Galapagos NV (GLPG)
Rating: Buy

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A Stat-Sig Phase 3 Win; But Commercial Impact and MANTA Uncertainties Loom; Target Lowered to $270

Stock Data	05/20/2020
Price	$221.27
Exchange	NASDAQ
Price Target	$270.00
52-Week High	$274.03
52-Week Low	$112.00
Enterprise Value (M)	$7,226
Market Cap (M)	$13,492
Shares Outstanding (M)	64.8
3 Month Avg Volume	189,500
Short Interest (M)	1.08
Balance Sheet Metrics	
Cash (M)	$6,266.0
Total Debt (M)	$0.0
Total Cash/Share	$96.67

General: Currency used is roughly 1 Euro to $1.095 US. Stock price is US$ as on NASDAQ

EPS (€) Diluted			
Full Year - Dec	2019A	2020E	2021E
1Q	€(0.89)	€(0.78)A	--
2Q	€(0.86)	€(1.12)	--
3Q	€5.83	€(1.35)	--
4Q	€(1.86)	€1.56	--
FY	€2.49	€(1.68)	€1.69

Revenue (€)			
Full Year - Dec	2019A	2020E	2021E
1Q	€40.9	€106.9A	--
2Q	€67.6	€102.7	--
3Q	€644.0	€102.7	--
4Q	€143.4	€285.3	--
FY	€895.9	€597.6	€907.8

The devil's in the details, none of which are currently available, so let the speculation begin. The SELECTION trial met its primary endpoint in UC. However, the stat-sig benefit across all primary endpoints was limited to patients treated with the 200 mg dose. Patients on the 100 mg dose failed the induction segment, but hit on the maintainence segment. The limited data being put out in the PR and subsequent management commentary suggest a differentiated safety profile vs. other JAKi's with no imbalance between the treatment and placebo cohorts with regards to PE/DVT rates. No information is currently available on HZ infection rates, which were a problem with Xeljanz. While the stat-sig benefit with the 200 mg dose is a welcome positive, comparisons with other JAKis, remains hard as the enrollment into the SELECTION trial was probably skewed to more advanced patients in the 200 mg dose. Recall, male patients treated with 200 mg dose had the additional requirement of disease progression on prior anti-TNFs and vedolizumab due to preclinically-detected effects on semen parameters that are being examined in the MANTA studies. The placebo-adjusted benefit of 8% to 11% in the induction segment on paper appears to be short of upadactinib's 12% to 20% and tofacitinib's 11% to 13%, but optics are skewed by the baseline enrollment criteria. Hence, we think an absolute comparison may be premature, with no clarity currently provided on percent of patients on corticosteroids, and baseline CRP, which could swing interpretations of efficacy. In the maintenance setting, the placebo-adjusted rates for the 200 mg dose rivaled that of tofacitinib, which is good. Given limited data being divulged, and the onus on the MANTA study to deliver a clean read to avoid a potential black-box, potentially excluding younger male subjects, the stock has trailed off about 6% in premarket trading. Given the lack of clarity on a number of key metrics, potential overhang from the MANTA study, and importantly implications for the Crohn's Phase 3, we are adjusting our target lower to $270 from our prior $302.

Key takeaways. While the response rates on the 200 mg dose appear to be undifferentiated vs. other JAKis, there are important caveats: (1) patients in the 200 mg dose cohort had more advanced disease, with 100% having failed a prior biologic, and all males having failed anti-TNFa and vedolizumab; (2) despite these, the outcomes in the maintenance segment appear to be modestly ahead of the Xeljanz recommended maintenance dosage of 5 mg BID; (3) by excluding the physicians global assessment portion, which is a subjective measure, the clinical remission criterion in the SELECTION trial is potentially more stringent than that used in the Xeljanz study; and (4) patients from the Phase 2b upadacitinib study may not come from a typical Phase 3 population implying reversion to the mean in the era of multiple treatment options, likely to be the norm in Phase 3 studies.

Management sticking by the best-in-class safety profile. (1) DVT/PE rates in line with placebo; (2) SAE rates in line with placebo and other JAKis; and (3) the two deaths reported are not drug related. Hence, while we do not expect either the safety or the efficacy profile of the 200 mg dose to hinder approval, the breadth of the label is likely to be dependent on the MANTA study. The MANTA study is trying to disprove some preclinical findings, which indicated a negative effect on semen parameters in younger males, which if clinically confirmed could lead to a black-box warning or contraindication for young men, a non-trivial segment of the UC population. The outcomes from the MANTA study would only affect the 200 mg dose, as the 100 mg dose was not expected to cause any reproductive effects, hence the 100 mg miss raises the stakes for the MANTA study.

Baseline characteristics matter in UC. An analysis of multiple prior Phase 3 programs in UC lead us to the following observation with regard to patient characteristics that either trended, or were significantly associated, with higher clinical remission rates compared with placebo: (1) gender, males have a better response; (2) age, patients older than 41 responded better; (3) baseline or concomitant corticosteroid use, users responded better; (4) baseline or concomitant immunosuppressant use, users responded better; (5) prior anti-TNF exposure, no exposure equates to better response; and (6) baseline hs-CRP level, <5 mg/L correlates with better outcomes. Surprisingly, baseline Mayo score and duration of disease did not improve clinical remission rates relative to placebo.

Normalized outcomes are consistent across multiple Phase 3 programs. Clinical remission rates increases from a range of 15% to 20% during induction therapy to 25% to 40% during maintenance therapy, see Exhibit 1, 2, and 3. Oral JAKi appeared to have similar efficacy compared with biologics after adjusting for patient baseline characteristics. For example, on paper adalimumab and vedolizumab appear superior to upadactinib and tofacitinib induction therapies, but the percent of patients with prior anti-TNF use in the VARSITY trial was only 21%, whereas in the studies with JAKi these rates were markedly higher, i.e., from 53% to 79%, implying a more advanced population. These, in turn, might have contributed to the higher infection rates compared with the VARSITY study. A concerning trend we found with upadacitinib is the higher rates of infections and cardiovascular events, relative to tofactinib and mAbs; however, these rates are derived from a relatively small number of patients, and could evolve with more patients. We note the inclusion and exclusion criteria for the Phase 3 SELECTION 1 study of filgotinib in UC are the same as peers, and use the same primary endpoints, see Exhibit 4. One metric to watch we think is the rates of Herpes Zoster (HZ) infection rates in the SELECTION program. Recall, in a pooled analysis of Phase 2, 3, maintenance, and OLE global tofacitinib data on 1,157 UC patients, which encompasses about 1,612.8 patient-years (PY) of exposure, indicated that 5.6% patients developed 69 events of HZ infection with incidence rate of 4.1 per 100 PY. The risk of HZ with tofacitinib 10 mg BID was higher (6.6 per 100 PY; 95% CI 3.2–12.2), compared with 5 mg BID (2.1 per 100 PY; 95% CI 0.4–6.0), and placebo (1.0 per 100 PY; 95% CI 0–5.4), suggesting a dose-response relationship.

Exhibit 1: Detailed Comparison of Moderate to Severe UC Clinical Trials for Induction Therapy

Study	NCT02819635			Octave 1		Octave 2		SELECTION, Naïve		SELECTION, Experienced	
Dose	-	30 mg QD	45 mg QD	-	10 mg BID	-	10 mg BID	-	200 mg	-	200 mg
Drug	Placebo	Upadacitinib	Upadacitinib	Placebo	Tofacitinib	Placebo	Tofacitinib	Placebo	Filgotinib	Placebo	Filgotinib
Study Phase	2b	2b	2b	3	3	3	3	3	3	3	3
% Pt Using Corticosteroids	54%	48%	50%	48%	45%	49%	46%				
Baseline CRP mg/L	5.4	6.7	6.3	4.7	4.4	5	4.6				
% Prior Biologic Use	76%	81%	77%	≥ 53%	≥ 53%	≥ 58%	≥ 55%	0%	0%	100%	100%
Baseline Mayo Clinic Score	9.3 (7-12)	9 (6-12)	9 (7-12)	9.1 ± 1.4	9 ± 1.4	8.9 ± 1.5	9	52% ≥ 9	52% ≥ 9	74% ≥ 9	74% ≥ 9
Safety											
Safety Patient N	46	52	56	122	476	112	429		659		689
% with SAE	11%	6%	5%	4%	3%	8%	4%	3%	1%	6%	7%
% Any Infections	35%	12%	23%	16%	23%	15%	18%				
% Herpes Zoster	0%	0%	2%	1%	1%	0%	0.5%				
% Cardiovascular Events	0%	0%	2%	0%	0.4%	0%	0.5%				
Efficacy											
Patient N	46	52	56	122	476	112	429		659		689
Induction Endpoint (Weeks)				8	8	8	8	10	10	10	10
% Clinical Remission Mayo, Induction	0%	12%	20%	8%	19%	4%	17%	15%	26%	4%	12%
% Endoscopic Remission Induction	0%	10%	18%	2%	7%	2%	7%				
% Histologic Remission Induction											

Source: N Engl J Med 2017; 376:1723-1736 DOI: 10.1056/NEJMoa1606910, Gastroenterology. 2020 Feb 22. pii: S0016-5085(20)30241-9. doi: 10.1053/j.gastro.2020.02.030, Galapagos press release May20, 2020.

Exhibit 2: Detailed Comparison of Moderate to Severe UC Clinical Trials for Maintenance Therapy

Clinical Trials	UNIFI		Octave Sustain			VARSITY,		SELECTION, Naïve and Experienced		
Doses	-	90 mg	-	5 mg BID	10 mg BID	40 mg	300 mg	-	100 mg	200 mg
Drug	Placebo	Ustekinumab	Placebo	Tofacitinib	Tofacitinib	Adalimumab	Vedolizumab	Placebo	Filgotnib	Filgotinib
Study Phase	3	3	3	3	3	3b	3b	3	3	3
% Concomitant Corticosteroids	54%	54%	51%	51%	44%	36%	36%			
Median Age	42	39.5	43.4	41.9	42.9	40.5	40.8			
% Male	61%	53%	59%	52%	56%	56%	61%			
Baseline weight	71.7	72				73.4	72.7			
Baseline CRP mg/L	3.4	4	1	0.7	0.9					
% Prior Biologic Use	50%	51%	≥ 47%	≥ 46%	≥ 51%	≥ 21%	≥ 21%	-		-
Safety										
Safety Patient N	175	176	198	198	197	386	385			
% with SAE	10%	9%	7%	5%	6%			7%, 0%	4.5%	5%
% Any Infections	49%	46%	24%	36%	40%					
% Cardiovascular Events			0%	1%	1%					
% Malignancy	1%	0%	1%	0%	2%					
Efficacy										
Patient N	175	176	198	198	197	386	385			
Maintenance Endpoint (Weeks)	52	52	52	52	52	52	52	58	58	58
% Achieving 6-Month Steroid Free Maintenance	23%	42%								
% Clinical Remission Mayo, Maintenance	24%	44%	11%	34%	41%	23%	31%	11%, 13.5%	23.8%	37%
% Histologic Remission Maintenance						3%	10%			
% Achieving 6-Month Steroid Free Maintenance						22%	13%			

Source: N Engl J Med 2019;381:1201-14 DOI: 10.1056/NEJMoa1900750, N Engl J Med 2017; 376:1723-1736 DOI: 10.1056/ NEJMoa1606910, N Engl J Med 2019;381:1215-26. DOI: 10.1056/NEJMoa1905725, and Galapagos press release May 20, 2020.

Exhibit 3: Trial Design for Phase 2/3b SELECTION Program Evaluating Filgotinib in UC

Component	SELECTION1
Phase	2b/3
Patient N	1351
Design	Randomized, Placebo Controlled
Doses	100 mg, 200 mg
Inclusion Criteria 1	Diagnosis of UC for at least 6 months with endoscopic and histopathologic evidence
Inclusion Criteria 2	Moderately to Severely Active UC
Inclusion Criteria 3	Inadequate clinical response to corticosteroids, immunomodulators, anti-TNF, or vedolizumab
Inclusion Criteria 4	Absence of Crohns disease, or other types of colitis
Induction Primary Endpoints	Percent Achieving Clinical Remission Based on Components of Mayo Clinic Score at Week 10
Secondary Endpoints	Percent Achieving Endoscopic Subscore of 0 at Week 10
Secondary Endpoints	Percent Achieving Histologic Remission at Week 10
Maintenance Secondary Endpoints	Percent Achieving Clinical Remission Based on Components of Mayo Clinic Score at Week 58
Secondary Endpoints	Percent Achieving 6-Month Corticosteroid-Free Remission Based on Components of MCS at Week 58
Secondary Endpoints	Percent Achieving Endoscopic Subscore of 0 at Week 58
Secondary Endpoints	Percent Achieving Histologic Remission at Week 58

Source: Adapted from Clinicaltrials.gov.

Valuation and risks to our investment thesis. We reiterate our Buy rating and new 12-month price target of $270, from $302 previously, on shares of Galapagos. Our target is derived from a 12-year DCF-based, sum-of-the-parts analysis, which includes a beta of 1.41, terminal growth rate of -3.0%, risk premium of 4.93%, calculated WACC of 8.2%, and tax rate of 20% beginning in FY 2025. Filgotinib (81%,), GLPG1690 and GLPG1972 (2% each) together make up about 85% of our value, with the remainder derived from the probability-adjusted, filgotinib-related milestone payments. For filgotinib, we assume probability of approvals of: 80% for RA, and 80% (increased from 65% following Phase 3 win) for UC. However, we are lowering our probability of success in Crohn's to 50% vs. our prior 60% for CD given the miss with 100 mg dose in UC. The other probabilities remain unaltered with 60% for PsA and AS each, 35% ‘1690 and 10% for ‘1972. Key risks include: emergence of safety concerns, clinical risks, regulatory risks, COVID-19 disruptions, and financial risks. Furthermore, regulatory and commercial strategy for filgotinib is under the control of partner, Gilead, not an established player in autoimmune indications. Hence, Gilead may not be able to drive rapid adoption of filgotinib, especially if the overall profile is relatively undifferentiated from AbbVie’s (ABBV; not rated) upadacitinib, in our view. Hence, our estimates could be negatively impacted if AbbVie successfully leverages its market positioning with Humira during the launch of RINVOQ.