Study 109 does not satisfy the FDA. The investigator believes this new trial will be required for U.S. approval, that Study 109 is not sufficient even if it is positive.
2. The new trial was designed for European registration, and Inspire is hoping that a strong showing in Study 109 might negate the need to conduct the new study.

TIMING OF STUDY 109

The last patient was enrolled on or before November 7, 2004. That means the last patient would have reached the Week 7 mark on or before December 26, 2004. Assuming, the last patient's final visit could have been delayed by no more than a week due to the holiday season, the trial should have been completed by December 31, 2004, at the latest.

When it initiated Study 109, Inspire said it hoped to report results and submit an amendment to its NDA by mid-2005. However, the results could be forthcoming at any time. One assumption would be that the longer it takes for the results to be released, the less likely it is that they are sufficiently positive for FDA approval.

DIQUAFOSOL APPROVAL OUTLOOK

There is a good chance the FDA will approve diquafosol quickly based on Study 109 if ***all*** of the following factors are met:

1. The FDA really is requiring only an objective measure, not a subjective (symptom) measure as well.
2. The primary endpoint is improvement in mean corneal staining, not clearing of corneal staining.
3. The trial meets its primary endpoint (at whatever p-value is specified).
4. Patients on diquafosol (but not placebo) show a loss of benefit in Week 7 (when the drug has been discontinued).

If diquafosol is approved, it is likely to find use. Among the comments made about the outlook for use were:

- "Restasis took a while to catch on, but use is going up. A lot of people feel the choice is between that and snake oil. The feeling is that at least Restasis feels like a real medicine. What is tough to assess is how much use is going up because doctors feel the need to do something, and this is the something they currently have available. Do I think that, on an everyday basis, there is an indication for as much Restasis as will start flowing out the door? Probably not, but that won't keep prescriptions from rolling out the door."
- "Diquafosol has great potential. It is unique. It actually increases cellular secretions of fluid. It is nothing like what we have currently available on the market. It is a different mechanism of action."
- "No one drug is a panacea. Diquafosol won't be a panacea, but it will be a complement. It will get woven into the general framework (of treatment), and it will change utilization."
- "Diquafosol has a more narrow band of application than Restasis. I think mucin-stimulating agents are valuable to have available, but they will compete with anti-inflammatories (such as Restasis)."
- "Diquafosol has tremendous potential because we are all looking for another bullet for the gun."

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