Evaluate Vantage

May 11, 2020

# Remember Chantix? It’s back – for dry eye disease

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## The smoking-cessation drug, reformulated for nasal delivery, could be launched for dry eye, Oyster Point hopes.

It was quite a leap of faith that investors backing Oyster Point’s $80m flotation last October were taking: that a reformulation of the smoking-cessation drug Chantix, backed by mixed data, would score in a pivotal study as a nasal spray for treating dry eye disease.

Today their faith was partly rewarded, with the phase III Onset-2 study of that new formulation, which the company codes OC-01, yielding positive results. What is less clear is whether this plus the earlier equivocal data will be enough for US approval, though Oyster Point is gunning for a second-half filing all the same.

And the jury is still out on whether the markets will be rewarded for their faith. Oyster Point stock had doubled since the IPO, including an 11% surge on Friday – one working day before the phase III data were revealed – but today’s press release elicited a 10% decline in early trade.

**No more burning?**

However unusual the trading, Oyster Point today insisted that in OC-01 it had an efficacious dry eye treatment that could avoid the burning and stinging sometimes present with approved eyedrops like Allergan’s Restasis or Novartis’s Xiidra. Some 90% of dry eye patients are not on either drug.

To back the efficacy claim Oyster Point toplined the phase III Onset-2 study, in which both OC-01 doses tested, 0.6mg/ml and 1.2mg/ml, met the primary endpoint, relating to signs of the disease, with a high level of statistical significance versus placebo.

However, for a dry eye disease approval the US FDA normally requires symptoms as well as signs to be improved, and it is here that the data become less clear. In Onset-2 only the higher of the two doses beat placebo in improving symptoms ($p<0.05$).

By itself this makes perfect sense: it is logical for a higher dose to outperform a lower one numerically. But Oyster Point’s problem is that the phase II Onset-1 study, the second of the two necessary pivotal trials, showed a benefit on dry eye symptoms for only the 0.6mg/ml, and not the 1.2mg/ml OC-01 dose.

Nevertheless, today Oyster Point determined that it would take the 1.2mg/ml dose to the regulator.

| Summary of Oyster Point's Onset-1 (NCT03636061) and Onset-2 (NCT04036292) studies | | | | | |
|---|---|---|---|---|---|
| | 0.6mg/ml | | | 1.2mg/ml (registrational dose) | |
| | Onset-1 | Onset-2 | | Onset-1 | Onset-2 |
| Primary (sign) endpoint – wk4 Schirmer's score vs placebo* | 7.7 (p<0.001) | 18 pct points (p<0.0001) | | 7.4 (p<0.001) | 21 pct points (p<0.0001) |
| Secondary (symptom) endpoint – wk4 eye dryness score vs placebo | -13.4 (p=0.02) | -3.9 (p=0.07) | | -9.8 (p=0.13) | -6.7 (p=0.002) |
| **In Onset-1 this concerned at the mean score from baseline; Onset-2 looked at the percentage of subjects who achieved ≥10mm improvement from baseline.* | | | | | |

That filing will take the form of a 505(b)2 submission, in which pharmacokinetic data will be bridged to that generated by Chantix. OC-01 and Chantix, a smoking-cessation drug developed by Pfizer, both contain the active ingredient varenicline, an alpha4/beta2 nicotinic acetylcholine receptor agonist.

Chantix had been hit by associations with mental health issues, although a black box warning was removed from the drug's label in 2016. It was the discovery that varenicline could re-establish tear film homeostasis by activating the trigeminal parasympathetic pathway – Restasis and Xiidra act relatively late to reduce inflammation, Oyster Point argues – that gave rise to OC-01.

Of course, proving an effect on signs and symptoms of dry eye disease is no easy task.

Recently Kala Pharmaceuticals found this out when developing Eysuvis, having to run three studies to demonstrate a benefit; and even then, it needed signs and symptoms benefits to be demonstrated, with statistical significance, not once but twice (*Persistence pays off for Kala, March 10, 2020*).

However you cut the Oyster Point dataset, OC-01 1.2mg/ml will be filed having shown a benefit on symptoms in only one pivotal trial.