MTSL Issue 1016

December 14, 2023

UPDATES: ACAD, ESPR, INCY, VKTX

IN THIS ISSUE: Biotech is Back For All The Right Reasons

Since Last Issue: BTK: 8.93%; NBI: 8.66%; XBI: 11.65%; Model Portfolio: 16.79%

(Please note: the next issue of the MTSL will be published in three weeks on January 4th. Happy Holidays!)

BIOTECH SECTOR ANALYSIS

SENTIMENT — XBI Strong as We Head Into 2024

Perfect Storm For Biotechs

It has been a bit of a perfect storm for biotechs since the last Issue after a very rocky year. The Fed signaling they will stop raising interest rates along with tax loss selling abating have been a breath of fresh air for the biotechs. Two MTSL recommendations have also delivered surprisingly good news, ACAD with fresh IP and ESPR's FDA label

TECHNICALS – XBI Phenomenal Run Only Back To July Levels

For all the right reasons, the XBI has finally been on a tear. Since reaching a nadir of ~64 on October 31, the index closed over 85 at press time – up an impressive 34% since then – with many individual stocks doing much better than that. Fundamentals have been strong – positive clinical trials, solid launches, favorable litigation and premium M&A deals. Large investors are taking big positions (e.g., Baker Brothers added sizably to MDGL, Point72 the same in CLDX). Most likely, the peak and subsequent pullback in interest rates and inflation has seen a major shit to risk assets and biotech is the poster child (see the XBI in green vs the 30-Year Bond in blue

were big winners. Biotech Big Caps VRTX and MRNA also delivered strong Phase II data for a new pain drug and a cancer vaccine/Keytruda combo respectively. We also saw more M&A and AbbVie has already stepped back up to the plate and bought Cerevel. Adding it all up to a perfect storm was a better macro environment (rates and tax loss selling), great biotech news with more M&A (AbbVie/Cereval & Roche/Carmot), good clinical data (VRTX & MRNA), good news (ACAD IP & ESPR FDA Label) and FDA approvals for both CRSP and BLUE.

AbbVie Not Done Shopping

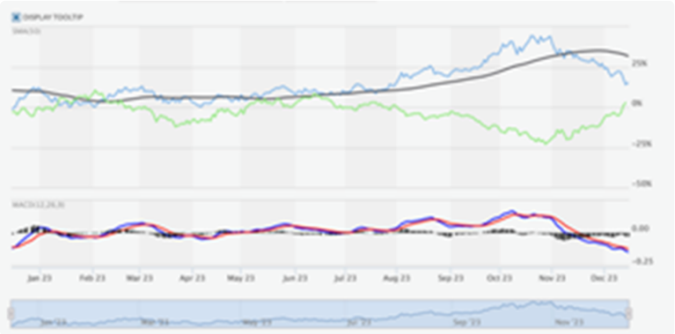
AbbVie was fresh from their very recent $10 billion acquisition of IMGN and we thought they might need some time for digestion. However, AbbVie said last week it will acquire neuroscience drugmaker Cerevel Therapeutics for roughly $8.7 billion. AbbVie will pay $45 per share for Cerevel. AbbVie said it expects to complete the acquisition in the middle of 2024. Additional M&A is always good for the biotechs as it points out both individual and sector under valuations. In AbbVie's case it was also good for the acquirer as its stock has risen significantly since the two acquisitions instead of the usual decline.

Roche Buys VKTX Obesity Competitor

We also saw Roche step up and buy a VKTX competitor, privately held Carmot Therapeutics for $2.7 billion in cash and up to $400 million in potential milestone payments. Carmot's pipeline includes CT-388, a QW sub-q dual GLP-1/GIP agonist for obesity in patients with or without Type 2 diabetes (T2D), CT-996, a Phase 1 oral GLP-1 agonist for obesity and T2D, and CT-868, a Phase II QD sub-q GLP-1/GIP agonist for overweight/obese T1D patients. We see the Carmot acquisition continuing to affirm Big Pharma's huge appetite for clinically validated incretin drug development programs like VKTX.

in the chart below). Lastly, tax loss selling has abated and fund managers are putting some dry powder to work in the oversold sector. Taken together, the shorts are getting squeezed and after 2+ years of depressed underperformance in their favor, some are throwing in the towel. Biotech is back.

XBI vs. 30 Year Bond



On a technical basis, it looks as though we have reached overbought levels – with the RSI at 76-77. There is still two more weeks to the end of 2023 and there is no question that the bio bulls are back and trying to make up for a pretty poor YTD overall. With the VRTX pain data followed by the MRK/MRNA melanoma cancer vaccine results, the XBI blew well above the 200-day moving average (79). The charts finally look impressive and positive but a pullback from overbought levels is likely after such a violent run – aided by short covering. The MACD also looks a bit extended. Nonetheless, despite the run and the all the good news, the index has only recovered to surpass Labor Day levels and is still below the June and February 2023 highs (~90). The 200-day MA is the new support level.

Specifically, VKTX and the very competitive efficacy/safety profile VK2735 has with CT-388 provides positive read through for VKTX causing shares to trade up significantly since the deal was announced. Next up are two catalysts for VKTX in 1H24, with data from the Phase II VENTURE study of subQ '2735 in obese patients in 1H24 as well as data from the oral formulation of '2735 in 1Q24 (was expected this month). In our view, VKTX is still significantly undervalued and could easily be worth more than the $2.7 billion Roche just paid for Carmot.

FDA Approves Competing Gene Therapies For Sickle Cell Simultaneously

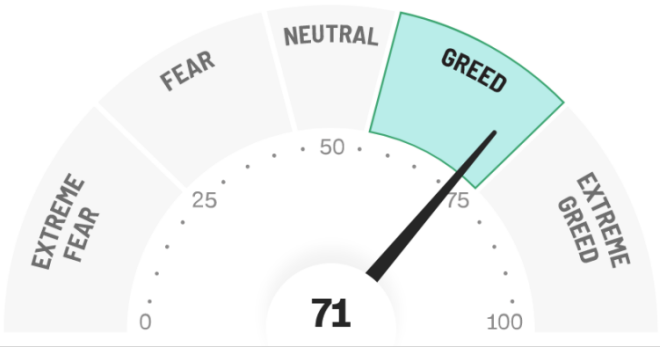
Last week, the FDA simultaneously approved Vertex/Crispr's CRISPR-based therapy, Casgevy and Bluebird's lentiviral-based therapy, Lyfgenia for sickle cell disease just in time to make these approvals the talk of ASH. The company's estimate that 16-20K patients with SCD are eligible for these treatments now, but the number may be a bit optimistic. Potential problems for the market opportunity for the first generation gene therapies are the long hospitalization times, the safety risks associated with mobilization, and the preconditioning treatments. Lastly, the potential for patients taking their shot on one of the first generation gene therapies will make them ineligible for something less onerous to come along in a few years.

The prices were announced almost simultaneously (Lyfgenia @ $3.1 million, Casgevy @ $2.2 million) but the almost one-million-dollar differential quickly became huge news. Either way, it puts Vertex at a significant competitive advantage, particularly with the absence of a black box warning. Vertex comes out looking like the comparatively good guy. Bluebird almost has to discount Lyfgenia on the back end to the $2.2 million range to even be competitive.

The weekly XBI finally went above its own moving average – in this case the 50-week MA of 80. Based on that breakout, it looks like the new resistance is 101 – the 200-week moving average. The weekly MACD is just turning positive so after a long run of selling, shorting and interest rate hikes we might continue to see positive XBI gains. As we head into 2024 – the science calendar will be quiet during holiday season, but the JPMorgan Healthcare Conference kicks off in San Francisco the second week of January. Yes, it will be a zoo, but stay with our new leaders and Best-In-Class ideas like CLDX, MDGL and VKTX. Long-term MTSL Recommendation INCY's R&D pipeline is finally delivering – and its shares are still very attractive even after the recent run up. IONS has been stellar even before the group's recent advance. Even ESPR is waking up fundamentally. We remind investors that when biotech works, it works big – see IMGN ($10 billion). So while a few of our favorites have had good runs of late – especially CLDX, MDGL and VKTX (in alphabetical order) – their stocks still remain well below recent highs despite exceptional fundamental news plus a number of potential competitor hiccups. A really good end to the year – and we expect more in 2024!

FEAR & GREED – Staying GREED

The Fear & Greed Index is firmly in the Greed zone at 71 after closing at 68 in the last Issue. While the F&G is only up modestly, being in the GREED zone is perfect for biotechs which do much better in a bullish low interest rate scenario.



Have a very Happy & Healthy New Year!!!!

John & Jay

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 Adverse Events and Effectiveness of Upadacitinib Oral Tablets in Adult and Adolescent

ABBV – An Observational Study to Assess Change in Disease Activity and Treatment Patterns of Upadacitinib Wh With Methotrexate in Adult Participants With Active Psori-atic Arthritis

ABBV – A Study to Assess Real-World Use, Safety, and Effectiveness of Oral Upadacitinib in Adult and Adolescent Atopic Dermatitis

ACAD – ACP-204 in Adults With Alzheimer's Disease Psychosis

AKRO – A Study Evaluating Efruxifermin in Subjects With Non-inva-sively Diagnosed Nonalcoholic Steatohepati Associated Steatohepatitis (MASH) and Nonalcoholic Fatty Liver Disease (NAFLD)/Metabolic Dysfunction-Assoc

INCY – Study to Evaluate the Pharmacokinetics, Safety, and Pharmaco-dynamics of INCB054707 in Participants Function and Participants on Hemodialysis

INCY – Ruxolitinib With De-Intensified HLH-94 for the Treatment of Hemophagocytic Lymphohistiocytosis (HL

INCY – A Study to Evaluate INCB099280 in Participants With Ad-vanced Cutaneous Squamous Cell Carcinoma

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

PGEN – PRGN-2009 in Combination With Pembrolizumab Versus Pembrolizumab in Patients With Recurrent or

PCRX – Efficacy and Safety of Liposomal Bupivacaine in Thoracic Par-avertebral Nerve Block

PCRX – A Study of Liposomal Bupivacaine Versus 0.25% Bupivacaine Hydrochloride Post Breast Reduction

Company Updates

UPDATES: ACAD, CLDX, ESPR, INCY, VKTX

ACAD — ACAD Scores Big With Summary NUPLAZID Patent Victory

ACAD recently had great news when the announced that the U.S. District Court for the District of Delaware has granted summary judgment to ACAD,

In addition to the positive court action vs. MSN Labs, recent court filings show ACAD has also resolved patent disputes with other generic developers. ACAD

confirming validity of the NUPLAZID (pimavanserin) '740 composition of matter patent. The court ruled in favor of Acadia on all grounds. The ruling came in ACAD's litigation against MSN Laboratories Pvt. Ltd., MSN Pharmaceuticals, Inc. and other ANDA (Abbreviated New Drug Application) filers and concludes this litigation in the District Court.

The '740 composition of matter patent protects NUPLAZID into 2030. ACAD markets two forms of NUPLAZID, a 34mg capsule and a 10mg tablet. In addition to the '740 patent, Acadia has an issued method of use patent that protects the 10mg tablet to 2037 and multiple issued formulation patents that protect the 34mg capsule into 2038.

stock investors are now closely focused on Daybue, Acadia's second drug, which has exceeded expectations out of the gate after receiving FDA approval earlier this year to treat patients with Rett Syndrome. The company is clearly executing well and with the NUPALZID IP significantly extended, ACAD is a perfect M&A candidate with two approved drugs with follow on indications and a pipeline to boot.

RECOMMENDATION

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

ESPR — CLEAR Light at End of Tunnel with Outcomes Label Approvals Coming in Q12024

ESPR has announced that the FDA has approved an updated LDL-cholesterol lowering indication for NEXLETOL and NEXLIZET to include the treatment of primary hyperlipidemia as a qualifier for existing approved populations. Additionally, the maximally tolerated qualifier for statin use has been removed, and the prior limitation of use stating "the effect of NEXLIZET or NEXLETOL on cardiovascular morbidity and mortality has not been determined" has also been removed. In our view, this is a CLEAR foreshadow of the upcoming FDA label approval adding the cardiovascular risk benefit. Our confidence is reinforced by this most recent FDA action as it demonstrates that the company and the FDA are on the same page.

These labeling modifications do not impact the full pending label approvals for cardiovascular risk reduction indications for NEXLETOL and NEXLIZET, which remain on track for anticipated approval in the first quarter of 2024. In June 2023, the Company announced its submission of four Supplemental New

While it has been a tough year for ESPR, 2024 is shaping up to be a much better year. We expect both the U.S. and European label approvals to include cardiovascular risk reduction indications for both NEXLETOL and NEXLIZET in the first half of 2024. We also expect ESPR to win their dispute with Daichi in Europe after the label is expanded there. The company is also an M&A candidate as the label expansions will significantly de-risk the stock and ESPR has retained full U.S. rights making them an even more attractive target for acquisition.

RECOMMENDATION

ESPR is a BUY under 10 with a TARGET PRICE of 25

Drug Applications based on the landmark Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) Outcomes trial, which demonstrated that bempedoic acid, contained in both NEXLETOL and NEXLIZET, can significantly reduce cardiovascular risk across a range of primary and second endpoints. These applications were accepted by the FDA which issued a PDUFA, or action, date of March 31, 2024. The Company's EMA applications also remain on track, with anticipated approval in the first half of 2024.

INCY — INCY Has Strong ASH as Stock Bounces Off Lows

INCY had a strong American Society of Hematology (ASH) meeting, where they hosted an investor event and provided the following updates on Jakafi lifecycle management: once-daily Jakafi – INCY will conduct an additional bridging study to show bioequivalence to Jakafi per FDA feedback early this month resulting in a ~2-year delay in approval; Jakafi combination studies with ALK2 and BET inhibitors – on the former additional dose optimization is required (proof-of-concept data by mid-24). INCY discussed the translational data on mutant CALR-targeting antibody (Phase I initiated and first patient has been dosed) and translational validation of INCB160058, a selective inhibitor targeting the JAK2V617F mutation (the most common mutation in MF, ET and PV; trial to begin in 1Q24). We view the updates as encouraging and look to further clarity from the aforementioned studies to determine Jakafi's outlook ahead of the mid-27/late-28 EU/US patent losses-of-exclusivity.

Also at ASH, INCY and partner SNDX presented additional data from the pivotal Phase II AGAVE-201 trial of axatilimab (CSF-1R antibody) in adult and pediatric patients with refractory chronic graft-versus-host disease (GVHD) who had received at least

Patients who received axatilimab at 0.3 mg/kg every two weeks achieved the highest overall response rate (ORR) of 74% within the first six months of treatment (95% CI; 63-83). Patients in this cohort experienced a median time to response to axatilimab of 1.7 months (0.9-8.1), and 60% of patients maintained a response at 12 months (measured from first response to new systemic therapy or death, based on the Kaplan Meier estimate). SNDX and INCY expect to submit a BLA by YE23.

INCY had a strong ASH with the axatilimab data in GVHD looking particularly impressive. Importantly, the drug candidate may help address the ongoing concerns regarding Jakafi's IP life cycle. ASH was also a boost to INCY's stock price as it has bounced nicely since the meeting and attracted additional sponsorship from Wall Street which has helped the stock maintain momentum.

RECOMMENDATION

INCY is a BUY under 85 with a TARGET PRICE of 108

two prior lines of systemic therapy. Across all dose cohorts of axatilimab (0.3 mg/kg every two weeks, 1.0 mg/kg every two weeks and 3.0 mg/kg every four weeks) the primary endpoint was achieved.

VKTX — (12/5 Update) Significantly Undervalued After Roche Pays $2.7 Billion For Competitor, Phase I '2735 Oral Proof-of-Concept Data in Q1 2024

Roche is buying a VKTX competitor, privately held Carmot Therapeutics for $2.7 billion in cash and up to $400 million in potential milestone payments. Carmot's pipeline includes CT-388, a QW sub-q dual GLP-1/GIP agonist for obesity in patients with or without Type 2 diabetes (T2D), CT-996, a Phase 1 oral GLP-1 agonist for obesity and T2D, and CT-868, a Phase II QD sub-q GLP-1/GIP agonist for overweight/obese T1D patients. We see the Carmot acquisition continuing to affirm Big Pharma's huge appetite for clinically validated incretin drug development programs like VKTX.

Specifically, VKTX and the very competitive efficacy/safety profile VK2735 has with CT-388 provides positive read through for VKTX causing shares to trade up 15% two consecutive days. Next up are the two catalysts for VKTX in 1H24, with data from the Phase II VENTURE study of subQ '2735 in obese patients in 1H24 as well as data from the oral formulation of '2735 in 1Q24 (was expected this month). In our view, VKTX is still significantly undervalued and could easily be worth more than the $2.7 billion Roche just paid for Carmot.

Obesity is a major risk factor for NASH. VKTX is developing VK2735, a GLP-1/ GIP dual agonist, for treatment of obesity. VK2735 is in Phase II as a weekly subQ injection and Phase I as an oral form with proof-of-concept data expected in 1Q 2024. VKTX is also developing VK2809 for NASH and VK5211 for lean muscle mass and bone protection, which we

On the AE profile between the two programs, we would argue VK2735 appears to have a significant edge of overall rates of nausea, diarrhea, and vomiting across dose cohorts, though we acknowledge the small N within each cohort. We continue to believe the weight loss profile for '2735 will get better with further follow up and look forward to data from the Phase II VENTURE study in 1H24 and data from the Phase I oral formulation study of '2735 in 1Q24.

Upcoming Catalysts

- VK2735 Phase 1 Oral Proof-of-Concept Data — 1Q24
- VK2735 Phase 2 VENTURE SubQ Data — 1H24
- VK0214 for X-ALD Phase 1b enrollment completion — 2H23
- VK2809 for NASH P2b data update — 1H24

In our view, VKTX is still significantly undervalued and could easily be worth more than the $2.7 billion Roche just paid for Carmot. Obesity is a major risk factor for NASH. VKTX is developing VK2735, a GLP-1/ GIP dual agonist, for treatment of obesity. VK2735 is in Phase II as a weekly subQ injection and Phase I as an oral form with new proof-of-concept data expected in 1Q 2024. VKTX is also developing VK2809 for NASH and VK5211 for lean muscle mass and bone protection, which we believe could both be combined synergistically with VK2735 in a once-daily oral pill.

RECOMMENDATION

believe could both be combined synergistically with VK2735 in a once-daily oral pill.

VKTX Shows Very Competitive Efficacy/SafetyProfile with Carmot's CT-388

Carmot's drug development platform focuses on the development of receptor biased incretin agonists to minimize recruitment of beta arrestin which can attenuate signaling. CT-388 is a QW sub-q GLP-1/GIP dual agonist in development for treatment of obesity with or without T2D. CT-388 showed placebo adjusted reductions in weight of -4.3% to -7.6% at up titrated peak doses of 7.5-12mg at day 29.

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	28.06	45	BUY under $28
ALKS	Alkermes	10.13	26.95	55	BUY under $35
BCYC	Bicycle	43.92	15.00	75	BUY under $50
BMRN	BioMarin	12.68	97.62	150	BUY under $100
CLDX	Celldex	10.50	36.15	100	BUY under $75
ESPR	Esperion	24.42	1.73	25	BUY under $10
INCY	Incyte	5.88	63.84	108	BUY under $85
IONS	Ionis	7.63	49.82	65	BUY under $50
MDGL	Madrigal	17.00	233.02	400	BUY under $300

PCRX	Pacira	15.78	30.79	100	BUY under $80
PGEN	Precigen	34.42	1.26	12	BUY under $5
SGMO	Sangamo	4.77	0.43	15	HOLD
TCRT	Alaunos	8.00	0.05	5	HOLD
VKTX	Viking	16.83	19.22	45	BUY under $28
VXRT	Vaxart	8.00	0.67	15	BUY under $5

**New recommendation.*

THE MODEL PORTFOLIO*

COMPANY	SHARES OWNED	TOTAL COST	TODAY'S VALUE
Long Positions			
Acadia (ACAD)	4,750	156,557	133,285
Alkermes (ALKS)	3,800	88,690	102,410
Bicycle (BCYC)	2,400	105,408	36,000
Celldex (CLDX)	15,832	174,993	572,327
Esperion (ESPR)	3,316	105,316	5,737
Incyte (INCY)	1,229	34,817	78,459

Ionis (IONS)	3,087	49,123	153,794
Madrigal (MDGL)	3,127	69,980	728,654
Pacira (PCRX)	2,375	63,887	73,126
Precigen (PGEN)	9,690	76,510	12,209
Sangamo (SGMO)	19,456	253,596	8,366
Alaunos (TCRT)	26,125	166,100	1,306
Viking (VKTX)	12,000	201,960	570,584
Vaxart (VXRT)	29,687	250,000	8,040
(12/14/23)		**Equities:**	**$2,484,298**
		Cash:	**$ 237,884**
		PORTFOLIO VALUE:	**$2,722,181**

**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	3.6%	8.9%	16.8%
2023 YTD	29.1%	18.6%	5.7%
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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← Viking Therapeutics (VKTX) – Significantly Undervalued After Roche Pays $2.7 Billion For Competitor

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