

Credit Suisse

Global Biotechnology

GLPG / GILD: SIK Inhibitor Mini Primer: Understanding the Mechanism Behind the Toledo Program & Stock Implications

10 December 2020

Equity Research

Americas | United States

Toledo/ SIK program could be an important value driver for Galapagos, but we need to see much more clinical data before we can fully assess the potential.

Following [the recent grand reveal of the target by Galapagos](#), we've dug a bit under the surface to better understand the target and the potential implications for both Galapagos and Gilead (if they opt in). With the filgotinib and OA setbacks, there is increasing pressure on Galapagos' other programs to deliver results. While the nearer-term investor focus is on the CRL resolution and '1690 in IPF, we think the Toledo program (if successful) could help drive GLGP shares. Still, the bar is high for novel assets in inflammation. To help better understand the potential impact of the program we've put together a mini primer on salt-inducible kinases and the Galapagos assets in the class. **As these are relatively early clinical stage programs, we're still cautious, supporting our Neutral thesis for GLPG and GILD shares.**

Galapagos is focusing on autoimmune diseases with the development of a series of salt-inducible kinase (SIK) inhibitors in its Toledo program. SIKs are enzymes that play a variety of roles in different regulatory pathways, and there are three isoforms, SIK1/2/3, that vary in terms of specific role. The literature shows that SIK enzymes are involved in cytokine regulation, suggesting potential for therapeutic benefit in a variety of inflammatory malignancies.

Recent data package confirms the dual Toledo MoA and supports clinical path forward. GLPG presented new preclinical and preliminary clinical data in healthy volunteers that support the MoA and role of SIK inhibitors. Recall that Toledo exhibits a dual MoA characterized by enhanced transcription of anti-inflammatory cytokines and inhibited transcription of proinflammatory cytokines. In a Ph1 trial of '3970 (selective for SIK2/3 isoforms), the drug showed a favorable PK profile and confirmed the dual MoA and a dose-dependent effect was observed in healthy volunteers.

We view the data so far as informative, but strong data from PoC/Ph2 trials is likely necessary to instill confidence for the future of the program. The data so far are informative and supportive of the mechanism of action, and the scientific rationale for SIK inhibition is supported in the literature. However, we believe clinical validation in a particular

indication remains to be seen (hence the need for additional studies). The company plans to address this need for additional data by exploring GLPG3970, the company's first Toledo compound, in three concurrent PoC studies: CALOSOMA in psoriasis, SEA TURTLE in ulcerative colitis, and LADYBUG in rheumatoid arthritis. We believe the company strategically chose psoriasis as the first indication to study '3970; the Ph1b study will be able to generate rapid data.

Overall, we are positive on the program, but as GLPG rounds out 2020 with '3970 and '4399 starts, we look to 2021 for readouts to affirm our conviction.

We are positive on the program, but want to see more data to be fully comfortable. For GLPG4399, we expect a readout of Ph1 in 2021 followed by the initiation of Phase 2b studies; We also expect data from the first three PoC studies with additional Ph1 starts and a potential IND opening for GLPG3970. We believe it is clear that LT success in targeted indications will require significant differentiation and a strong clinical profile, especially considering the filgotinib setback. As such, we do not assign formal credit to '3970 yet in our model as we await elucidation of the profile.

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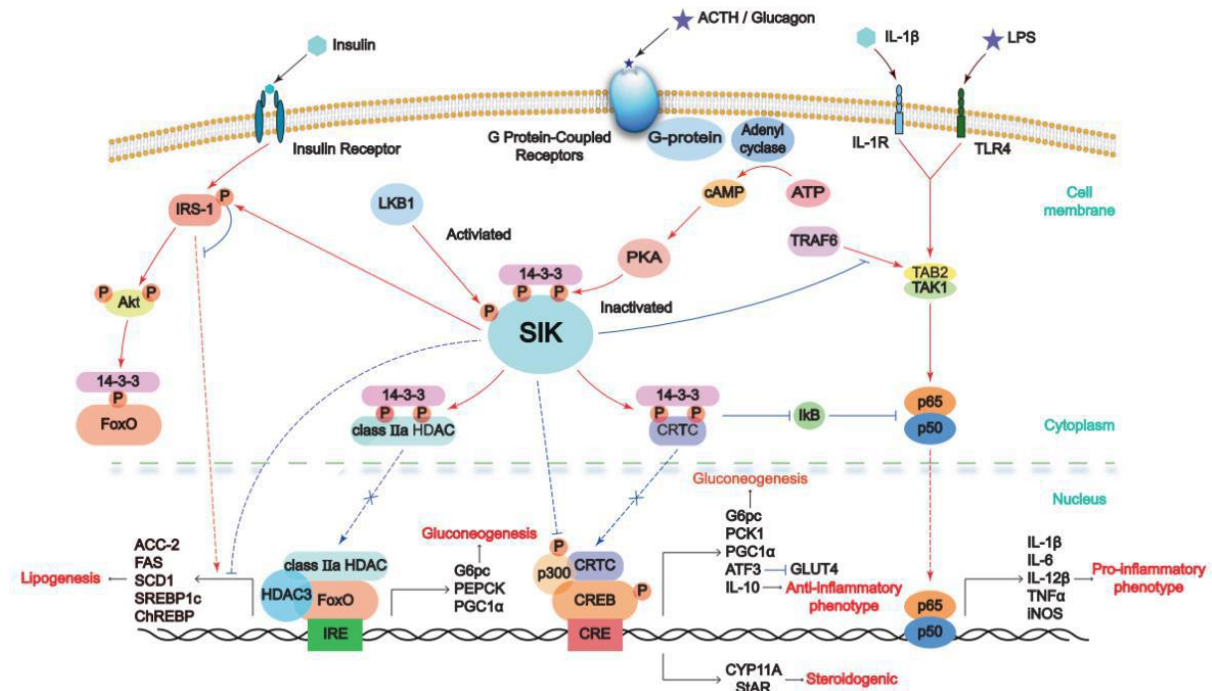
SIK Inhibitors 101: A Brief Overview and Discussion

Salt-inducible kinase (SIK) inhibitors are the target family for the Toledo Program.

SIKs are enzymes belonging to the AMP-activated protein kinase (AMPK) family that were first discovered in the adrenal glands of rats on a high salt diet over 20 years ago. There are three SIK isoforms (SIK1/2/3) that are similar in structure and contain relatively conserved phosphorylation motifs; SIKs are Ser/Thr protein kinases, meaning that they catalyze phosphorylation at Serine and Threonine amino acid sites on a target protein. SIKs play a variety of roles in different regulatory pathways, as summarized in **Figure 1** per [Sun, et al., 2020](#).

Figure 1: Complex Role of SIK Enzymes in Several Regulatory Pathways, Including Inflammation

Source: Company data, Sun, Z., Jiang, Q., Li, J. *et al.* The potent roles of salt-inducible kinases (SIKs) in metabolic homeostasis and tumorigenesis. *Sig Transduct Target Ther* **5**, 150 (2020). Open Access article, please see a copy of the Creative Commons license here: <https://creativecommons.org/licenses/by/4.0/>



SIKs have other functions beyond inflammation, such as involvement in cancer. While SIKs are implicated in inflammatory pathways, they have also been shown to have a variety of other functions in the literature. Most recently, these enzymes have been implicated in cancer. For example, SIK2 has been proved to promote tumorigenesis by modulating PI3K/ACT; the activation of this signal is associated with the promotion of the Warburg effect and resultant tumorigenesis. The literature has also shown that SIK3 promotes tumor cell migration and that SIK1 may overexpress in several non-adipose tissues, such as in the ovaries and lungs, and act as an oncogenic signal transmitter during the occurrence and progression of tumors in the aforementioned organs (Sun, et al., 2020).

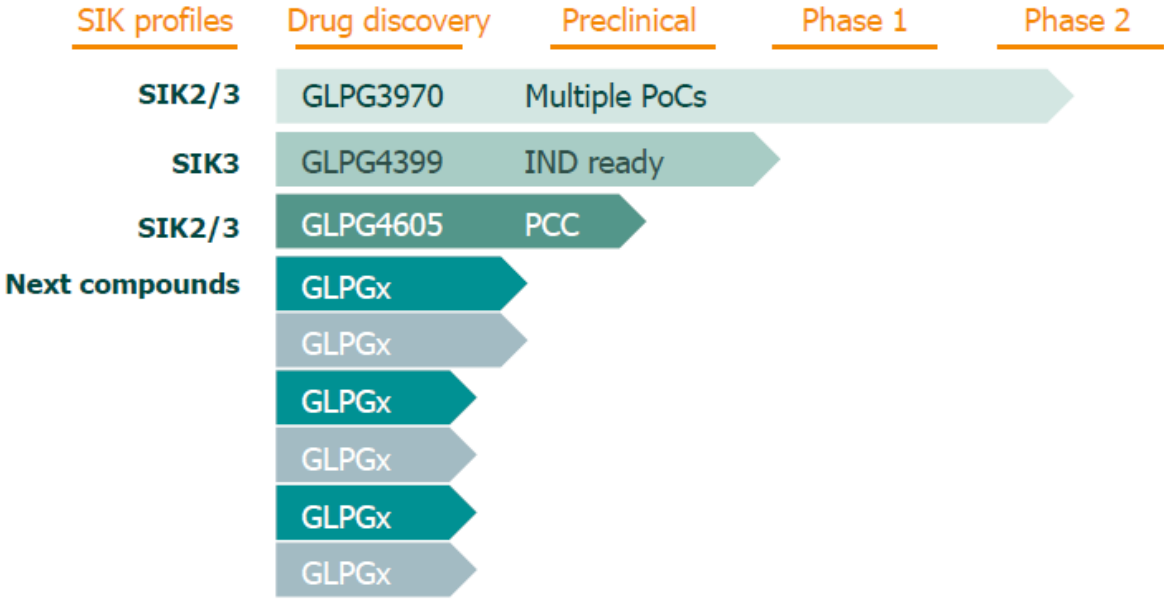
While SIK inhibitors such as the SIK2 inhibitors HG-9-91-01, ARN-3236, and KIN-112 have succeeded in preclinical cancer therapy approaches, we view the potential for SIK modulation of cancer cells as a potential risk to the Toledo program given the possibility of unforeseen effects. For more on SIKs and selected additional literature, please see the **Literature Review** section.

Galapagos' Approach to SIK Inhibition

Galapagos is focusing on autoimmune conditions with the development of a series of Toledo compounds to thoroughly address unmet need populations. The company is developing a series of SIK inhibitor Toledo compounds, namely GLPG3970, GLPG4399, and GLPG4605 that have differing SIK profiles with plans for next compounds currently undisclosed. GLPG3970 is the furthest along in the Toledo portfolio, and GLPG plans to explore this compound in multiple PoCs.

Figure 2: Toledo Portfolio: A Series of SIK Compounds to Address Multiple Indications

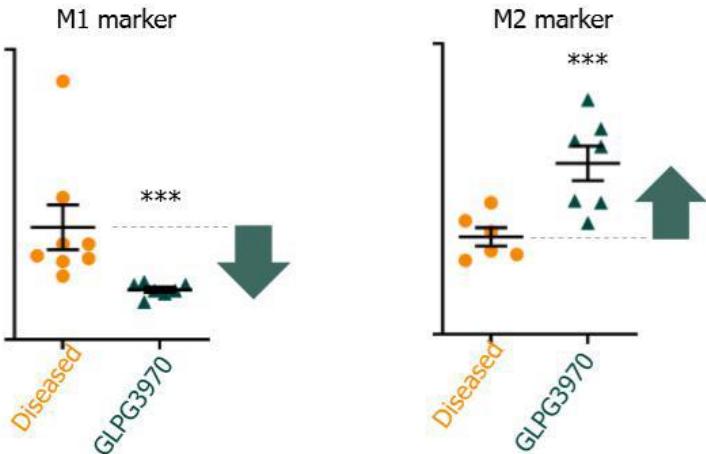
Source: Company data



Current data package confirms the dual MoA and supports clinical path forward.

GLPG3970 preclinical data in various autoimmune models and preliminary clinical data in healthy volunteers support the mechanism of action (MoA), the role of SIK inhibitors and help to define the path forward. Recall, Toledo exhibits a dual MoA characterized by enhanced transcription of anti-inflammatory cytokines and inhibited transcription of pro-inflammatory cytokines; the drug has been shown to reduce pro-inflammatory macrophages as well as induce immunoregulatory macrophages in IBD colon tissue (T-cell transfer model), and has also shown robust activity in vivo in multiple models of IBD. For more, please see Figures 3 and Figure 4.

Figure 3: Impacting Both Sides of the Balance In-Vivo



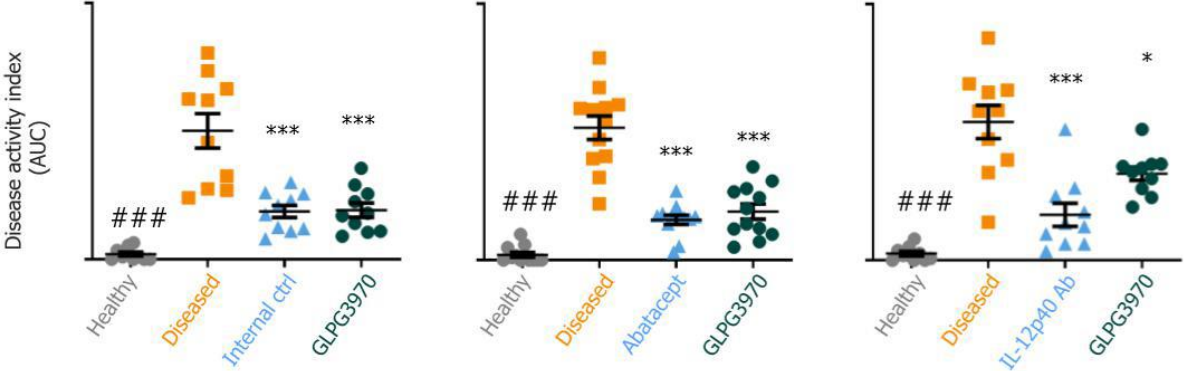
*** =p<0.001 (vs diseased)

Source: Company data

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Figure 4: Robust Activity of GLPG3970 Observed In Vivo in 3 IBD Models: DSS (Left), T-cell Transfer (Middle), and MDR1 (Right)



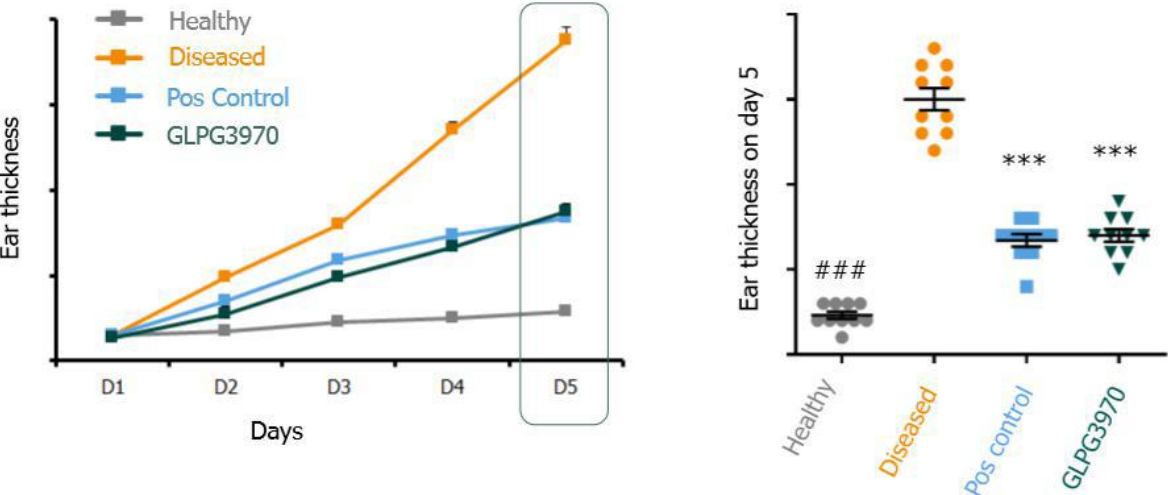
= p<0.001, *** =p<0.001 (vs diseased), * = p<0.01

AUC: area under the curve

Source: Company data

Additionally, the drug has shown preclinical activity in models of psoriasis, arthritis, and fibrosis. These positive data are supportive of further exploration for efficacy in inflammatory diseases in clinical trials.

Figure 5: Activity in IL-23-Induced Model of Psoriasis (Left) and Ear Thickness (Right)



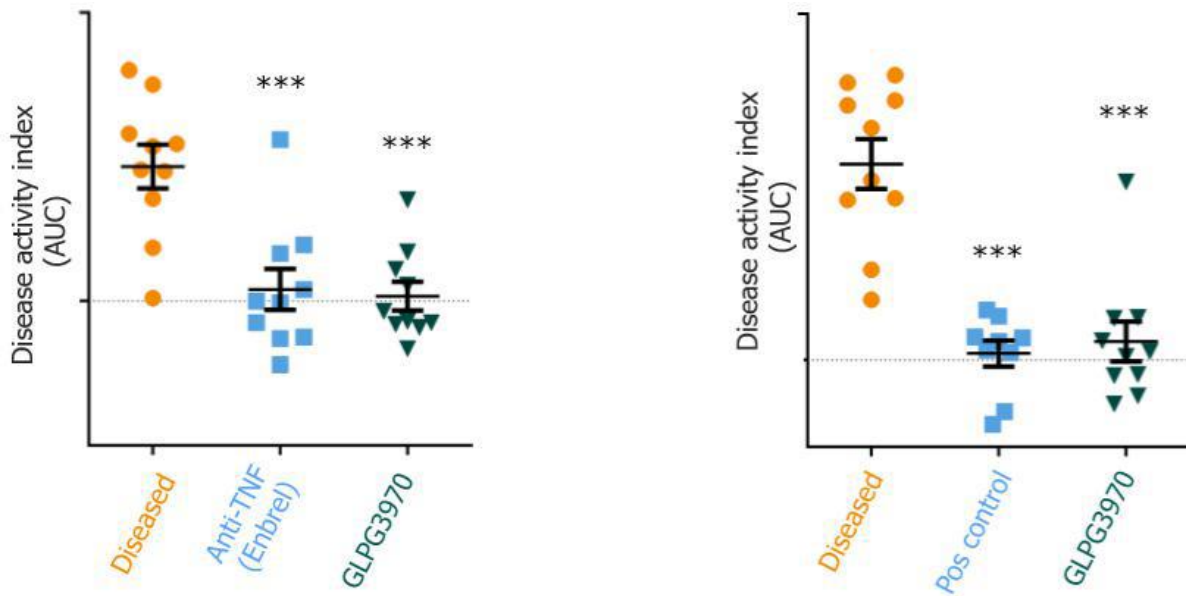
= p<0.001, *** =p<0.001 (vs diseased)

Source: Company data

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Figure 6: Robust Activity in CIA (Left) and PsA II-23-Induced (Right) Arthritis Models

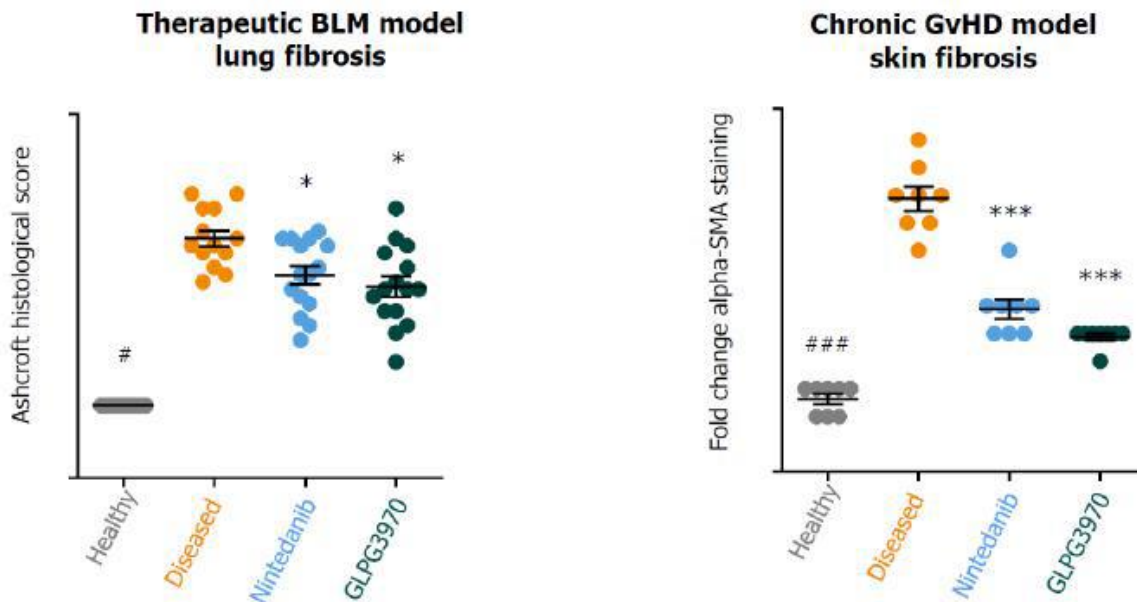


*** = $p < 0.001$ (vs diseased)

CIA: collagen induced arthritis; PsA: psoriatic arthritis; AUC: area under the curve

Source: Company data

Figure 7: Robust Activity Observed In Vivo in Two Models of Fibrosis



= $p < 0.001$, *** = $p < 0.001$ (vs diseased), * = $p < 0.01$

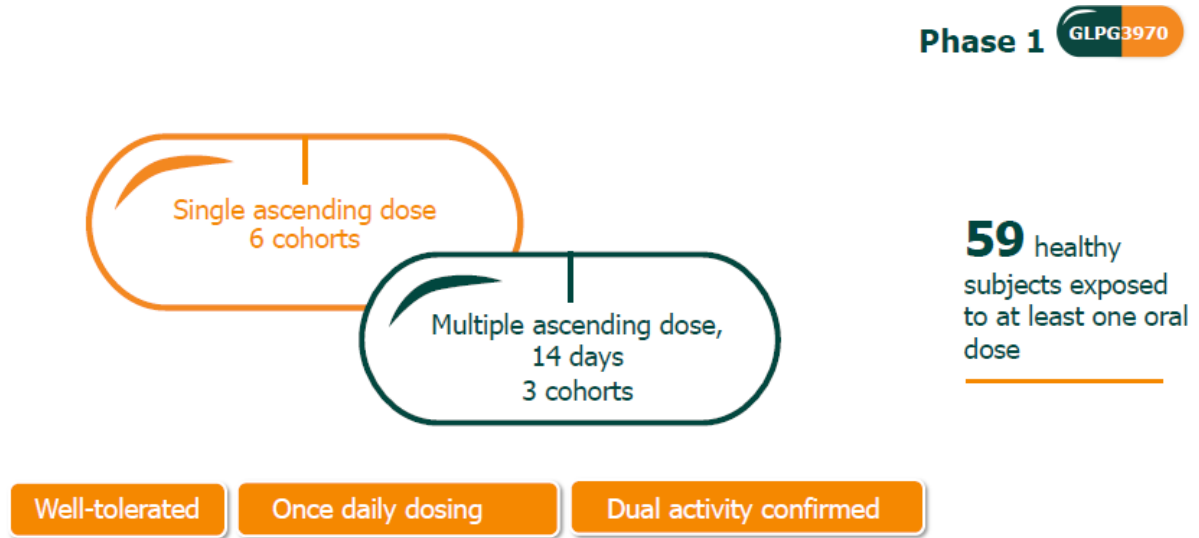
BLM: bleomycin; GvHD: graft versus host disease

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In the Ph1 trial of GLPG3970, the drug showed a favorable PK profile and confirmed the dual MoA and a dose-dependent effect was observed in ex vivo healthy volunteers. For more on the Ph1 trial, please see below and on [clinicaltrials.gov \(NCT04106297\)](https://clinicaltrials.gov/ct2/show/study/NCT04106297).

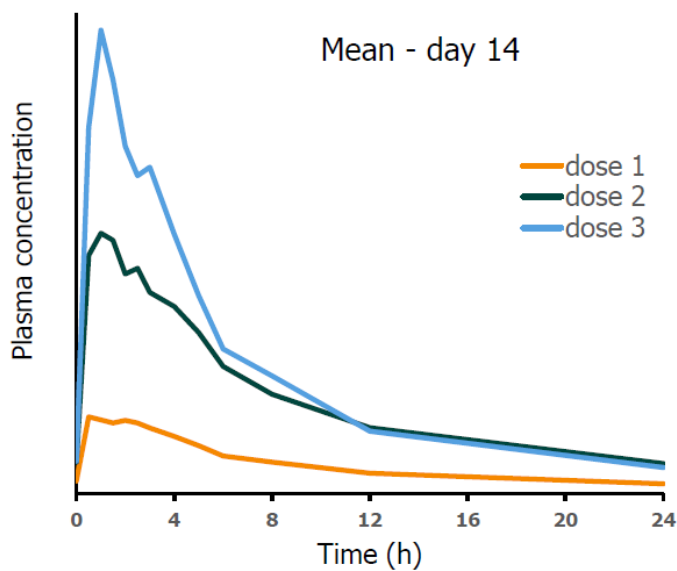
Figure 8: Ph1 Trial of GLPG3970, a SIK Inhibitor Selective for Isoforms 2 and 3.



Source: Company data

In clinic, the drug showed a predictable pharmacokinetic profile, fast absorption, and dose proportional exposure. The half-life also is supportive of once daily dosing, and Galapagos believes there is a low propensity for clinical drug-drug interaction.

Figure 9: GLPG3970 Plasma Concentrations



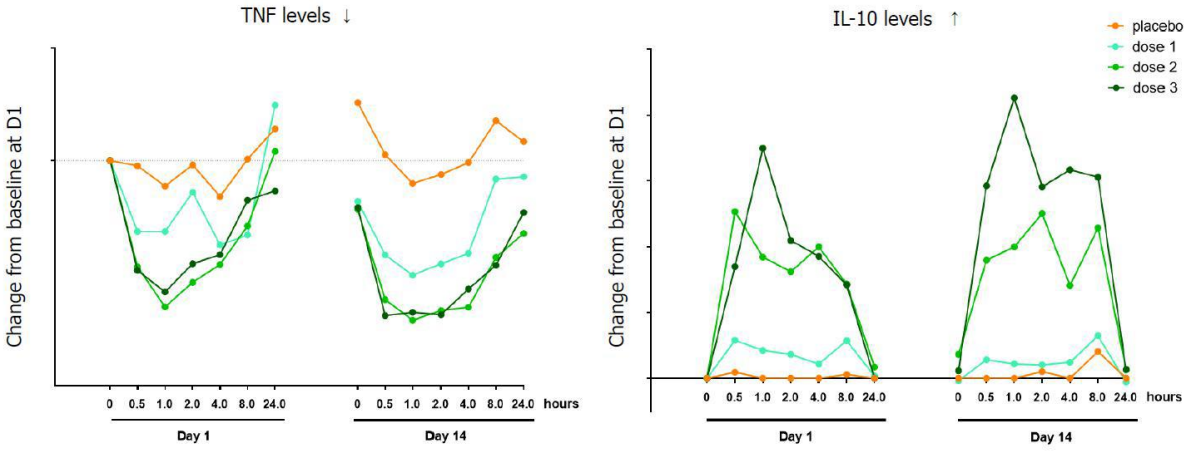
Source: Company data

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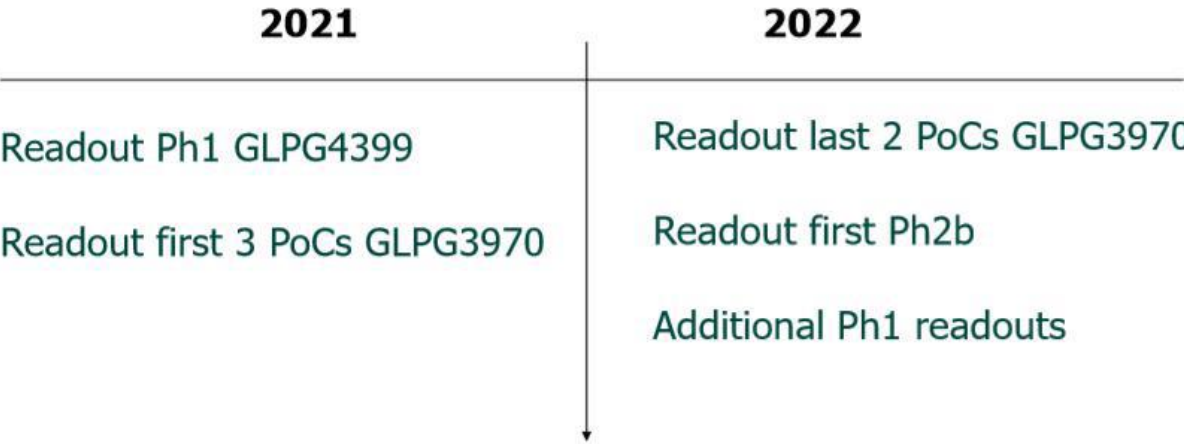
Figure 10: Dual activity of GLPG3970 Confirmed Ex-Vivo; the Drug Reduced TNF Levels (Left) and Increased IL-10 Levels (Right)

Source: Company data



Next Data Update Likely in Mid-2021 from PoC Studies. Given the preclinical and positive early clinical data with GLPG3970, the company will likely have multiple readouts in 2021 and beyond with '3970 alone. Galapagos plans to explore GLPG3970 in multiple PoC studies targeting psoriasis, ulcerative colitis, and rheumatoid arthritis called CALOSOMA, SEA TURTLE, and LADYBUG respectively. These trials are actively recruiting and the company is guiding that these first 3 PoCs will readout in **2021** (potentially mid 2021). Additionally, the company is planning PoC trials for systemic lupus erythematosus (SLE) and primary Sjögren's syndrome. GLPG intends for these last 2 PoC trials to readout in **2022**. For more on overall Toledo newsflow, including assets other than GLPG3970, please see below.

Figure 11: Galapagos Toledo Program 2021/2022 Newsflow Guidance



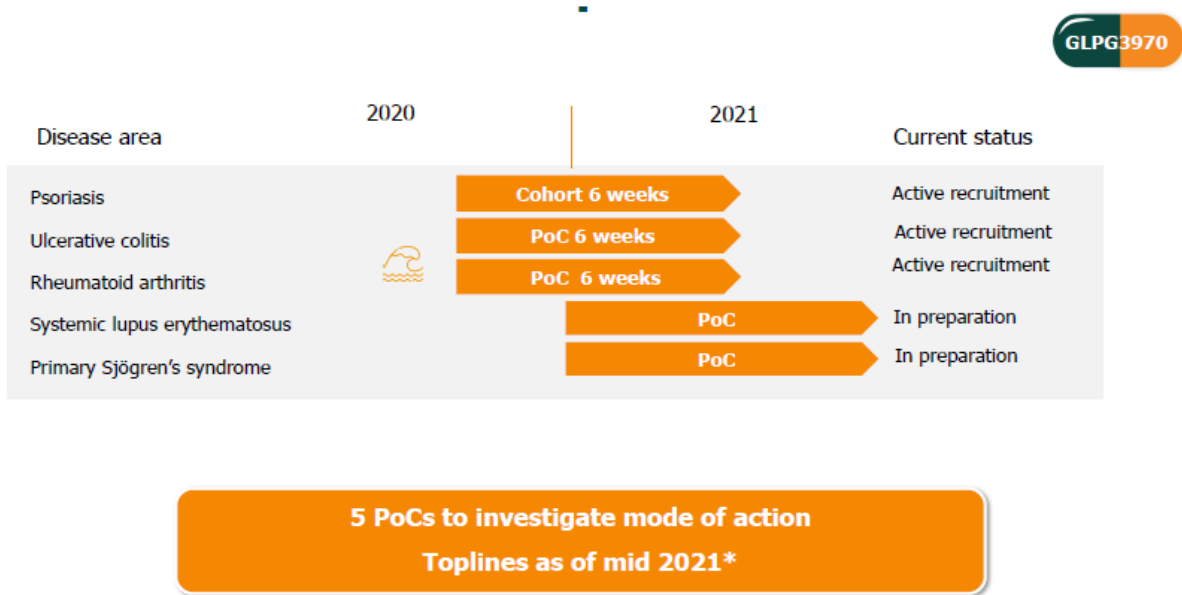
Source: Company data
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Our Take on the Toledo Targeting SIKs and Initial Data

The literature is supportive of the rationale for SIK inhibition to be therapeutic for a variety of malignancies, including inflammatory diseases. For example, SIK inhibitors have been shown to increase anti-inflammatory cytokines such as IL-10 and decrease proinflammatory cytokines such as IL-6, in addition to acting as molecular switches for M1-M2 macrophage transformation; SIK inhibitors have also been shown to regulate the NF- κ b pathway. However, it remains, controversial as to why certain SIK isoforms perform redundant and/or distinct functions; for example, SIK2 is known for its pro-inflammatory role, repressing IL-10 secretion of regulatory macrophages, while SIK3 specifically is known to negatively regulate IL-6 and IL-12. Full understanding is limited by the lack of SIK protein crystal structures in the [Protein Data Bank](#); little is known about why the structural similarity of the SIK family leads to different biological functions.

We view the data so far as informative, but think strong data from planned PoC/Ph2 trials is likely necessary to instill confidence for the future of the program. The data so far are informative and supportive of the mechanism of action, and the scientific rationale for SIK inhibition is supported in the literature. However, we believe clinical validation in a particular indication remains to be seen (hence the need for additional studies). Recall, the company plans to address this need for additional data by exploring GLPG3970, the company's first Toledo compound, in three concurrent proof-of-concept (PoC) studies: CALOSOMA in psoriasis, SEA TURTLE in ulcerative colitis, and LADYBUG in rheumatoid arthritis. We believe the company strategically chose psoriasis as the first indication in which to study GLPG3970, as the Phase 1b CALOSOMA study will be able to generate rapid clinical data.

Figure 12: Parallel PoC Studies Potentially Allow for Multiple 2021 Datapoints
Source: Company data



* Timelines subject to delays due to global COVID-19 pandemic

Management has made it clear that these PoC studies are viewed as “signal finding studies,” from which three distinct outcomes would occur:

- 1) the company gets poor data/lack of activity, indicating they should drop the compound and look elsewhere
- 2) the data provides clear and compelling evidence, leading the company to pursue the compound more quickly
- 3) the data shows a signal that’s worth looking into, but perhaps with better refinement of the study (such as selecting a more appropriate population).

Following the company’s setback in filgotinib (recall, FDA issued a CRL for filgotinib in rheumatoid arthritis when it was largely expected to be approved) and failure in GLPG1972 (the company’s novel osteoarthritis compound), it has become increasingly important for the company to show a well-tolerated profile alongside a clear signal(s) in target indications in their respective studies (e.g., Mayo clinical score, RA symptom reduction).

Targeted indications are already competitive, and ‘3970 is not the only SIK inhibitor.

We believe it is clear that longer-term success in targeted indications will require significant differentiation from other SIK inhibitors under investigation.

We would like to flag that the target indications are already very competitive. Moreover, perhaps more importantly, Galapagos' 3970 asset is not the only SIK inhibitor that has been or is being evaluated. For example, other SIK inhibitors such as HG-9-91-01, ARN-3236, and KIN-112 have succeeded in cancer therapy approaches.

- The SIK2 inhibitors **HG-9-91-01, ARN-3236, and KIN-112** have succeeded in cancer therapy approaches, validated in cultured cells and *in vivo* animal models
- it is possible that **HG-9-91-01, MRT-67307, ARN-3236, and YKL-05-099** represent relatively early efforts in the development of small molecule SIK inhibitors
- The small molecule SIK inhibitor **ARN-3236** showed promising efficacy in ovarian cancer xenograft models

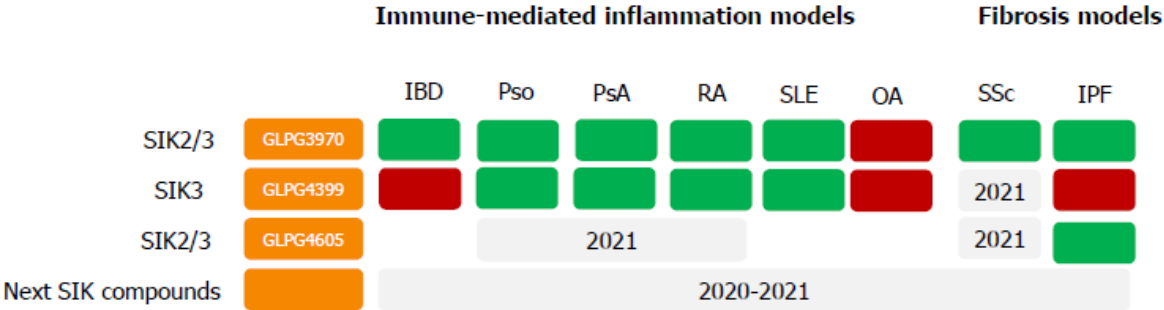
In addition, iOmx Therapeutics has a SIK3 inhibitor that is approaching IND enabling studies, and Arrien Pharmaceuticals has **ARN-3261**, a SIK2/3 inhibitor (the company plans to initiate Ph1a/b trials beginning Q1 2021. While not in the same indications, it is possible the development of any these assets pivot to be directly competitive; however, it is especially important to note that there are no SIK inhibitors that are approved, representing a potential for GLPG to develop a first-in-class drug.

We think the market opportunity is substantial in high unmet need indications, resulting in a potential for high sales if a strong clinical profile is elucidated.

While we are positive on the data so far, we think it is too early to ascribe value in our GLPG model. We await incremental clinical data points, and think the PoC trials will likely give more clarity on which indication(s) the company will focus on. We do have some idea, though, of what unmet needs could be addressed by SIK inhibitors; the company has demonstrated promising and broad *in vivo* activity in several immune-mediated inflammation models and fibrosis models. We discuss some of these above, but please see a full tabulation below in **Figure 13**.

Figure 13: In-Vivo Activity Suggests SIK Inhibitors May Address Multiple Indications

Source: Company data



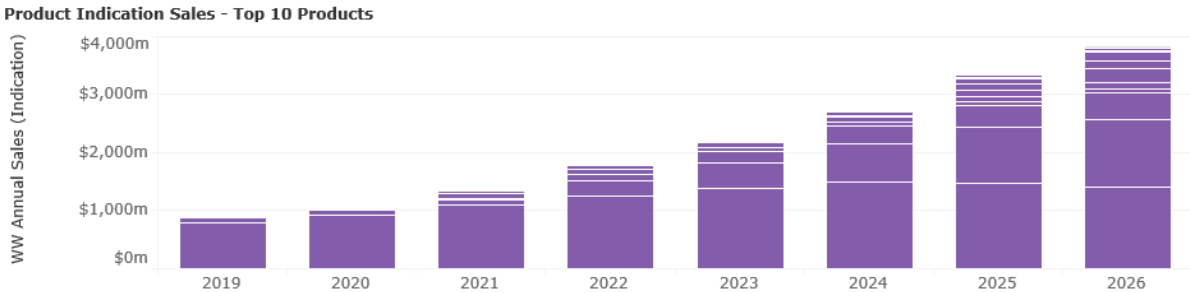
■ Activity demonstrated
■ No activity

We acknowledge that the company is using psoriasis as a PoC and is furthest in terms of clinical PoC trial progress with this indication, and the company is also exploring other indications such as RA and UC in PoC, but we feel that other indications, namely SLE and Sjögren’s syndrome, represent opportunities with higher unmet need; there is a largely untapped market for SLE and Sjögren’s syndrome has no real therapeutic options at the moment (for clarity, this is now part of our GLPG thesis, but not GILD).

GSK’s Benlysta (approved 2011) is the first and only drug specifically developed for and FDA approved to treat lupus, and leads the SLE market with annual worldwide sales approaching almost \$1b. Evaluate Pharma estimates that, given there are other drugs in development, the global market for SLE could grow substantially on an annual basis and approach \$4b by 2026. This excludes any projected revenues from Galapagos.

Figure 14: Global Market in Systemic Lupus Erythematosus is Estimated to Approach \$4b by 2026

Source: Evaluate Pharma



Importantly, the diagnosed lupus population in the US is estimated to be 1.5m according to the Lupus Foundation of America, and the foundation believes that this number is actually much higher with cases that go undiagnosed.

For Sjögren’s, the overall market is likely a fraction of the size of SLE; Evaluate Pharma estimates that by 2026, total worldwide sales may approach ~\$300m, but that excludes any

sales from novel Galapagos assets and most other in development. There are between 400k and 3.1m adults with Sjögren's syndrome, and symptoms usually arise between ages of 45 and 55. Interestingly, ~1/2 of patients with Sjögren's have RA, lupus, or another connective tissue disease. While there are a few drugs used off label for Sjögren's, there are currently no FDA approved, marketed drugs. So, while the opportunity is potentially smaller in size than SLE, we still believe it to be potentially important given the essentially untapped market.

Overall, we are positive on the program, but it is difficult and too early to make a call as to the upside potential for GLPG and GILD (if ultimately any) as of right now. We

think it makes sense that Galapagos is investigating SIKs for inflammatory diseases. With regards to UC and Crohn's, the imbalance of pro-anti-inflammatory cytokines are thought to be responsible for IBD per the literature, and the recent successful example of JAK inhibitors for RA highlights how small molecule kinase inhibitors can be used to target redundancies within cytokine signaling networks for chronic diseases. Overall, we are positive on the program given the recent data, but it is difficult and too early to make a call as of right now; strong data from the PoC/Ph2 trials indicating differentiation is likely needed to have high conviction going forward.

Implications for the GILD/GLPG Partnership

It is important to remember that Gilead paid Galapagos \$3.95B (+ a \$1.1B equity investment) to maintain the option to in-license the ex-European commercial rights to each of the Toledo molecules following completion of Phase 2 Trials. Under terms of

the agreement, the 10-year collaboration gives Gilead commercial rights everywhere outside of Europe, while Galapagos will lead clinical development through Ph2 testing. Depending on the data, **Gilead will be able to opt in to each molecule and split development costs going forward in Ph3; we note that Gilead has not opted in as of publication of this note.**

On the Q3 2020 earnings call, Merdad Parsey (CMO, Gilead) mentioned that Gilead would like to see the program de-risked, of course, and that if a huge response in one indication that was really unexpected was observed, it is possible that the company opts in earlier. While Gilead remains committed to the partnership and inflammation, we get the sense that the company is more focused on oncology with the recent acquisitions of Immunomedics and FortySeven.

Figure 15: Gilead-Galapagos R&D Collaboration

Source: Company data



With ~\$5.3B in cash, the Galapagos remains well capitalized to finance the “hefty investment” required for the Toledo Program. GLPG recently acknowledged the relatively steep R&D trajectory, as it has been for the last couple of years, but remains confident that costs will not be a significant concern. While we do not have specifics, management has noted

that Ph2 trials would not financially strain their balance sheet given the strong cash position. Further, if the data justifies Ph3 trials, it's likely at that point that Gilead will opt in and split the development costs 50/50, per their agreement.

As the company rounds out 2020 with the initiation of GLPG 3970 and GLPG 4399, we look to 2021 for critical data readouts to affirm our conviction in the Toledo Program.

For GLPG4399, we expect a readout of Ph1 in 2021 followed by the initiation of Phase 2b studies. We also expect data from all three (CALASOMA, SEA TURTLE, and LADYBUG) proof of concept studies, with additional Phase 1 starts and a potential IND opening for GLPG3970. Overall, we are encouraged with this program but want to see more data to be fully comfortable.

Literature Review – Tidbits and Additional SIK Information

General SIK Information:

- SIK is a major part of the AMPK family
- First discovered in rat adrenal cortex on high salt diet (Okamoto et al 1999)
- Originally called Salt-Inducible Kinase because dietary salt regulated expression
- Now thought to also control gene expression via extracellular cues to increase cAMP in the cell
- Ser/Thr protein kinase
- Remains unclear if other important intracellular SIK substrates exist beyond class IIa HDACs and CRTC proteins
- There are no crystal structures of SIK in the [Protein Data Bank](#); efforts for structurebased drug design are currently limited by the lack of SIK crystal structures.
- There are 3 SIK isoforms: 1, 2 and 3; all have various lengths
- Little is known about why the structural similarity of the SIK family leads to different biological functions.
- Makes sense that Galapagos is investigating SIKs for UC and Crohn's; imbalance of pro/anti inflammatory cytokines are thought to be responsible for IBD in general
- Going after RA makes some sense too; the recent successful example of JAK inhibitors for rheumatoid arthritis highlights how small molecule kinase inhibitors can be used to target redundancies within cytokine signaling networks for chronic diseases.
- IL-10 implicated as well; the central role of PKC, GSK3 β and SIKs in IL-10 production suggesting that kinase inhibitors are likely to modulate IL-10 production
- All three SIK family kinases are expressed broadly

SIK1

[Chen et al 2019](#)

- Initial studies have found that SIK1 is most abundant in the adrenal cortex and an important regulator in the early phase of hormonal stimulation of the adrenal cortex, adipose tissue, and neural tissue
- It may overexpress in several non-adipose tissues, such as in the ovaries and lungs, and act as an oncogenic signal transmitter during the occurrence and progression of tumors in the aforementioned organs

[Kim et al 2019](#)

- SIK1 regulates bone anabolism; regulation of osteogenesis via proliferation and differentiation
- SIK1 gene knockdown (but not SIK2 or SIK3 expression) increased osteoblast differentiation
- SIK1 knockout mice (vs WT) showed higher bone mass / osteoblasts / bone formation rate
- BMP2 suppressed SIK1 expression and SIK1 activity by PKA mechanisms
- Suppression of SIK1 activity was determined to be critical to osteogenesis
- Supportive of SIK inhibition in bone anabolic approach to treating conditions like osteoporosis

SIK2

[Wein, et al., 2018](#)

- SIK2 expression is ubiquitous; highest levels are in adipose tissue
- SIK2 is perhaps best suited for blockage by PKA-activating agents due to 4 PKA phosphorylation sites vs 2 PKA phosphorylation sites on SIK1/3
- For example, SIK2 is over-expressed in certain high grade serous ovarian cancers, in which it functions as a centrosome kinase in cell cycle progression
- SIK2 may promote omental ovarian cancer metastasis by activating the PI3K pathway

[Chen et al 2019](#)

- SIK2 is overexpressed in several cancer cell lines and boosts cancer cell tolerance to different stresses, such as deprivation of nutrients and Taxol chemotherapy
- SIK2 is a potential oncogenic marker in ovarian (Chen 17, 49), prostate (Chen 50), osteosarcoma (Chen 51), and colorectal (Chen 52) cancers by controlling different cellular mechanisms

· pro-inflammatory role by repressing IL-10 secretion of regulatory macrophages

- The SIK2 inhibitors **HG-9-91-01**, **ARN-3236**, and **KIN-112** have succeeded in cancer therapy approaches, validated in cultured cells and in vivo animal models (Chen sources 17,36,48)
- While most reports suggest that SIK2 is an oncogenic marker, one study in Turkey claimed that SIK2 is a potential tumor suppressor in breast cancer (source 23 of Chen et al)
- Since SIK2 plays a distinct role in different tissues and divergent pathways, its dysregulation may lead to conflicting phenotypes

SIK3

[Itoh et al 2015](#)

- SIK3, not SIK1/2, acts as the predominant suppressor in gluconeogenic gene expression
- Pterostilbene inhibited SIK3 up to 1; HG9-91-01 completely inhibits at 1 uM
- SIK3 down regulates gluconeogenesis

[Wein et al 2018](#)

- SIK3 expression is ubiquitous; highest levels are in the brain
- Interestingly, brain phosphoproteomic analysis of these SIK3 gain of function mice

versus littermate controls revealed increased phosphorylation of synaptic regulatory proteins, indicating a novel role for SIK3 in sleep-related neurotransmission

- global-SIK3 deficient mice are hypoglycemic
- most SIK3 knockout mice die shortly after birth due to abnormal chondrocytes

Valuation, Methodology and Risks

Target Price and Rating

Valuation Methodology and Risks: (12 months) for Galapagos NV (GLPG.AS)

Method: Our €105 target price and NEUTRAL rating for Galapagos NV are based on a DCF (discounted cash flow) valuation. We use a 9.5%

WACC (weighted average cost of capital) and forecast discounted cash flows through 2029, with terminal growth rate of 1% thereafter.

Risk: Risk to our €105 target price and NEUTRAL rating: Clinical and developmental: Some of our valuation and share upside potential is based on outcomes from clinical trials. If any of Galapagos' late-stage assets are shown to be clinically ineffective or unsafe, we would expect negative pressure on shares. Regulatory: Food and Drug Administration (FDA), European Medicines Agency (EMA), and other regulatory body approvals are required for Galapagos to market and sell its therapeutics. Any delay or outright rejection of the approval of investigational assets could have a negative impact on the future cash flows and value of Galapagos shares. Furthermore, FDA or EMA could revoke the marketing authorization of any marketed product due to safety or efficacy concerns. Commercial: EU sales and US sales royalties drive the majority of our cash flow and earnings estimates. If sales are worse than our or consensus expectations, we could see a negative impact on shares. External/Market Risk: Biotechnology remains a volatile sector that can be affected by external factors, including drug pricing legislation, intellectual property law, healthcare policy, and the overall economy. Negative policy developments and/or a weakening of the economy could affect Galapagos' share price.

Target Price and Rating

Valuation Methodology and Risks: (12 months) for Gilead Sciences, Inc (GILD.OQ)

Method: Our \$70/share TP and NEUTRAL rating for GILD are based on a DCF with an 7.0% discount rate which is in-line with peers, we forecast revenues to 2030. Beyond our forecast period, we apply a - 5.0% terminal growth rate to cash flows. We expect that Gilead's continued investment in R&D and business development efforts will be successful in replacing a portion of revenues lost to erosion, but do not yet have conviction on the company's strategy beyond infectious disease.

Risk: Downside risks to our \$70 TP and NEUTRAL Rating rating for GILD are: (1) clinical, regulatory or manufacturing setbacks with the Car-T platform, (2) new HIV Gilead drug launch underperforms, as the majority of older HIV pills go generic, (3) HIV TAF sales are worse than our and the Street expectations, (4) HCV competition from Merck's protease-based regimen is greater than we expect, (5)

greater- or faster-than-expected impact from HIV generics, (6) greater than anticipated competitive pressures in the HCV market, (7) pricing and payer pressure for HCV, (8) lower-than-expected volumes for HCV, and (9) late stage pipeline asset failure. Upside risks for GILD are: (1) greater than expected HCV sales, (2) maintenance of HIV share, (3) a faster than anticipated Yescarta launch, and (4) M&A.