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Bristol-Myers setback another blow to hep C field

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The once-crowded field of candidates jostling to be part of the first all-oral hepatitis C antiviral cocktail got decidedly emptier today with the news that Bristol-Myers Squibb had cancelled development of its $2bn asset BMS-986094. The safety worries that had triggered a clinical hold on the drug turned out too deep to accept – a death in the original heart failure patient, plus nine other hospitalised subjects resulting from heart and kidney toxicity.

Excitement around the space has already dissipated with Gilead Sciences' seemingly uninterrupted march towards the all-oral holy grail and signs that the untreated population might be smaller than was originally believed. Failure of a closely watched candidate – and indeed one validated by a big pharma deal – will do nothing to reinvigorate the interest of investors whose interest may be turning elsewhere.

Hefty price tag

The news is not necessarily a setback for the nucleoside NS5B polymerase inhibitor class or for Bristol-Myers, which still has a decent pipeline in spite of some failures (see tables). However, it is another knock to sentiment for developers in the hep C space – at least, the ones that are not called Gilead (*Signs are growing that the hep C ship is sailing, August 1, 2012*).

Hepatitis C nucleoside NS5B polymerase inhibitor pipeline

Status	Product	Company	Selected trial IDs
Phase III	GS-7977	Gilead Sciences	NCT01497366 NCT01542788 NCT01604850 NCT01641640
Phase II	RG7128	Gilead Sciences/Roche	NCT00869661 NCT01057667 NCT01278134
	IDX184	Idenix Pharmaceuticals	Partial clinical hold
Phase I	RO5303253	Roche	NCT01181024
	RO5428029	Roche	NCT01371162 NCT01345942
	ALS-2200	Vertex Pharmaceuticals	NCT01590407
	ALS-2158	Vertex Pharmaceuticals	NCT01554085

As if further confirmation were needed, California-based Gilead is now decisively in the lead to get a much-heralded all-oral hepatitis C combination to the market and address those patients thought to be awaiting a therapy free of interferon and its side effects.

The failure of '094 makes Gilead's decision to go it alone rather than pairing its own $11bn NS5B, GS-7977, with Bristol-Myers' daclatasvir all the more painful for Bristol-Myers (*EASL - Gilead-BMS score all-oral hep C win but will pairing last?, April 19, 2011*).

It also calls into question the company's judgement when it decided to snap up Inhibitex earlier this year for $2.5bn in order to gain access to '094 (*Bristol-Myers Squibb lays claim to new hep C stake with Inhibitex*

buyout, January 9, 2012). The New York group announced today that it was taking a $1.8bn charge in the third quarter related to R&D costs.

Selected abandoned Hepatitis C nucleoside NS5B polymerase inhibitor projects			
Abandoned phase	**Product**	**Company**	**Termination Date**
Phase II	Valopicitabine (NM283)	Novartis/Idenix Pharmaceuticals	13/07/2007
	BMS-986094	Bristol-Myers Squibb	23/08/2012
Phase I	HCV-POL	Johnson & Johnson/Medivir	06/04/2012

Collateral damage

It has not been stated exactly why, but only one other drug in the class has been subject to regulators' caution flag: Idenix Pharmaceuticals' IDX 184, a project that was under a partial clinical hold once before (*Idenix hep C drug hit by cardiovascular worries, August 16, 2012*). Analysts contend that the reason IDX 184 and '094 are structurally similar and have an identical active metabolite suggests that the metabolite is the toxic agent.

Massachusetts-based Idenix did not make any statements today in the wake of Bristol-Myers' announcement. Its shares were down 1% to $6.01 in early trade today.

Benefiting from the Bristol-Myers news was Achillion Pharmaceuticals, which other than Idenix remains one of the last independent hep C plays. Its shares were up 3% to $6.80 this morning. It does not hurt the Connecticut firm that it is not testing an NS5B at all, and its lead candidate, sovaprevir, is a protease inhibitor, a drug class that has already seen hep C success in the form of Vertex Pharmaceuticals' Incivek and Merck & Co's Victrelis.

For a while, hep C had seemed to be the exception to the rule in drug development, producing almost nothing but success and generating some jaw-dropping M&A deals. Although it seems inevitable that an all-oral regimen will soon be launched, it was equally inevitable that expectations would fall back to earth.

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