Evaluate Vantage

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Upcoming events – Cara, Heron and Seres get ready for next phase

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Welcome to your weekly digest of approaching regulatory and clinical readouts. Cara Therapeutics and Heron Therapeutics are both progressing with postoperative pain candidates, with Cara due to resume enrolment in its paused phase III trial of intravenous CR845 next month, and Heron expecting more phase II data with HTX-011.

Meanwhile, the microbiome specialist Seres Therapeutics is soon set to report phase II results with its lead therapeutic, SER-109, in *Clostridium difficile*.

Cara restart

Cara started the phase III Clin3001 study in September, but it was put on hold in February after reports of elevated serum sodium levels in four of the first 90 patients enrolled.

A subsequent safety review concluded that the sodium increases were dose dependent – so Cara will now only test two lower doses of CR845, 0.5µg/kg and 1.0µg/kg, versus placebo. The trial had originally included 1µg/kg, 2µg/kg and 5µg/kg dosing arms.

This change has also cut the number of study participants, from 600 to 450. The primary endpoint is the change in pain intensity over the 24 hours following abdominal surgery, measured using the patient-reported numeric rating scale.

Results should come in at the end of this year or the beginning of next, but Cara has already analysed unblinded data from the initial 90 patients and claims it saw signals of efficacy. Those patients, enrolled before the clinical hold, will be excluded from the final analysis.

Cara plans to start a phase III study of IV CR845 in dialysis patients with uremic pruritus in the first half of this year, and to begin a phase IIb trial of the oral version in osteoarthritis in the second half. The group should have enough cash until the first quarter of 2018.

CR845, the most advanced kappa opioid agonist in development, could bring in around $500m by 2022, according to *EvaluatePharma* consensus forecasts – similar to the $458m forecast for Heron's HTX-011.

But Heron is going for a more tried and tested formula; its asset is a reformulation of bupivacaine/meloxicam. Positive topline phase II data in bunionectomy have raised hopes that it can get approved in the tricky pain arena, and its potential 72-hour duration could give it an edge over current long-acting anaesthetics (*Heron soars with phase II pain success, September 23, 2015*).

The company has a phase II study ongoing in hernia, with results due in the first half of the year. However, Heron does not seem too confident about the outcome – it has increased enrolment from 60 to 160 patients to improve statistical power, and to allow inclusion of a new formulation, HTX-011b. The primary endpoint is summed pain intensity scores over 24 hours.

Heron has also begun a 100-patient dose-finding phase II trial of HTX-011b in abdominoplasty, which has the same primary endpoint and a primary completion date of June 2016.

Seres tackles C *diff*

Seres's so-called Ecobiotic drugs are made up of combinations of microbes that are designed to help restore a healthy microbiome – the term for the genes of the microbes living in the human body.

The company is initially targeting *C difficile* infection, with results from the phase II Ecospor trial of SER-109 due mid-year. The study is evaluating prevention of recurrent infection, versus placebo, for up to eight weeks after treatment.

Seres will be hoping that the data echo impressive results from a 30-patient single-arm phase Ib trial, which

found that 87% of patients achieved the primary endpoint, absence of *C difficile*-positive diarrhoea up to eight weeks after dosing.

The results put SER-109 on a par with more invasive faecal transplants, note H C Wainwright analysts, who believe that Seres, which is backed by Nestlé, could become a leader in microbiome medicine. Others in the space include Vedanta Biosciences and Enterome Bioscience (*Interview – Enterome has a good gut feeling about 2016, January 28, 2016*).

If the phase II results match up to phase I Seres might be able to use them as a basis for filing SER-109 with the FDA, especially as the project has breakthrough therapy designation. But this scenario is fairly unlikely, say Leerink analysts, and Seres will probably still need to carry out a pivotal trial, which should start later this year if all goes well.

Project	**Study**	**Trial ID**
IV CR845	Clin3001	NCT02542384
HTX-011/b	Phase II hernia trial	NCT02504580
HTX-011b	Phase II abdominoplasty trial	NCT02689258
SER-109	Ecospor	NCT02437487

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