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No hiding the Toledo disappointment for Galapagos

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GLPG3970 is biologically inert in ulcerative colitis and rheumatoid arthritis, so Galapagos's search for something better goes on.

Galapagos's efforts to put a brave face on the latest of many recent disappointments have come to nothing. Last night's revelation that the group's second "Toledo" project was, like the first, a dud prompted a 12% selloff this morning, notwithstanding the smokescreen of early data from an unrelated asset, the Tyk2 inhibitor GLPG3667.

Though compared with the competition the Tyk2 data are actually not that great either, investors' concerns will centre on the disappointment of the much vaunted Toledo programme. With $6bn of cash Galapagos is compelled to continue this work, but the vague possibility of a Gilead opt-in will serve as an overhang.

The opt-in is one of the remaining elements of a disastrous 2019 tie-up between Gilead and Galapagos, under which the US group can pick up ex-Europe rights for $150m per Toledo programme. Galapagos's cash is probably better spent elsewhere at this point, as given the poor data so far Gilead looks unlikely to pull the deal trigger any time soon.

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Galapagos quietly shelved the first clinical Toledo project, GLPG3312, after running a phase 1 trial whose results it has not revealed. Now the second, GLPG3970, looks to be headed for the scrapheap after showing no activity in two small phase 2 studies, Ladybug in rheumatoid arthritis and Sea Turtle in ulcerative colitis.

The former GLPG3970 trial showed no difference versus placebo on week-six DAS28 response and most other efficacy endpoints. The latter drew a blank on week-six Mayo Clinic score despite positive signals in other parameters, Galapagos said after market close yesterday.

The company instead played up a small phase 1 study in which four of 13 psoriasis patients recorded a Pasi 50 response to GLPG3970; while this is uncompetitive it is enough for Galapagos to "bring forward improved molecules". GLPG3970 itself looks dead, however, especially given sellside reports of toxicity putting a ceiling on its dosing.

It was only recently that Galapagos confirmed the Toledo mechanism as inhibition of salt-inducible kinases (SIKs). GLPG3312 was a pan-SIK inhibitor, while GLPG3970 hit SIK2/3; preclinical Toledo projects include

GLPG4399, GLPG4876 and GLPG4605. The only apparent industry rival is Greenfire Bio's SIK2/3 inhibitor GRN-300, paradoxically in a cancer trial.

Waiting for Gilead... selected Galapagos pipeline projects		
Project	**Deal details**	**Mechanism/uses**
GLPG4399	"Toledo" programmes; Gilead has option over ex-Europe rights for $150m per programme, plus 20-24% royalties	SIK3 inhibitor; "IND ready"
GLPG4605		SIK2/3 inhibitor, preclinical
GLPG4876		SIK2/3 inhibitor, preclinical
GLPG2737	Gilead has option over ex-Europe rights for all Galapagos pipeline projects	CFTR inhibitor; had been in CF trials, now in ph2 Mangrove study for autosomal dominant polycystic kidney disease
GLPG3667		Tyk2 inhibitor; ph1 psoriasis trial showed 40% wk4 Pasi 50 at high dose
GLPG0555		Jak1 inhibitor that completed ph1 in 2011; now said to be in ph1 osteoarthritis study, not on clinicaltrials.gov
GLPG1205		GPCR84 antagonist; claimed win in ph2 Pinta trial in IPF; no active trials since 2020
GLPG4716		CHIT1/AMCase inhibitor licensed from Oncoarendi; ph2 IPF trial planned
Source: Galapagos.		

Gilead also has options over other Galapagos pipeline projects, including the Tyk2 inhibitor GLPG3667. Galapagos yesterday tried to play up phase 1 psoriasis data showing four of 10 high-dose GLPG3667 patients scoring Pasi 50 responses at week four, versus one of 10 placebo recipients, though there were zero responses among 11 low-dosed patients.

Again this looks uncompetitive, though a precise comparison is impossible. The most advanced Tyk2 rival, Bristol Myers Squibb's deucravacitinib, showed 54-59% responses on a tougher measure, Pasi 75, albeit at 16 weeks. Galapagos said one of the four high-dose GLPG3667 Pasi 50 responders achieved Pasi improvement of 81%, making them a Pasi 75 responder, and a second came up just short, at 74%.

While the efficacy of neither Tyk2 looks close to that of injected biologicals, in the oral space deucravatinib looks superior to Amgen's PDE4 inhibitor Otezla. Galapagos, it would seem, still has some way to go to show that GLPG3667 is competitive against the Bristol project.

Much of this will today be weighing on the minds of the Gilead execs who decided to give Galapagos $5bn two years ago, but who then had to suffer the clinical failures of filgotinib, ziritaxestat, GLPG1972, GLPG3312, and now GLPG3970. You can hardly blame Gilead if it thinks this deal is cursed.

But since Galapagos sees the prospect, however dim, of a future Gilead opt-in it will continue ploughing cash into Toledo. It might be wiser to seek a new licensee, or even to can the project entirely, but while Galapagos remains beholden to Gilead its investors have to grin and bear it.