Evaluate Vantage

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Gilead’s Galapagos hopes now rest on Toledo

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Toxicity worries send yet another Gilead/Galapagos project, ziritaxestat, to the scrapheap.

Gilead’s $5bn deal with Galapagos had already been falling apart at the seams. Another setback yesterday, for the late-stage idiopathic pulmonary fibrosis project ziritaxestat, further exposes how little Gilead has got for its money.

Hopes for the deal now rest even more heavily on the early-stage “Toledo” programme, and initial data from the first of these projects, the SIK2/3 inhibitor GLPG3970, are due this year. However, even success here is not going to rescue this tie-up.

In striking the deal Gilead had bought into Galapagos’s aggressive development decisions. One move that now looks foolhardy was advancing ziritaxestat into a large phase III programme on the basis of a mid-stage trial in just 23 IPF patients.

In a damning note yesterday, Leerink’s Geoffrey Porges contended that the project had “clearly [been] rushed into phase III for commercial reasons, rather than based on clear and convincing evidence of the drug’s safety and efficacy”.

Toxic

It was toxicity that tripped up ziritaxestat, an autotaxin inhibitor. The companies stated yesterday that the pivotal Isabela 1 and 2 trials had been halted after an independent data monitoring committee concluded that the project’s risk-benefit profile did not support their continuation.

The fact that Galapagos also discontinued a trial in systemic sclerosis raised eyebrows, and the company later confirmed to analysts that a dose-dependent increase in death had been seen in the Isabela studies. It is unclear whether this was an on or off-target effect; the former would be bad news for the other two autotaxin inhibitors in clinical development, Bridge Biotherapeutics’ BBT-877 and Blade Therapeutics’ BLD-0409.

Still, perhaps the warning signs for this class were already there: Boehringer Ingelheim had handed back rights to BBT-877 last November over toxicity concerns, without giving details on the specific issue.

One beneficiary of the news could be Fibrogen, whose anti-CTGF antibody pamrevlumab is now the most advanced pipeline project in IPF. However, this disease has proved tough to crack, so assuming victory here seems premature.

Galapagos also has various other projects in development for IPF, but expectations cannot be too high for its next most advanced asset, GLPG1205. Although the company claimed a win in another small study in November, GLPG1205 was not statistically significantly better than placebo on the primary endpoint, forced vital capacity (*Galapagos "win" highlights crowded idiopathic pulmonary fibrosis pipeline, December 4, 2020*).

The group's main aspirations now rest on its Toledo programme, which until recently was shrouded in secrecy. Galapagos disclosed late last year that its targets were the salt-inducible kinases (SIKs).

Two trials of the lead Toledo project, GLPG3970, in rheumatoid arthritis and ulcerative colitis are set to read out in mid-2021. However, both are small, at 25 and 30 patients respectively, which might make it hard to ascertain whether the asset can differentiate itself, Stifel analysts noted. Differentiation would be vital in the crowded immunology space.

And opting in, with the fees involved, could further damage Gilead's reputation given the fate of the other Galapagos projects.

A very short engagement: what's left for Gilead and Galapagos

Project	Deal details	Mechanism/uses
Still in play…		
GLPG3970	"Toledo" programmes; Gilead has option over ex-Europe rights for $150m per programme, 20-24% royalties	SIK2/3 inhibitor; in ph2 for RA (Ladybug), UC (Sea Turtle) & Sjögren Syndrome (Glider)
GLPG4399		SIK3 inhibitor; "IND ready"
GLPG4605		SIK2/3 inhibitor, preclinical
GLPG1205	Gilead has option to buy ex-Europe rights for all Galapagos pipeline projects	GPCR84 antagonist; claimed win in ph2 Pinta trial in IPF, phIIb dose-ranging study planned
GLPG2737		CFTR inhibitor; had been in CF trials, now in ph2 Mangrove study for autosomal dominant polycystic kidney disease
GLPG3667		Tyk2 inhibitor; in ph1 for psoriasis
In limbo…		
Jyseleca (filgotinib)	Initially 50/50 deal, Gilead handed back most development rights in Dec 2020, but Crohn's and UC still in play	Jak inhibitor; US CRL for RA; Manta/ Manta-Ray safety study data due mid-2021; ph3 in UC positive (Selection), ph3 in Crohn's ongoing (Diversity)
On the scrapheap…		
Ziritaxestat (GLPG1690)	Gilead had full rights, $395m milestone due on US approval	Autotaxin inhibitor; discontinued on toxicity findings in Isabela trials
GLPG1972	Gilead option over US rights for up to $550m after ph2b; Servier had ex-US rights	AdamTS-5 inhibitor; failed ph2 in osteoarthritis
GLPG3312	"Toledo" programme	3 undisclosed inflammatory targets; discontinued after ph1 (no data)

Source: Company statements, clinicaltrials.gov.

Galapagos might also be clinging to the hope that filgotinib is not dead, despite being largely written off after Gilead abandoned most of its plans for the project in December (*Gilead would rather forget filgotinib, December 16, 2020*).

Inflammatory bowel disease is still in play, and Gilead and Galapagos expect to say more about US filing plans here after the Manta and Manta-Ray testicular toxicity trials read out; 26-week data are due in mid-2021.

But the chances of getting approval here, let alone making filgo a commercial success, look slim, particularly given the toxicity worries now attached to this project.

Gilead’s stock barely moved yesterday, suggesting that investors had already written off any contribution from Galapagos. But it is an embarrassing outcome for Gilead’s chief executive, Daniel O’Day, as Galapagos marked his first big deal at the helm.

Galapagos, meanwhile, slumped 18%, and is now trading below cash. With any substantial readouts a long way off, the group has a tough road ahead.

This story has been updated to include GLPG3667's mechanism of action.