Evaluate Vantage

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Cymabay is out, but for Genfit the band plays on

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A day after seladelpar is canned over toxicity fears elafibranor passes a safety review, but should Genfit holders worry all the same?

Genfit came close to becoming the biggest casualty of yesterday's discontinuation of Cymabay's seladelpar. Little wonder that the French group was moved this morning to issue a statement protesting that its own Nash project, elafibranor, was not affected by the toxicity that had done for seladelpar.

It is true that, with over 2,000 cumulative years of patient exposure to elafibranor and no worrying findings, toxicity should not be a worry. But it is efficacy, not safety, that is the Genfit project's major challenge, and today's move to continue the pivotal Resolve-It trial was not driven by a futility analysis.

Rather, Genfit pointed out that this was a routine safety review – the seventh such analysis to show no toxicity signals in the Resolve-It Nash trial, which will continue to its all-important interim readout in the first quarter (*Genfit's liver disease Hail Mary approaches, September 19, 2019*).

No such luck for Cymabay, which yesterday canned its own Nash asset, seladelpar, citing evidence of interface hepatitis in liver biopsies.

Cymabay stock crashed 76%, which is surprising to the extent that it implies that seladelpar had much value to begin with. In reality the asset already looked like a dead duck, having flunked a phase II Nash study in June; a pivotal trial in primary biliary cholangitis was, until yesterday, under way.

The PPAR fallout

So the net tightens around PPAR agonists, a once promising class of metabolism drugs. The disaster encompasses gamma-specific assets – the "glitazone" diabetes drugs like Avandia, which have been contraindicated out of existence – as well as the "glitazars", which act on the alpha and gamma PPAR subtypes, and which have all been discontinued owing to toxicities.

Cymabay's seladelpar setback could spell curtains for delta-specific PPARs, too; development of another PPAR delta agonist, Glaxosmithkline's GW501516, is known to have been scrapped 12 years ago over tumours seen in rodent studies.

The big question for Genfit followers is what this might mean for elafibranor, a dual PPAR agonist active at alpha and delta receptors. Genfit fell 8% yesterday as the Cymabay discontinuation was announced, but recovered to end the day flat.

Today the group took the unusual step of directly naming its competitor to differentiate its mechanistic specificity from that of elafibranor. “In trials with elafibranor to date there have been no issues with interface hepatitis,” Genfit stated, prompting its stock to climb 6% today.

The focus for Genfit remains whether elafibranor is efficacious – a question that today’s safety all-clear does not answer. Given that the project’s mid-stage Golden study was a failure, success in phase III looks like a long shot; should Resolve-It fail Genfit’s move to press on without a confirmatory phase II trial will be criticised.

Interestingly, two competing PPAR delta-specific industry assets remain in early clinical trials: Abionyx’s CER-002 and Reneo’s REN001, licensed from VTV Therapeutics. Though neither is being studied in Nash their days might be numbered.

The fate of selected PPAR agonists			
Project	**Company**	**Status**	**Reasons**
PPAR gamma-specific "*glitazones*"			
Avandia (rosiglitazone)	Glaxosmithkline	Contraindicated	Cardiovascular toxicity
Actos (pioglitazone)	Takeda	Contraindicated	Liver & cardiac toxicity
Rezulin (troglitazone)	Glaxosmithkline	Withdrawn	Liver toxicity/hepatitis
PPAR alpha & gamma agonist "*glitazars*"			
Pargluva (muraglitazar)	BMS/Merck & Co	Discontinued (filed)	Cardiovascular risk
Ragaglitazar	Novo Nordisk	Discontinued (phase III)	Mouse tumours
MK-767	Merck & Co/Kyorin	Discontinued (phase III)	Mouse tumours
Imiglitazar	Takeda	Discontinued (phase III)	Liver toxicity
Galida (tesaglitazar)	Astrazeneca	Discontinued (phase III)	Renal injury
Aleglitazar	Roche	Discontinued (phase III)	Bone fractures, heart failure & GI bleeding
PPAR delta agonists			
GW501516	Glaxosmithkline/Ligand	Discontinued (phase II)	Mouse tumours
Seladelpar	Cymabay	Discontinued (phase III)	Interface hepatitis
CER-002	Abionyx	Phase I for cardiovascular diseases	–
REN001/HPP593	Reneo	Phase I for fatty oxidation disorders	–
PPAR alpha & delta agonist			
Elafibranor	Genfit	Phase III for Nash	–
Source: EvaluatePharma & company statements.			

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