MTSL Issue 1020

February 15, 2024

UPDATES: ALKS, MDGL, SGMO, VKTX

IN THIS ISSUE: "The Wheel Is Turning And It Can't Slow Down"

Since Last Issue: BTK: 1.67%; NBI: 2.96%; XBI: 4.27%; Model Portfolio: -9.89%

BIOTECH SECTOR ANALYSIS

SENTIMENT — XBI Poised To Break Out

More M&A as GILD Buys CBAY and NVS Buys MorphoSys

Biotech M&A remains hot with GILD's acquisition of CBAY for $4.3 billion validating the potential of seladelpar as a treatment option for PBC patients, and importantly biotech M&A remains red hot. GILD as an ideal partner for CBAY based on its expertise in liver diseases. The FDA has granted priority review for seladelpar as well with a 8/14/24 PDUFA and no AdCom scheduled. We expect the ongoing Phase III

However, the forces of rotation back to the sector remain intact with major cash inflows and a broader investor audience. The GLPs/obesity market remains center stage and Eli Lilly with a $720 billion valuation could easily scoop up VKTX which has a novel oral/subQ drug ('2735) in development. The latest quarterly earnings calls at Big Pharma/Big Biotech show that the coiffures are overflowing with cash and a bolt-on buyout in the ~$5 billion range feels like a rounding error financially to most with expanding clinical pipelines at the same time. As a reminder, since the ABBV/IMGN acquisition both the target's AND the buyer's stocks have risen substantially – creating the best of all worlds.

The index's RSI closed at a positive 60 – not yet overbought either with room to go. Both the 50- and 200-day moving averages are heading higher, with

IDEAL study to eventually improve the standard of 2L PBC treatment while broadening the population. PBC is a much smaller liver disease than NAFLD/NASH and in our view, the acquisition points out the even bigger price we expect that will be paid for MDGL.

Novartis (NVS) plans to buy MorphoSys AG for $2.9 billion, representing a 60% premium from the closing price on February 2nd before M&A rumors were published by Reuters. The deal has some controversary as lead drug pelabrasib (BET inhibitor) met the primary endpoint of spleen size reduction in the Phase III MANIFEST-2 trial in myelofibrosis, but missed the key secondary endpoint of symptom reduction. Analysts had been debating the likelihood of approval given the mixed data.

Novo Holdings plans to acquire Catalent (CTLT) for $16.5 billion enterprise value or $63.50 in cash, representing a 16.5% premium over the prior days closing price. Novo Holdings will immediately sell three key CTLT fill/finish sites (Belgium, Bloomington, Anagni) to Novo Nordisk A/S (NVO) to build out diabetes/obesity GLP-1 manufacturing capabilities. GLP-1s are so in demand that Novo cannot make enough drug cementing the class as the largest in the history of drugs.

VRTX reached an all-time-record high on positive primary endpoint data in the Phase III trials for NaV1.8 inhibitor VX-548 in acute pain post abdominoplasty and bunionectomy compared to placebo. VX548 did not show superiority to active control Vicodin in either study; however, and was statistically inferior to active control Vicodin in the bunionectomy study. In our view, the market opportunity will be challenging as they try to compete against inexpensive generic Vicodin by charging a premium for a new pain drug the same or even less efficacy.

support at 88 below and no resistance above. After a bout of profit taking, the MACD is once again in the positive and turning upwards as well.

The weekly XBI also looks constructive after the roughly one month pause, settling right in between the two moving averages – 50-week below (81) and 200-week above (101). With the busy event calendar nearing – many in our MTSL Recommended names — we believe the rally will broaden to more subsectors other than just obesity and oncology like immunology/allergy (CLDX), NASH (MDGL, VKTX), cardiology (ESPR), neurology (ALKS, ACAD) and gene editing (SGMO). The market is easily absorbing public financings in biotechnology, yet the amount of new stock being issued is dwarfed by the takeover activity that doesn't appear to be ending anytime soon. Small company quarterly earnings calls are kicking in this week and next. Moreover, scientific and investor conferences plus FDA approvals in February and March will keep biotech very busy indeed. Support at 88 and resistance at 101.

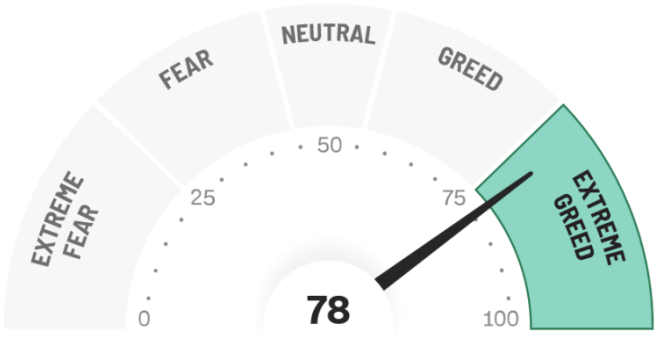
BIIB & ALNY Have Disappointing Earnings Calls

AMGN lead off the biotech earnings with a disappointment as they reported that just 2,000 patients have been treated so far with Leqembi, warning that the Alzheimer's drug developed with Eisai Co. may miss its target of 10,000 recipients by the end of March. Leqembi gained full US approval last year after a large trial clearly showed slowing of Alzheimer's progression. Many analysts have been expecting a slow rollout of the drug due to reimbursement issues and that the drug must be intravenously infused at a hospital or clinic every two weeks.

ALNY announced an updated statistical analysis plan and revised timing for its Helios-B phase 3 study evaluating vutrisiran (Amvuttra) in treating rare genetic disease transthyretin amyloid cardiomyopathy (ATTR-CM). Alnylam will now focus on "outcome measures in overall and monotherapy populations." It also tweaked secondary endpoints and added up to three months to the trial. The stock sold off over 10% as the changes to the clinical trial design are being viewed as a "lack of management's confidence" in the Helios-B results.

FEAR & GREED – EXTREME GREED

The Fear and Greed Index has crossed over into extreme greed at 78 after closing at 70 in the last Issue. We are not fans of Extreme Greed as it basically leaves nowhere to go but down, eventually.



MTSL Events Due Near-Term

- CLDX Q1 – Barzo SubC CSU Phase II Data at American Academy of Asthma, Allergy & Immunology, Abstract released on line Feb. 5, 2023, followed by Late Breaker Oral presentation at meeting Feb. 23-26
- VKTX Q1-Phase I Data from Oral Formulation and Phase II SubQ data for VK2735 Expected in Q1
- MDGL Q1 – March 14 PDUFA for Resmetirom for NASH
- ACAD Q1 – ADVANCE-2 Phase III study of pimavanserin in Negative Symptoms of Schizophrenia expected Q1
- ESPR Q1 – CLEAR Label expansion PDUFA March 31st, Earnings Call Feb 27th at 8 am ET
- PGEN Q2 – Pivotal Phase II RRP data for PRGN-2012 in Q2 which will lead to an FDA filing

TECHNICALS – Looking Good After Pause & Strong Calendar Ahead

With biotech M&A heating up again, the XBI (93) has resumed its ascension towards new 52-week highs (~95). The index had been basing and consolidating since mid-January – as no major M&A deals had occurred coupled with the reversal in interest rates.

Clinical Trials Watch

Relevant New Studies or Changes Posted on ClinicalTrials.gov for our MTSL Portfolio and/or Related Companie

ABBV – A Study to Assess Change in Disease Activity and Adverse Events of Oral Upadacitinib in Adult and Adolesc Severe Hidradenitis Suppurativa Who Have Failed Anti-TNF Therapy

ABBV – A Study to Assess Adverse Events and Change in Disease Activity From Intravenous (IV) and Subcutaneous Participants With Active Ulcerative Colitis

ABBV – Study to Evaluate the Effectiveness of Risankizumab in Participants With a Recent Diagnosis of Moderat Setting in Greece

BIIB/IONS – A Study to Evaluate Higher Dose (HD) Nusinersen (BIIB058) in Participants With Spinal Muscular Atr Risdiplam

Genentech – Pre-operative Atezolizumab in Patients With Resectable, Human Papillomavirus Related Oropha

INCY – A Study to Evaluate the Safety and Efficacy of Ruxolitinib Cream With Phototherapy in Participants With

INCY – Rollover Study to Provide Continued Treatment for Participants With B-Cell Malignancies Previously Enr (INCB050465)

INCY – Evaluate the Efficacy and Safety of Ruxolitinib on Hair Regrowth in Patients With Autoimmune Polyendo Dystrophy (APECED)-Associated Alopecia Areata

INCY – A Study to Evaluate INCB099280 in Participants With Select Solid Tumors Who Are Immune Checkpoint In

INCY/Innovaderm – Study to Evaluate the Efficacy of Ruxolitinib 1.5% Cream in Adult Subjects With Discoid Lupu

INCY – A Study to Evaluate the Efficacy and Safety Study of Povorcitinib in Participants With Inadequately Contr

INCY – Interventional Study of INCB 99280 With Ipilimumab in Participants With Select Solid Tumors

INCY – Study to Compare Maternal, Fetal, and Infant Outcomes of Women With Mild to Moderate Atopic Dermat During Pregnancy With an Unexposed Control Population

PCRX – Exparel vs. Marcaine ESP Block for Post-cardiac Surgical Pain

PCRX – Liposomal Bupivacaine vs Bupivacaine With Dexmedetomidine in Erector Spinae Plane Blocks for Mastec

Company Updates

UPDATES: ALKS, MDGL, SGMO, VKTX

ALKS — ALKS Poised For Strong 2024 With '2680 Data & LYBALVI Sales

2024 will be an important year for ALKS as they are well positioned to deliver on their strategic

The data supported dose selection of 4 mg, 6 mg, and 8 mg once daily for the planned Phase II in

priorities to drive growth of their commercial products, advance the clinical development of ALKS 2680 for the treatment of narcolepsy, and generate significant cash flow. Key for ALKS in 2024 will be the focus on maintaining strong momentum in the launch of LYBALVI. LYBALVI is currently selling at an annualized rate of $225 million and the company's 2024 guidance is $275-$295. In our view, this may be low and we would not be surprised to see ALKS exceed $300 million in sales.

In January, the company announced that it had completed the narcolepsy type 1 cohort in its Phase Ib trial of ALKS 2680, the company's novel, investigational orexin 2 receptor agonist in development for the treatment of narcolepsy. narcolepsy type 1, which the company plans to initiate in the first half of 2024. Going forward we expect both good data from '2680 and sales beats for LYBALVI to drive ALKS shares in 2024.

RECOMMENDATION

ALKS is a BUY under 35 with a TARGET PRICE of 55

MDGL — Resmetirom NASH Data Published in the *New England Journal of Medicine*, March 14 PDUFA Up Next

MDGL recently announced the publication of the pivotal Phase III MAESTRO-NASH trial of resmetirom in the *New England Journal of Medicine (NEJM).* This is a tremendous validation by the world's leading medical journal and is timed to coincide with the upcoming PDUFA date of March 14th. The article will be an excellent marketing tool for the sales force as they introduce the first drug ever approved for NASH. According to many KOLs there is a significant pool of NASH/NAFLD patients waiting for the drug's approval which will translate into a strong launch.

The *NEJM* said that based on the results of the 52-week biopsy portion of the trial, MAESTRO-NASH is the only Phase 3 study in NASH to achieve both primary endpoints that FDA proposed as reasonably likely to predict clinical benefit: NASH resolution with no worsening of fibrosis and fibrosis reduction with no worsening of NAFLD activity score (NAS). Approximately 50% of patients treated with MAESTRO-NASH also included many biomarker and imaging assessments that may be used in real world clinical practice to identify appropriate patients for treatment and monitor response to resmetirom.

Next up for MDGL is the March 14th PDUFA. We expect an approval from the FDA and the recent publication in the prestigious *NEJM* adds to our confidence. The article will be an excellent marketing tool for the sales force as they introduce the first drug ever approved for NASH. According to many KOLs there is a significant pool of NASH/NAFLD patients waiting for the drug's approval which will translate into a strong launch.

RECOMMENDATION

MDGL is a BUY under 300 with a TARGET PRICE of 400

resmetirom 100 mg with biopsies at Week 52 showed either NASH resolution or fibrosis improvement. More than 80% of patients with biopsies at Week 52 had either fibrosis reversal or no progression of fibrosis.

Additionlly to the two primary endpoints, multiple secondary endpoints were achieved in the MAESTRO-NASH study, including statistically significant reduction from baseline in liver enzymes (ALT, AST and GGT). Reductions in atherogenic lipids and lipoproteins, fibrosis biomarkers and imaging tests (MRI-PDFF, CAP and liver stiffness measures) were observed in resmetirom treatment arms as compared with placebo.

MDGL/VKTX — (2/6/24 Update) LLY's Phase II MASH Data Puts Pressure on MDGL (March 14 PDUFA) & VKTX (Q1 Phase I Oral Data)

Both MDGL and VKTX are under pressure today as a result of top line data from the Lilly Phase II Tirzepatide (Zepbound) GLP-1/GIP duel agonist Trial SYNERGY which enrolled 196 MASH patients with stage 2 or 3 fibrosis; three doses 5mg, 10mg, 15mg and placebo. The trial met the primary endpoint of absence of MASH with no worsening of liver histology. % of patients with absence of MASH and no worsening of fibrosis on liver histology at 52 weeks:

5 mg-51.8%
10 mg-63.1%
15 mg-73.9%

As for VKTX, also a GLP-1/GIP dual agonist play, we would argue that the LLY data validates VKTX which may have both a safer drug candidate with less nausea. VKTX also is about to release oral data in Q1 which we expect to be positive.

We also find it interesting that LLY is down or flat the data after an initial pop. Phase III is a long road in MASH/NASH drug development and resmetirom remains the clear leader and will be the first to market by multiple years. Both MDGL (March 14 PDUFA) and VKTX (Q1 Phase I oral data) have upcoming catalysts, and are still strong buys after today's overreaction to the Lilly data.

LLY also said that the secondary endpoint of decrease in fibrosis by at least one stage with no worsening of MASH on liver histology was clinically meaningful across doses. No detailed efficacy or side effect data was released, LLY said will present at future medical conference. Without any detailed data on drop outs and side effects it is difficult to compare LLY's MASH data to MDGL at this point. What we do know is that tirzepatide is an injectable drug with significant side effects with nausea making the drug intolerable for many from the very start of treatment and over time.

Real world observations estimate maybe less than 50% of potential patients are able to stay on a GLP-1 for over 52 weeks. MDGL's resmetirom is a very safe pill that has an excellent data set for both efficacy and safety IN both NASH and NAFLD with a upcoming March 14 PDUFA date (we expect a positive FDA decision).

RECOMMENDATION

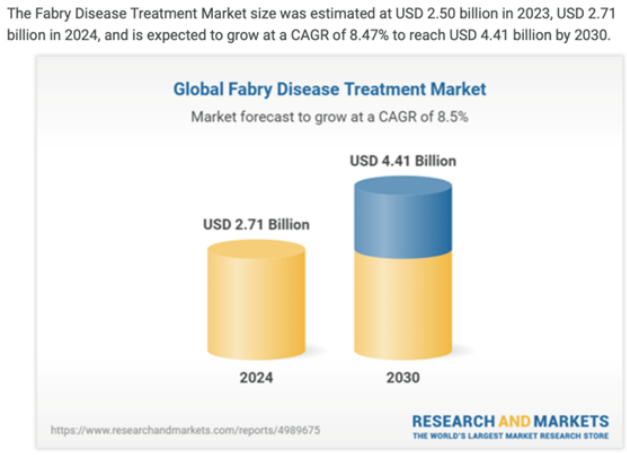
MDGL is a BUY under 300 with a TARGET PRICE of 400
VKTX is a BUY under 28 with a TARGET PRICE of 45

SGMO — Sangamo Gets FDA & EU OK For Simplified and Accelerated Pivotal Fabry Trial After Data Update – Upgrading to BUY

SGMO has come back to life. We are upgrading the stock to BUY from HOLD.

FDA Agrees To Accelerate ST-920 For Fabry

Last week the Company announced important U.S. and European regulatory updates for isaralgagene civaparvovec, or ST-920 – its wholly-owned gene therapy product candidate for the treatment of Fabry disease. The FDA has agreed in a Type D meeting that data from a single, adequate, and well-controlled study may form the primary basis of approval of a BLA for isaralgagene civaparvovec. The proposed study would enroll up to 25 patients, both male and female, without the need for a control arm.



Cash And/Or Partner Next – Upgrade To BUY

A head-to-head comparison with Enzyme Replacement Therapy (ERT) is not part of the proposed study design deemed acceptable by the FDA. This approach enables a potentially more rapid, efficient and cost-effective pathway to BLA submission than originally anticipated, with a much lower bar for success.

EU Regulators on Board, Too

Isaralgagene civaparvovec has already received Orphan Medicinal Product designation from the EMA, as well as Orphan Drug, Fast Track and RMAT designations from the FDA. Additionally, along with FDA agreement above, Sangamo also announced that the EMA has granted PRIME eligibility to isaralgagene civaparvovec. PRIME is a program designed to enhance support for the development of medicines that target an unmet medical need and is intended to optimize development plans and expedite review and approval processes so that these medicines may reach patients as early as possible.

Positive Clinical Update At WORLD

On February 5, the company presented updated Phase 1/2 STAAR study data showing sustained clinical benefit and a differentiated safety profile across 24 patients at the 20th Annual WORLD*Symposium*^{TM} in San Diego, CA on February 7, 2024. A total of 29 patients have been treated to date in the Phase 1/2 STAAR study. All 13 patients withdrawn from ERT remain off ERT as of February 12, 2024. Screening and enrollment are complete in the study and dosing of the remaining enrolled patients is expected in the H1:24.

Sangamo is deferring additional investments in planning for a registrational trial until a collaboration partnership is secured or additional funds are raised. With the current positive news concerning this particular pipeline compound, in this biotech bull market we expect that will not be a problem, and likely occur sooner than later. The global Fabry market is estimated to reach $2.7 billion this year rising to $4.4 billion by 2030. The current treatment is predominantly made up of nutritional support and ERT players and include Amicus Therapeutics, BioMarin, Nestle, Sanofi and Takeda – any of which can simply partner with SGMO (or at this cheap valuation – $186 million – one could easily take out the whole company). The combination of important U.S. and European regulatory updates and data for ST-920 has been a boost to the Company's depressed share price, but we see a lot more to go.

We are upgrading SGMO to a BUY From HOLD.

RECOMMENDATION

SGMO is a BUY under 2 with a TARGET PRICE of 5

VKTX — VKTX To Release Both Phase I Oral & Phase II SubQ '2735 Data in Q1

VKTX recently held their quarterly conference call and importantly reported that in addition to Phase I oral data for '2735 in Q1, the Phase II subQ trial will also report in Q1, moved up from Q2 expectation. In Phase I we saw a 6% placebo-adjusted weight loss in just 4 weeks. So with longer dosing of up to 13 weeks using up to 50% higher dose, what's a reasonable expectation of rate loss in the upcoming VENTURE trial? The company believes that an 8% hurdle for the VENTURE trial would be sufficient to move forward and measures up well against other drug candidates at 13 weeks.

The Phase I SAD/MAD trial of VK2735 oral formulation continues enrolling, with data expected later in 1Q24. We believe a realistic bar for efficacy is 1-3% placebo-adj. weight loss at 28 days. VKTX notes that wide safety margins could enable escalation to higher doses in a potential subsequent Phase II trial. The oral data has the potential to drive further upside in VKTX shares.

The Oral Market Opportunity: The first oral market would be as a lead in to subQ therapy for someone who doesn't want to start with an injection. A second oportunity would be in the maintenance setting. This could be a really important setting because if you come off a large amount of weight loss and you don't want to continue to take the injection, transitioning to an oral would be a potentially really attractive option. And in that sense, you maybe wouldn't require the same level of efficacy as a subQ to maintain a certain target body weight.

Thus 1-3% placebo-adj. weight loss at 28 days for an oral would be a win. Another potential market opp would be in the temporary use. You have an event coming up in 6 months or whatever, and you want to lose some weight ahead of that. So you wouldn't necessarily need the magnitude of weight loss that could be provided by a subQ dosage form and oral would be suitable there. While we view the subQ as the majority of the market, we also view the oral opportunity as a really important incremental opportunity.

Lastly, VK2809 in NASH provides attractive optionality for potential partnership and/or combinations, pending supportive Phase IIb VOYAGE histology data expected 1H24 and potential resmetirom FDA approval (PDUFA 3/14/24). We view VKTX as internally hedged and favorably positioned in NASH with both VK2809 and VK2735, especially following recent tirzepatide Phase II data in NASH. In our view, VKTX is well-positioned following its recent 4Q23 update and is a prime M&A candidate with Lilly looming.

RECOMMENDATION

VKTX is a BUY under 28 with a TARGET PRICE of 45

The Back Page

Symbol	Company	Orig.Rec.	Current	Target	Recommendation
ACAD	Acadia	33.79	31.31	45	BUY under $28

ALKS	Alkermes	10.13	27.74	55	BUY under $35
BCYC	Bicycle	43.92	18.08	75	BUY under $50
BMRN	BioMarin	12.68	96.42	150	BUY under $100
CLDX	Celldex	10.50	39.66	100	BUY under $75
ESPR	Esperion	24.42	2.99	25	BUY under $10
INCY	Incyte	5.88	63.84	108	BUY under $85
IONS	Ionis	7.63	50.59	65	BUY under $50
MDGL	Madrigal	17.00	231.38	400	BUY under $300
PCRX	Pacira	15.78	33.74	100	BUY under $80
PGEN	Precigen	34.42	1.34	12	BUY under $5
SGMO*	Sangamo*	4.77	0.54	5*	BUY under $2*
TCRT	Alaunos	8.00	.07	5	HOLD
VKTX	Viking	16.83	18.61	45	BUY under $28
VXRT	Vaxart	8.00	0.57	8	BUY under $3

**New recommendation.*

THE MODEL PORTFOLIO*

COMPANY	SHARES OWNED	TOTAL COST	TODAY'S VALUE

Long Positions			
Acadia (ACAD)	4,750	156,557	148,723
Alkermes (ALKS)	3,800	88,690	105,412
Bicycle (BCYC)	2,400	105,408	43,392
Celldex (CLDX)	15,832	174,993	627,897
Esperion (ESPR)	3,316	105,316	9,915
Incyte (INCY)	1,229	34,817	78,459
Ionis (IONS)	3,087	49,123	156,171
Madrigal (MDGL)	3,127	69,980	723,525
Pacira (PCRX)	2,375	63,887	80,133
Precigen (PGEN)	9,690	76,510	12,985
Sangamo (SGMO)	19,456	253,596	10,570
Alaunos (TCRT)	26,125	166,100	1,847
Viking (VKTX)	12,000	201,960	223,320
Vaxart (VXRT)	29,687	250,000	17,005
(02/15/24)		**Equities:**	**$2,239,354**

Cash:	**$ 237,884**
PORTFOLIO VALUE:	**$2,477,237**

**The Model Portfolio is designed to reflect specific recommendations. We began the Model Portfolio on 12/23/83 with $100,000. On 4/13/84, we became fully invested. All profits are reinvested. Stocks recommended since then may be equally attractive, but may not be in the Model Portfolio. Transactions and positions are valued at closing prices. No dividends are created, and we don't use margin. Interest income is credited only on large cash balances.*

BENCHMARKS

	NASDAQ	S&P 500	MODEL
Last 2 Weeks	1.7%	1.7%	-9.9%
2024 YTD	5.1%	4.9%	0.0%
Calendar Year 2023	43.4%	24.2%	-3.5%
Calendar Year 2022	-33.1%	-19.4%	-12.7%
Calendar Year 2021	21.3%	26.9%	-15.2%
Calendar Year 2020	43.6%	16.3%	13.8%
Calendar Year 2019	35.2%	28.8%	10.7%
Calendar Year 2018	5.7%	6.6%	4.5%
Calendar Year 2017	29.3%	19.9%	65.6%

Calendar Year 2016	7.5%	9.5%	-29.6%
Calendar Year 2015	-0.1%	-0.1%	25.1%
Calendar Year 2014	13.4%	11.4%	29.2%
Calendar Year 2013	38.3%	29.6%	103.4%

New Money Buys

BioInvest

(Based on Market Cap when under our limit)

1st Tier: ACAD, ALKS, BMRN, INCY, IONS, MDGL

2nd Tier: BCYC, CLDX, PCRX, VKTX

3rd Tier: TCRT, ESPR, PGEN, SGMO, VXRT

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← Madrigal (MDGL) & Viking Therapeutics (VKTX) – LLY's Phase II MASH Data Puts Pressure on MDGL (March 14 PDUFA) & VKTX (Q1 Phase I Oral Data)