Galapagos

Everything you always wanted to know about MANTA, but were afraid to ask

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We expect recruitment to accelerate in 2019

Enrollment for MANTA has been trailing behind the original schedule, posing a risk of a later filing in the US. However, considering the increased number of active sites in the most populous territories, diminishing competition from other clinical trials, and potentially expanded patients pool, we believe it is feasible for the trial to recruit remaining patients at a higher pace and have the primary readout before YE'19.

Rolling submission seems feasible

In its Q3 call, Gilead indicated contemplating to discuss with the FDA the possibility of a rolling submission, i.e. filling MANTA later than clinical RA data (n.b. the submission will still require the full 52w data from FINCHes that is expected May-Jun'19). Considering an upfront request from the FDA for MANTA, foregoing the study for filing completely might not be the best option, however considering rather lenient treatment of FDA approved drugs with preclinical testicular tox, the FDA could be flexible to allow for the rolling submission.

MANTA outcome is positively skewed

The degree of the FDA's attention to the preclinical findings suggests some likelihood that the observed testicular toxicity is not a random fluke. However, the combination of (i) no effect in the other animal models, (ii) indirect evidence of no change in hormones, and (iii) a beneficial effect of TNF inhibitors on sperm, as well as (iv) a wide non-inferiority margin of 20-30% seen in similar studies, make us believe that the results are positively skewed.

Scenario analysis points to upside regardless of MANTA

Our scenario analysis based on the pace of recruitment and the outcome of the MANTA study suggests 38% upside to the current share price in case of fast recruitment and positive outcome (most likely outcome in our view) and 10% in case of slow recruitment and negative outcome (least likely outcome).

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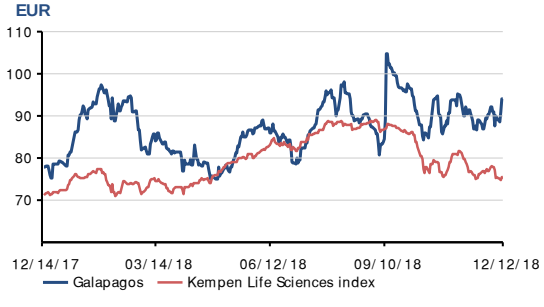
Rating	BUY
Price Target	€125.00
Closing price (12 Dec 2018)	€94.02

Company data

Market Cap	€5,120.8m
52-week range	€70.64 - €105.35
Number of shares	54.5m
Free float	61.6%
Avg. daily volume (20d)	369,754
Avg. daily turnover (20d)	€33,628,380
Daily turnover	€41,553,520
Next announcement date	21 February 2019
Reporting Period	FY'18 results



Source: Bloomberg

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While Galapagos' share price stabilized in anticipation of FINCH 1 and 3 readouts (see "JAK of all trades" here), the testicular safety study MANTA emerged as a new source for market concerns, in particular, due to its potential impact on filgotinib's filing timelines and the label. Based on the trial's protocol, and discussions with Galapagos and KOLs, we believe the recruitment for MANTA should substantially accelerate in the coming months with a high likelihood of results in late 2019, clarifying filing timelines and removing overhang from the shares. We also estimate that similar to other testicular toxicity studies, MANTA was designed with a 20-30% non-inferiority margin, making a low bar to succeed and thus see a limited risk for the label and commercial potential.

Every sperm is sacred

Gilead's communication in Q3 call and the history of MANTA study at clinicaltrials.gov - primary completion moved from Jun'19 to Jan'21 in Feb'18 - clearly indicate that recruitment has been slow and been trailing behind the plan. We see the following reasons:

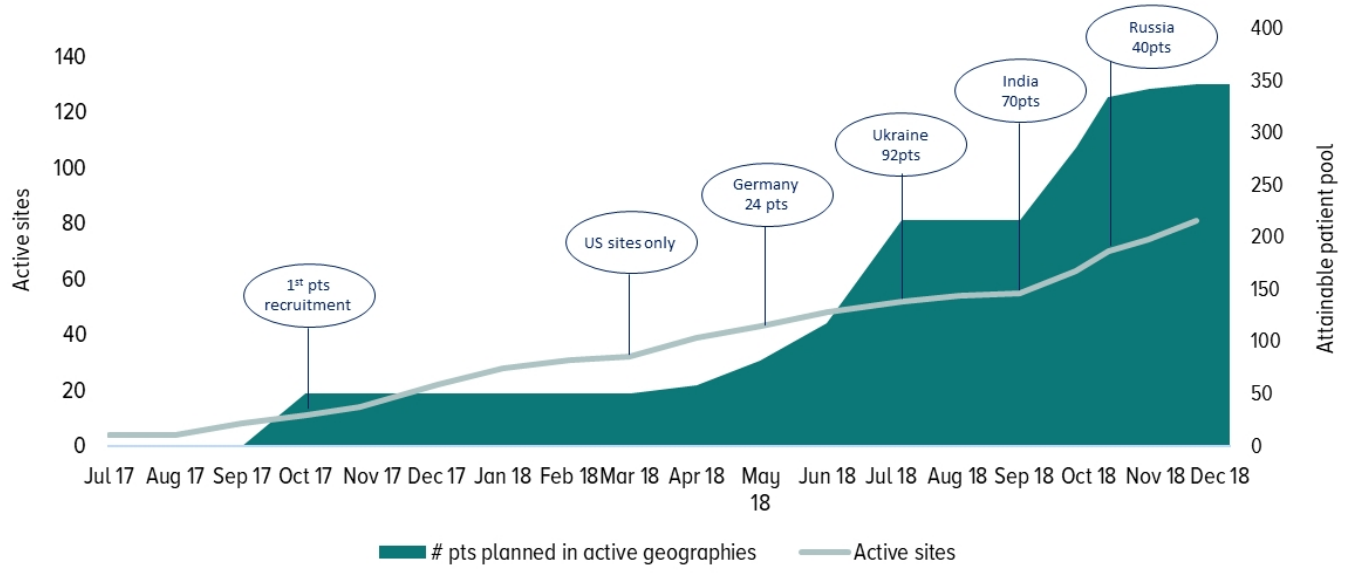
- **Restrictive recruitment criteria (good men are hard to find):** The inclusion criteria require endoscopy confirmed moderate-to-severe ulcerative colitis (UC) and semen quality a bit below "normal" characteristic. On its own, endoscopy requirements leads to ~38% screening errors (Tofa trial in UC, Sandborn 2017), and while UC is not known to significantly impact fertility (Shin 2016), even in healthy volunteers the screening error is ~70% (Hellstrom 2003), thus making recruitment of UC males with normal sperm especially challenging.

- **Competition from other UC clinical studies:** There are 3 other studies ongoing with filgotinib and upadacitinib in UC that have rather similar inclusion criteria to MANTA, ex-sperm mobility requirements (e.g. 50%/66% in total/US of MANTA trial sites participate in filgo's phase III UC SELECTION study). Furthermore, there are several large phase III trials with novel biologics (SHP647, etrolizumab, mirikizumab, RPC1063) recruiting at the same time. Lacking the requirement for 6 sperm samples and associated procedures and restrictions (e.g. abstain from ejaculating at least 48 hours and a maximum of 7 days before each semen collection), those trials are likely more appealing for patients and physicians.

- **Western patients have many options:** MANTA offers patients two options: filgotinib for 6 month or a stable dose of sDMARD (e.g. ASA-5, MTX or corticosteroids), which considering the broad availability of biologics is less attractive to patients.

- **Late openings of the most populous sites:** According to clinicaltrials.gov, for the first 9 months recruitment has been limited to US centers. Meanwhile, Ukraine, India and Russia, that are expected to provide the majority of the patients (92, 70 and 40 out of 250), opened sites only in July, September and October 2018 respectively. We understood from the company and discussions with KOLs that late opening of these sites is partially explained by a lack of appropriate infrastructure to process sperm samples in accordance with the FDA requirement. The FDA guidelines (here) require all the sperm samples to be handled in a standardized manner and analyzed in a single central laboratory.

Figure 1 - MANTA site openings and targeted population



Source: Kempen analysis, clinicaltrials.gov, EudraCT, WHO, clinical protocols with Russian, Ukrainian and Indian health authorities * US target recruitment NA, assumed 50 patients pts = patients

We expect recruitment to accelerate in 2019

We believe that several important impediments for recruitment have been resolved and we expect recruitment to accelerate in 2019 to allow for the filing late 2019/early 2020 and approval in 2020:

- **Most populous sites are ramping up:** As mentioned above, the study protocol has been approved in Russia, Ukraine and India that combined are responsible for 80% of the trial population. There is no visibility on recruitment pace, but sites are opening up rapidly with 7/30 active sites in India in only 2 months and 11/16 in Ukraine in 5 months. There is limited access to biologics treatments and a limited overlap from other JAK trials in targeted territories which should facilitate enrollment. Galapagos confirmed to us that proper sperm processing infrastructure has been installed in these sites prior to opening.
- **Competition from SELECTION trial should subdue:** According to the company, the recruitment for SELECTION is approaching completion. Thus in the US MANTA would be the only filgotinib option for UC patients, which considering a significant overlap in trial sites should facilitate recruitment in the US.
- **New indications are being added to the protocol:** Gilead is in discussion with health authorities to expand inclusion criteria to include RA, AS, PSA patients. We understood from the KOL that to avoid competition with the ongoing studies the inclusion criteria might focus on patients with mild inflammation (vs usual moderate to severe) who represent >60% of screened patients for filgotinib phase II trials in RA. Such a protocol amendment should further increase the pool of attainable patients and improve recruitment speed.

Rolling submission seems a feasible option

In its Q3 call, Gilead indicated contemplating to discuss with the FDA the possibility of a rolling submission, i.e. filling MANTA study later than clinical RA data (n.b. submission will still require the full 52w data from FINCHes that is expected May-Jun'19). Considering an upfront request from the FDA for MANTA, foregoing the study completely for filing might not be the best option, however considering the

historical approach of the FDA to testicular tox in animal models, the FDA could be flexible to allow for the rolling submission.

The FDA approval history shows that the agency has been historically lenient to the drugs that showed an adverse impact on spermatogenesis in preclinical toxicology studies (PDE5 class, Tracleer, Soliris, Solodyn). The majority of these drugs were approved with an occasional request for human testicular toxicity studies as a part of post-marketing commitment (e.g. Tracleer, Avantifil, Table 1) that were submitted several years after the initial approval with no impact on the label in the interim.

Table 1 - Approved drugs with preclinical testicular toxicity finding

Drug	Indication	Use	Evidence in animals and human	Testicular tox in the label
Tadalafil	Erectile dysfunction	Chronic	**Animal**: decreased spermatogenesis in dogs **Human:** 2 trials in healthy and ED males showed no effect on spermatogenesis, hormones	**2003**: no warnings, animal tox mentioned in nonclinical toxicity, no effect on human sperm
Avanafil	Erectile dysfunction	Acute	**Animal:** abnormal sperm motility and morphology in rats **Human**: trial in healthy volunteers no effect on sperm concentration, sperm count motility , morphology and semen volume	**2012**: no warnings, no acute effect on sperm motility or sperm morphology in a group of healthy male subjects. The effect of avanafil on human spermatogenesis is unknown. Testicular tox trial requested post marketing **2018**: clinical data submitted, no adverse effect on sperm
Vardenafil	Erectile dysfunction	Acute	**Animal:** Testicular atrophy/degenerative in dogs and rats **Human:** no effect	**2003**: no warnings, there was no effect on sperm motility or morphology after single 20 mg oral doses of vardenafil in healthy volunteers **2003+**: sperm study done, not reflected in the label
Pregabalin	pain	Acute	**Animal:** decreased sperm counts and sperm motility in male rates **Human:** no difference between pregabalin and placebo on sperm motility in healthies adverse effects of pregabalin on sperm morphology, sperm motility, serum FSH or serum testosterone levels	**2006**: no warnings, animal data mentioned in toxicology **2016**: label updated for sperm study, no warnings
Minocycline Extended-Release	severe acne vulgaris	Acute	**Animal:** adversely affected spermatogenesis in male rats **Human:** in healhy volunteers study human spermatogenesis and circulating levels of FSH and testosterone were unaffected	**2006:** no warning, limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis **2009**: study completed, not reflected in the label
Bosentan	PAH	chronic	**Anlimal:** increased incidence of testicular tubular atrophy in rats at low doses **Human:** decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment	**2001:** Precautions: animal data mentioned, no data on the effects of bosentan or other endothelin receptor antagonists on testicular function in man **2009:** Warning for decreased sperm counts, clinical data submitted
Ambrisentan	PAH	chronic	**Animal:** increased incidence of testicular tubular atrophy in rats at low doses	**2011:** Warning for decreased sperm counts based on bosentan data
Dutasteride	benign prostatic hyperplasia	chronic	**Animal:** reduced sperm counts in rats **Human:** clinical trial in healthies showed decrease in sperm counts and motility with in - noninferiority margin	**2001**: no warning , mentioned in preclinical tox

Source: Ding, 2017; FDA drug approval database, respective labels and clinical reviews

MANTA has a low bar to meet

Following the industry practice for testicular toxicity evaluation guidelines, MANTA will recruit 250 men with moderate-severe UC and reasonably normal semen quality. The primary endpoint is a percentage of patients with a 50% decrease in sperm concentration from baseline at week 13, the week 26 observation is the key secondary endpoint. Although not explicitly disclosed, based on similar trials (e.g. avanafil, udenafil) we expect that trial was powered for a 20%-30% non-inferiority margin thus setting a very low bar for the trial to succeed.

What do we know?

In the preclinical tox models, damage to testis in rats and dogs was observed at doses producing blood levels of filgotinib slightly higher than blood levels produced by filgotinib 200mg bid (200mg qd is used in the clinical trials). At these doses, while sperm counts in rats and dogs increased after filgotinib was stopped, they stayed low overall and did not return to normal. At the highest doses tested in male rats and dogs, these adverse effects did not go away. These adverse effects were not seen in the testes of rats and dogs when these animals were given a dose that produces blood levels of filgotinib similar to blood levels produced by the 200 mg daily dose in humans. (MANTA patient consent form).

What to expect?

The degree of the FDA's attention to these preclinical findings suggests some likelihood that the observed testicular toxicity is not a random fluke, however, we find comfort in the combination of the following facts:

- There is was no toxicities in rats and dogs at exposures equal to 200mg qd filgotinib in human. Furthermore, the findings were not replicated in another animal species. And in general, as seen from the table above the predictive value of animal models in regards to is not extremely high.
- Although changes in testosterone are poorly correlated with sperm concentration, no impact on hormone levels in the phase II RA trials at least suggests a limited impact of filgotinib on spermatogenesis.
- Meta-reviews suggest that TNF-a inhibitors (particularly infliximab) have a positive impact on spermatogenesis by improving sperm count and motility (Puchner 2012) potentially due to reducing underlying disease activity (Villiger 2010). Conceptually, the resolution of underlying disease through JAK inhibition could counteract a potential negative impact on spermatogenesis.
- The 20-30% non-inferiority margin for the primary endpoint as seen in other trials sets a very low bar for the trial to succeed. Essentially, such criteria implies a massive reduction in sperm concentration in a high proportion of patients (>25%), which in our view is not supported by the preclinical data.

Limited impact on label and marketing

In the case of a positive outcome, the mention of testicular toxicity is likely to be limited to the preclinical pharmacology section with a negligible impact on prescription and marketing as seen with examples mentioned above.

In case of a negative outcome - a low likelihood event in our view - we believe the chances of approval will not be impaired. Following the FDA guidelines, the testicular tox will just contribute to the overall risk-benefit assessment which based on FINCH 2 data is strongly skewed to the positive. However, the sperm toxicity will likely to be reflected in the warning section of the label.

It is too early to speculate on how potential testicular toxicity could impact the market potential for filgotinib in various indications. However, on a high-level thinking, we expect a negligible impact in RA as the target population is primarily women (66-75%) and men aged 45+ years. In other indications in the filgotinib pipeline, especially psoriatic arthritis, US and Crohn's which have more balanced gender distribution and the highest incidence between the age of 20-50, the male fertility issues could be a more important consideration. However, in our discussions with KOLs we understood that matter of male fertility is maybe more important to individual patients compared to treating physicians as exemplified by rather limited research on the impact of approved therapies (uptodate.com 2018) on male reproductive health. It is also important to note that IBD patients already have impaired fertility due to the drugs that they received frontline (e.g. sulfasalazine, ASA 5 etc), which makes the concern regarding testicular toxicity less pronounced.

Scenario analysis of MANTA

Our scenario analysis is based on the recruitment timelines and the potential outcome of MANTA study with time to market in RA and market shares for filgotinib as the main variables. We leave other assumptions on likelihood to market as well as timelines for other indications unchanged.

The analysis suggests 38% upside to the current share price in case of fast recruitment and positive outcome (most likely outcome in our view), 10% in case of slow recruitment and negative outcome (least likely outcome) and 30% risk-adjusted.

				Peak sales, €m				
		Probability	RA US Launch	RA	CD	UC	Total, prob. adj.	PT
2019 75%	Positive 80%	60%	2020	2822	1350	639	4556	125
MANTA completion	MANTA outcome							
	Negative 20%	15%	2020	2519	1012	512	4028	115
2021 25%	Positive 80%	20%	2022	2217	1350	639	4012	100
	MANTA outcome							
	Negative 20%	5%	2022	1915	1012	512	3484	100
								117