Evaluate Vantage

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Upcoming events – Zogenix to get Dravet data while Tetraphase concentrates on IV

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Welcome to your weekly digest of approaching regulatory and clinical readouts. Phase III data are expected in the third quarter on Zogenix's Fintepla in Dravet syndrome, a rare form of epilepsy. Fintepla has shown promise in small single-arm studies, but this is the real test.

Also, Tetraphase is expecting phase III data from its intravenous antibiotic eravacycline in complicated intra-abdominal infections. Its stock crashed spectacularly two years ago when the oral formulation failed to show non-inferiority.

Fenfluramine

Dravet syndrome normally begins in the first year of life with frequent prolonged seizures. Current treatment options include the use of antiepileptic medicines, but Dravet seizures can be difficult to control and rescue medications are needed.

The phase III trial, known as Study 1, tested Zogenix's Fintepla, or ZX008, as an adjunctive treatment. Owing to enrolment difficulties Study 1 is actually a pool of two placebo-controlled phase III studies called 1501 and 1502; it now consists of 120 patients aged 2-18 who are on stable epilepsy medications excluding stiripentol. The patients were titrated up over two weeks then held at a fixed dose of either 0.2 or 0.8mg/kg/day for 12 weeks.

The primary outcome measure is to be the change from baseline in frequency of convulsive seizures. The trial is 90% powered to see a 40% drug-placebo difference on seizure reduction.

Open-label extension studies are ongoing, and another phase III called Study 1504 is due to read out in Q1 2018; this includes patients on stiripentol.

Fintepla contains low-dose fenfluramine, and is a selective 5-HT (serotonin) reuptake inhibitor & sigma-1 receptor modulator. Fenfluramine was also the ingredient in Wyeth's Pondimin, a weight loss treatment that was withdrawn in in 1997 because of suspected heart valve damage and pulmonary hypertension.

Data from a nine-patient single-arm prospective study of Fintepla showed a 75% median reduction in seizure frequency, with a range of 28-100% and a median duration of treatment of 1.5 years. However, without a control arm the real treatment effect is difficult to interpret. The most common adverse events were somnolence and anorexia, and no evidence of cardiac valvulopathy or pulmonary hypertension was observed.

Two years ago Zogenix sold off its painkiller business, which included Zohydro ER, to Pernix and is now left with Fintepla and Relday, a once-monthly depot injection of Risperdal. The company has $80m in cash, which should last until mid-2018.

Fintelpla sales are forecast to reach $298m according to consensus from *EvaluatePharma*. In terms of competition GW Pharma is the one to beat. Its Dravet syndrome treatment Epidiolex showed a 39% median reduction in seizures versus 13% reduction for placebo (p=0.0123) in its pivotal phase III trial.

Consensus forecasts from *EvaluatePharma* see Epidiolex selling $1bn by 2022, with nearly half assigned to Dravet and the remainder to Lennox-Gastaut syndrome, another rare form of epilepsy, and tuberous sclerosis. Filings for the epilepsy indications are due this year.

Trial	ID
1501	NCT02682927
1502	NCT02826863
1504	NCT02926898

Intravenous eravacycline

Two years ago Tetraphase suffered a huge crash when the oral version of its antibiotic eravacycline failed in complicated urinary tract infections (cUTI). Shares plummeted 79% and $1.3bn was wiped off the company's market cap.

The phase III Ignite 2 study had tested eravacycline as an IV-to-oral transition therapy; it did not achieve the primary endpoint of non-inferiority compared with levofloxacin. Another trial, Ignite 1, did meet non-inferiority; this tested the intravenous version in complicated intra-abdominal infections (cIAI) versus ertapenem, showing that the oral version was the problematic one *(End of an era for Tetraphase, September 9, 2015).*

But eravacycline's true value sat with the oral formulation as the market is overcrowded with intravenous options. The oral form is now back in phase I trials, with an update on the programme due in the third quarter.

The intravenous version, meanwhile, has plodded along, and data are also due in the third quarter from the Ignite 4 trial comparing intravenous eravacycline with meropenem in cIAI. This is the same indication as the successful Ignite 1 trial, albeit versus a different comparator.

Ignite 4 has enrolled 400 adult patients and the primary endpoint is the number of participants with a favourable clinical response at the test-of-cure visit (25-31 days after first dose) in the microbiological intent-to-treat population.

Ignite 1 and Ignite 4 are expected to support an NDA filing in cIAI.

According to consensus data from *EvaluatePharma*, 2022 sales are set to reach $154m, including $35m from partnering outside the US. Looking at archived data, the forecast had sat at $342m before the Ignite 2 study failure. The company has $128m in cash, which it says is sufficient to fund operations into the second half of 2018. Investors will be jittery over the prospect of more setbacks, and will be eager for the oral version to make a comeback.

Trial	ID	Indication	Note
Ignite 1	NCT01844856	cIAI	IV vs ertapenem, trial met non-inferiority.
Ignite 2	NCT01978938	cUTI	IV to oral vs levofloxacin, trial failed.
Ignite 3	NCT03032510	cUTI	Minimum 5 days IV treatment, then eligible to switch to oral levofloxacin vs ertapenem. Primary completion Dec 2018.
Ignite 4	NCT02784704	cIAI	IV vs meropenem, data due Q3.

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