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Upcoming events: Genfit in liver disease and Astra's new respiratory play

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Welcome to your weekly digest of approaching regulatory and clinical readouts. Genfit is approaching a binary date with the readout of GFT505 in non-alcoholic steatohepatitis (NASH), which could put it on an equal footing with Intercept Pharmaceuticals.

Meanwhile, AstraZeneca hopes to prove that its half-billion-dollar takeout of Pearl Therapeutics was worth it as the Pinnacle progamme reads out in the coming weeks.

GFT505 in NASH

In the booming area of NASH, the bettors' odds-on favourite remains Intercept Pharmaceuticals with its obeticholic acid (OCA). But the dark-horse entrant is Genfit, whose GFT505 is due to report phase IIb data by the end of the first quarter.

OCA has surprised with its clear benefit in resolving NASH disease activity, but its Achilles heel has always been questions over safety. Specific worries of the farnesoid X receptor (FXR) agonist have been its effect on lipids, with a rise in low-density lipoprotein in patients who are already at cardiovascular risk, in addition to the itchiness side effect experienced by many patients.

Now comes GFT505, which works by stimulating the peroxisome PPAR alpha and delta receptors. It does not stimulate PPAR gamma, the mechanism of action that has created worries in diabetes.

Early clinical data suggest that GFT505 has beneficial effects on lipid, glucose and inflammation markers, but the Golden trial will provide better clarity on these questions. It is the first time GFT505 has been tested in this setting.

Golden is testing 270 patents, roughly the same size as the National Institutes of Health-led Flint study of OCA that propelled Intercept into the stratosphere last year (*Boom! Trial halt turns Intercept into an improbable midcap company, January 10, 2014*). Two doses of GFT505, 80mg and 120mg daily, are being tested against placebo. The primary endpoint is NASH clearance, a measurement of liver fat, inflammation and hepatocyte ballooning. Secondary endpoints include fibrosis, liver enzymes, lipid parameters, insulin and inflammatory markers.

Genfit's shares have tripled in the past year as the critical data readout has approached. A number of companies are still fighting for this space, including Gilead Sciences, which recently scooped up FXR assets from Phenex (*Gilead puts small deposit down to snare NASH properties, January 7, 2015*).

With a market capitalisation now pushing $2bn, Genfit still could have some room to run in today's biotech market if the results are golden. But as the binary date approaches the risk of the balloon popping from a negative safety signal or less-than-stellar efficacy data needs to be considered.

AstraZeneca's dual COPD play

AstraZeneca's PT003, meanwhile, is not only rather late to the game in LAMA/LABA combinations for treating COPD, it also faces intense competition within Astra's own pipeline. Nevertheless, the project, which combines formoterol with glycopyrrolate in a metered-dose inhaler, is in a phase III programme comprising no fewer than seven studies in almost 6,000 patients.

Two of the three most advanced trials, the so-called Pinnacle programme, were to have been completed at the end of last year, and are expected to yield data during the current quarter.

Pinnacle 1 and 2 both test PT003 in moderate to very severe COPD, using change in FEV1 over 24 weeks as the primary endpoint. The first compares PT003 against its standalone components separately, while the second also throws Boehringer's Spiriva into the mix, on an open-label basis.

It is thus obvious that Astra is stacking the odds in its favour. What the trials do not test is the potentially

embarrassing question of whether PT003 is any better than its standalone components delivered together but via separate inhalers; both formoterol and glycopyrrolate are available generically.

There is little to suggest failure. At the 2013 American Thoracic Society meeting a phase IIb study showed PT003 to be superior to standalone glycopyrrolate or formoterol or Spiriva, with a dose-response backing use of the 18µg/9.6µg dose in Pinnacle.

EvaluatePharma consensus data forecast 2020 sales of $528m for PT003. Ahead of it two LAMA/LABA combos – GlaxoSmithKline/Theravance's Anoro Ellipta and Novartis/Vectura's Ultibro Breezehaler – have already been launched, and neither has excited so far, while Boehringer Ingelheim's tiotropium plus olodaterol is awaiting approval.

AstraZeneca got PT003 through its $560m takeover of Pearl Therapeutics last year. Its pipeline includes another LAMA/LABA – LAS40464, acquired through Almirall – as well as a triple combo and two bifunctional muscarinic antagonist/beta agonists (*Astra's bargain basement move sends competition a message, July 30, 2014*).

First readout of the Pinnacle programme will give clues as to whether the bet was worth it, though in reality the real battle will take place in the crowded market.

Selected studies of GFT505 and PT003

Study	Enrolment	Design	Trial ID
Golden	270	80mg and 120mg daily vs placebo	NCT01694849
Pinnacle 1	1,751	PT003 vs PT001 vs PT005 vs placebo (BID, double-blind) vs Spiriva (open-label); FEV1	NCT01854645
Pinnacle 2	1,376	PT003 vs PT001 vs PT005 vs placebo (BID, double-blind); FEV1	NCT01854658
Pinnacle 3	850	Open-label extension vs Spiriva.	NCT01970878

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