Evaluate Vantage

April 09, 2015

Zero-sum hep C space awaits next-generation agents

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It has not taken long for the hepatitis C space to blossom from a $3bn to nearly a $20bn market – however, each new entry looks like it will have to rely on stealing share from competitors. Long-awaited data from Merck & Co's phase III trial of grazoprevir/elbasvir due later this month underscore that price and marketing muscle, not scientific knowhow, will now determine winners and losers (see table below).

It will be very difficult to dislodge Gilead Sciences and its first-mover advantage immediately, but Merck stands a decent chance of using its dosing advantage to move into the number two spot ahead of AbbVie. For its part, the latter company is now pivoting to its hep C pipeline as the complicated Viekira Pak dosing regimen threatens to hold it back.

The European EASL meeting beginning in just over two weeks will put a spotlight on the phase III C-Edge trial of Merck's "doublet", a fixed-dose combination of a protease inhibitor and nucleotide polymerase inhibitor that could rival Gilead's Harvoni, which is on course to become the world's second-biggest selling drug this year.

The New Jersey-based big pharma has a featured slot at one of the general sessions to unveil the phase III data, which are expected to include cure rates 12 weeks after cessation of therapy in patients with genotypes 1, 4 and 6.

Edgy

Merck has so far kept the data from public viewing – no abstract is available even though the presentation is not listed as a late-breaker. A cure rate of more than 90% will be necessary for the Merck combination to have a chance to thrive, as marketed products from Gilead and AbbVie have achieved that benchmark.

Interim analyses from the C-Edge trial are featured in abstracts from EASL posters: four weeks after finishing a course of the doublet treatment plus ribavirin patients who have not responded to treatment with interferon and ribavirin achieved a cure rate of 98%. In patients co-infected with HIV the four-week cure rate was 97%, states the abstract from a second poster.

These are good signs that the full trial will achieve the 90%-plus benchmark, although it cannot be assumed that the broader population will necessarily respond; adverse events as well as relapses will also be closely watched.

Merck announced yesterday that the combination, for which the FDA had said it would be rescinding breakthrough therapy designation, had now been granted that regulatory benefit in all genotype 4 patients and genotype 1 patients with end-stage renal disease.

Duopoly

Bernstein analyst Timothy Anderson wrote that the designation puts Merck in a position to overtake AbbVie in hep C and become part of a "duopoly" with Gilead's Harvoni because of its convenience compared with the multi-pill Viekira Pak.

This is clearly demonstrated by *EvaluatePharma's* forecasts for the sector. Hepatitis C sales start to plateau at around $20bn next year, and the top marketed products will be in retreat by 2020 as new projects premiere and begin to erode revenue.

Hep C growth not perpetual – the outlook for marketed and clinical-stage agents (ww sales, $m)							
	Product	**Company**	**2013**	**2015e**	**2017e**	**2019e**	**2020e**
Marketed	Harvoni + Sovaldi	Gilead Sciences	139	13,546	12,643	10,048	9,458
	Viekira Pak	AbbVie	-	2,436	2,989	2,646	2,499
	Daklinza	Bristol-Myers Squibb	-	465	732	693	671
	Sunvepra	Bristol-Myers Squibb	-	127	200	190	184
	Olysio	J&J/Medivir	23	602	102	35	27
	Victrelis	Merck & Co	428	80	25	12	11
	Incivo/ Incivek	J&J/Vertex	983	57	19	4	3
Phase III	grazoprevir/ elbasvir	Merck & Co	-	-	1,397	1,895	1,841
	Sovaldi/ GS-5816	Gilead Sciences	-	-	219	154	122
Phase II	GS-9857/ Sovaldi/ GS-5816	Gilead Sciences	-	-	-	1,781	2,449
	sovaprevir	Achillion	-	-	-	1,032	1,478
	IDX21437	Merck & Co	-	-	-	655	717
	danoprevir/ ritonavir	Roche	-	-	40	86	91
	RG7227	Roche	-	-	-	7	14
	TMC647055	J&J	-	-	-	1	2
Total hep C*			3,729	18,573	19,540	20,645	21,314

**Includes sales from non-direct acting antivirals. Source: EvaluatePharma.*

Payers were quick to complain last year when Gilead launched Sovaldi at a list price of $1,000 a day, and have used the competition from Viekira Pak to squeeze out price concessions (*Hep C price war evolves into value competition, January 20, 2015*).

The data show that despite the high price tags treatment has expanded significantly over the past two years as physicians and patients keen to avoid the side effects and long treatment courses of interferon-based therapies have moved to the new direct-acting antivirals; starting next year, however, every sale gained for one drug comes at the cost of another.

Merck's doublet promises to be a Harvoni-like entry: a one-pill once daily interferon- and ribavirin-free combination that can achieve a cure in many patients with just 12 weeks of medication. It is no surprise, then, that Gilead is hard at work with new combinations, including a triple, with the goal of getting treatment down to a single four-week prescription.

Likewise, Merck's rise explains why AbbVie's next-generation agents also figure large at EASL. The Illinois-based group will be publicising pharmacokinetic and safety data from the combination of ABT-530 and ABT-493 in phase I. In a press release yesterday AbbVie disclosed that a ribavirin-free combination of those two agents achieved a 99% cure rate four weeks after treatment concluded; these phase II data will not be featured at EASL, however.

How significant these next-generation regimens can be is an open question. The initial "warehouse" of patients already progressing to cirrhosis and other complications might well pass in the next couple of years, and payers will be reluctant to pay top dollar for patients who do not appear to be progressing. The value proposition is about to change in hep C.

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