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EASL – The hunt for niches in Gilead's world

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Regulus Therapeutics's slump following interim data from its mid-stage trial of RG-101 in hepatitis C looks a little surprising given strong signs of efficacy using one of the shortest regimens yet. Critics could point to a high, but not necessarily unexpected, rate of adverse events as a cause, but the bigger question is the commercial promise of a standalone RNA-based treatment in a space dominated by small-molecule antiviral combinations.

AbbVie, meanwhile, has given itself a fighting chance against the dominance of Gilead Sciences with a series of data releases of its first once-daily combination. The pan-genotypic effectiveness of ABT-493/ABT-530 should make it competitive against sofosbuvir/velpatasvir, but with the latter pill nearing launch the advantage remains with Gilead.

One-month cure

Regulus fell 11% to $7.23 on Friday after it released proof-of-concept data from RG-101 ahead of a presentation at the European Society for the Study of the Liver meeting in Barcelona. The drug is an oligonucleotide that disrupts microRNA-122, expression of which is necessary for replication of the hep C virus.

The California-based group has decided to test it as part of a combination therapy with Gilead's Harvoni, Johnson & Johnson's Olysio or Bristol-Myers Squibb's Daklinza, shortening the 12-week treatment regimens of those direct acting antivirals to just four weeks thanks to a booster injection of RG-101 on the first and 29th day of the trial. The four-week target has been sought by many researchers as it would allow patients to achieve a cure without having to refill a prescription.

On efficacy, Regulus has reason to be encouraged by RG-101. At 12 weeks after the end of treatment, all 14 patients taking RG-101 with Harvoni and all 12 taking Daklinza demonstrated viral clearance, along with 14 of 15 taking Olysio.

Data at the eight-week follow-up suggests that there will be at least one relapse in the Daklinza arm at 12 weeks, the primary endpoint of the trial. Regulus said complete 12-week data will be available at the end of the second quarter, but signs point to a cure rate above 90%, which has been a benchmark for several years.

Adverse events or commercial concerns?

An adverse event rate of greater than 70% in all arms has to be of some concern. However, the most common, fatigue and headache, do not have rates out of line with that of Harvoni; injection site reactions, an adverse event attributable only to RG-101, occurred in nine of 79 patients that have completed treatment so far. A single patient in the Daklinza arm suffered from elevated bilirubin levels, a severe adverse event that has been determined to be possibly related to the study medications.

Perhaps more worrying for investors is the state of play in the hep C space, where direct acting antiviral combinations are capturing a huge share of chronically infected patients in need of immediate treatment. In 2015, nearly 200,000 of the 3.5 million American patients were prescribed one of the three main drugs, according to *EvaluatePharma* data.

The approach of combinations that work in all six genotypes must also be a concern – most treatments have so far focused on genotype 1. Price competition has also improved access to less severely ill patients – Leerink's Geoffrey Porges reports that EASL attendees reported that commercial insurers in the US and payers in other countries are allowing patients with less advanced liver fibrosis to receive antiviral treatments.

Thus it could be the case that if Regulus is successful and launches in 2018 as analysts from BMO Capital Markets forecast, the market will have been saturated and RG-101 will need to show differentiation in addition to its four-week regimen. A trial with a long-acting formulation of GlaxoSmithKline's GSK2878175 could provide that differentiation, but right now this combination is currently being tested with a once-daily version of the Glaxo drug.

In the world of the pills

AbbVie, which has seen 2020 forecasts of its multi-drug hep C treatment Viekira Pak nearly halve in the last six months, may have a second shot with positive looking data for its two-agent combination, the first time it has been able to deliver a single-pill treatment. ABT-493/530 achieved cure rates of 97-100% in non-cirrhotic patients infected with any hep C genotype, with an eight-week regimen in genotypes 1-3 and 12 in the rest, and 100% in cirrhotic patients with genotype 3.

It is just phase II data, however. Gilead's pan-genotypic sofosbuvir/velpatasvir is before the FDA and due a decision by late June, putting it perhaps two years ahead of AbbVie's new entry.

Leerink's Mr Porges points out that Gilead's main weakness against AbbVie is its expected lack of an eight-week treatment for any genotype outside 1, where Harvoni can be used in patients with a low viral load who have never been treated before.

The advantages potentially offered by the rivals being advanced by AbbVie and Regulus are narrow ones, however, and both groups will need clever commercial strategies to exploit them. No hep C competitor yet has come close to laying a glove on Gilead, and it is not for lack of trying.

Trial	**ID**
RG-101 with Harvoni, Olysio or Daklinza	2015-001535-21
ABT-493/ABT-530 in GT 1, 4, 5 or 6	NCT02243280
ABT-493/ABT-530 in GT 2,3, 4, 5 or 6	NCT02243293

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