MTSL Issue 1017

January 4, 2024

UPDATES: ALKS, BCYC, ESPR

IN THIS ISSUE: This Week – The Busiest JPMorgan Healthcare Conference In Years

Since Last Issue: BTK: 1.81%; NBI: 4.42%; XBI: 4.44%; Model Portfolio: 0.72%

BIOTECH SECTOR ANALYSIS

SENTIMENT — 2024 – Biotech Optimism With Improving Interest Rates and Hot M&A Environment

In our view, biotech is poised for a strong 2024 as three underperforming years in a row have cleared a lot of the dead weight out of biotech. The combination of lower interest rates and strong biotech fundamentals has led to a significant uptick in M&A with Bristol Myers making two acquisitions fresh on the heels of AbbVie making two acquisitions. Overall, we like the setup for the biotech sector and expect 4Q23 M&A momentum to continue into 2024.

TECHNICALS – Slight Retreat After Major Run

The XBI (89) ended 2023 with exceptional performance – an astounding ~40% off the low of October 31. It therefore is more than reasonable for biotech stocks to take a pause to start the New Year. There is no doubt that interest rate expectations rule the day and recent, unexpected hawkish Fed rhetoric helped the rate sensitive companies. In addition, strong jobs reports are dividing the growth vs. value camps again. Nonetheless, biotech sector fundamentals are solid – M&A and collaborations are back, certain new drug launches are exceeding expectations – as we head into the most crowded and busiest JPMorgan Healthcare Conference week that we have seen since before the pandemic. Of course,

Interest rates going down in 2024 should also boost biotechs. The past six months especially have shown an extremely tight inverse correlation between the XBI and the 10-year Treasury. Higher-for-longer is part of the current bear thesis on the sector, but we side with the bulls here that the US government (especially a Biden administration trying to drum up excitement for the economy during an election year) will have levers at its disposal and lower rates.

We also think the macro set-up of lower interest rates should bode well for primary and secondary biotech offerings (anemic the last two years) helping address the sector's cash concerns. Additionally, a continuation in 2024 of the strong 2H23 uptick in M&A would further boost the sector.

Despite the Biden administration having done fundamental damage to the industry (drug pricing), we do not expect politics to play a big role this year. We expect fiscal and monetary policies to be implemented this year in order to have another term will benefit investment in the biotech sector more than his additional saber rattling will hurt it.

Bristol Myers Follows AbbVie's Lead & Makes Two Holiday Acquisitions

Bristol Myers announced that it will acquire the biopharmaceutical company Karuna (KRTX) for $14 billion, $330 per share, to strengthen its neuroscience portfolio. Bristol also announced the acquisition of RayzeBio for $4.1 billion, $62.50 per share, to add their radiopharmaceutical platform to treat cancer. KRTX is focused on developing drugs for psychiatric and neurological conditions. Its lead asset, KarXT (xanomeline-trospium), is an antipsychotic with a novel mechanism of action and differentiated efficacy and safety. The new drug application for KarXT for the treatment of schizophrenia in adults is under review, the FDA has set a target action date of Sep 26, 2024.

the respiratory illnesses – including COVID – are spiking again; hence, big rallies in the vaccine stocks MRNA and BNTX, even PFE. After breaking sharply over and staying well above the 200-day Moving Average (79), the XBI hit oversold levels but has pulled back to a positive/neutral 62-63 range with rates creeping up again. The charts show that the XBI is heading towards a Golden Cross – as the 50-day MA (77) is steamrolling toward the longer-term index. For the first time in years, people will be smiling in San Francisco (and the weather report looks favorable too). What is impressive is that the very top tier biotech stocks – REGN, VRTX – continue to soar – somewhat akin to the Big 7 tech monsters that reached trillion dollar valuations. Investors are appreciating the blockbusters drugs (e.g., the GLP-1s) like they haven't in a long time. While the index might continue to see some post rally, post JPM profit taking, in our view the stars and charts will remain supportive in the near term. We see strong support at 79.

The longer-term XBI chart also looks constructive. The index is just about the levels of the highs seen back in both June and January of 2023, It temporarily went slightly above those levels and it will be interesting to see if some really good news comes out of the conference (and not just press releases for press release sake) that could take us back up and over those 52-week highs. A majority of our MTSL names will be present this week although we are not

The drug development candidate is also in a pivotal trial for the treatment of psychosis in patients with Alzheimer's disease. The acquisition will diversify its broad portfolio and enable it to establish a presence in the schizophrenia space, which is challenging but has enormous potential given the lack of treatments. We are not surprised by BMY pulling the trigger (especially after ABBV purchased CERE) given headwinds BMY faces on new product launches. At BMY's R&D event, the company highlighted neuroscience as one of the key therapeutic areas with a goal to build a deep pipeline there.

BMY is also acquiring a clinical-stage radiopharmaceutical therapeutics (RPT) company, RayzeBio RYZB for $4.1 billion, $62.50 per share in cash. The move adds RayzeBio's proprietary radiopharmaceutical platform, along with its innovative pipeline of potentially first-in-class actinium-based RPTs, to Bristol Myers' oncology portfolio which is poised to lose patent protection on Keytruda in 2028.

RayzeBio's lead drug development candidate, RYZ101, targets somatostatin receptor 2 (SSTR2), which is over-expressed in GEP-NETs and extensive-stage small cell lung cancer (ES-SCLC). RYZ101 is currently being evaluated in Phase III in patients with SSTR-positive GEP-NETs who have previously been treated with lutetium-177-based somatostatin therapies. Enrollment in the late-stage study is ongoing. A phase Ib clinical trial is also currently enrolling patients to evaluate RYZ101 as a first-line treatment of ES-SCLC in combination with standard-of-care therapy. The addition of these candidates will further diversify Bristol Myers' oncology pipeline. M&A is clearly heating up with Bristol's two acquisitions following just weeks after AbbVie also made two acquisitions.

Novo Nordisk Inks Obesity Deal With Omega

expecting specific news except for maybe PGEN (which filed a large shelf last Friday). The first quarter news we are anticipating is early oral data from VKTX's obesity pill, the CLDX AAAAI presentation in late-February and March PDUFA dates for MDGL and ESPR. These are value drivers for biotech stocks. After a long absence and steady outflows, we believe fund flows will continue to rotate into biotech funds after the powerful Q4:23. Long-term chart support is at 80 and resistance is 101. Can we see

100 again on the XBI? Absolutely. Takeover activity will continue as long as both the target's AND the acquirer's stocks go up post-deal (see ABBV after buying IMGN and CERE). In the next Issue will discuss the multitude of company updates/outlooks for 2024 that will be presented at JPMorgan.

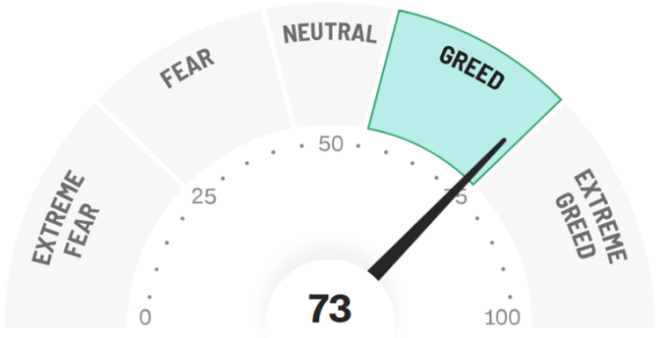
MTSL Companies at JPMorgan:

- BMRN: Monday January 8 at 10:30 am PT
- ACAD: Tuesday January 9 at 9:00 am PT
- PCRX: Wednesday January 10 at 8:15 am PT
- ESPR: Wednesday January 10 at 2:15 pm PT
- IONS: Wednesday January 10 at 3:00 pm PT
- MDGL: Wednesday January 10 at 4:30 pm PT
- PGEN: Wednesday January 10, 5:15 pm PT

Novo Nordisk (NOVO) recently inked a deal with Omega (OMGA) to develop a novel therapy for obesity management via OMGA's epigenomic controller (OEC) platform. Under the terms of the agreement, NOVO will reimburse research and development costs and has the right to select one target to advance for clinical development. OMGA and Flagship's Pioneering Medicines will share in the financials and are eligible to receive up to $532mn in upfront, development and commercial milestone payments, as well as tiered royalties (high single-digits to low double-digits) on net sales. This deal is another positive validation for VKTX/obesity program after the recent Roche obesity acquisition.

FEAR & GREED – EXTREME GREED

The Fear & Greed Index has been in the Extreme Greed zone recently before pulling back to 73. While the F&G is only up modestly, being in the Extreme Greed zone always makes us nervous as more often than not a pullback is approaching.



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 – A Study to Evaluate Adverse Events and Change in Disease Ac-tivity Comparing Oral Upadacitinib to Subc and Adult Participants With Moderate to Severe Atopic Der-matitis

ABBV – A Study To Assess Adverse Events and Effectiveness of Upadacitinib Oral Tablets in Adult and Adolescent

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

ACAD – Study of Carbetocin Nasal Spray for the Treatment of Hyper-phagia in Prader-Willi Syndrome

AMGN – A Study to Investigate Efficacy and Safety of Apremilast 30 mg Twice Daily (BID) in Chinese Participants
Psoriasis (PsO)

AMGN – Long-term Safety and Efficacy of Efavaleukin Alfa in Partici-pants With Moderately to Severely Active Ul

AMGN – A Study of Apremilast in Children With Oral Ulcers Associ-ated With Behçet's Disease or Juvenile Psoriat

AMGN – A Study of Apremilast in Pediatric Participants in Children With Mild to Moderate Plaque Psoriasis

Genentech – A Study to Evaluate the Efficacy and Safety of Astegolimab in Participants With Chronic Obstructiv

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

INCY – A Study to Evaluate Efficacy and Safety of Povorcitinib in Par-ticipants With Nonsegmental Vitiligo (STO

INCY – A Study to Evaluate the Efficacy and Safety of Ruxolitinib Cream in Participants With Prurigo Nodularis (P

INCY – A Study to Evaluate INCB161734 in Participants With Ad-vanced or Metastatic Solid Tumors With KRAS G1

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

NTLA/REGN – MAGNITUDE: A Phase 3 Study of NTLA-2001 in Par-ticipants With Transthyretin Amyloidosis With

PCRX – Supraclavicular Bupivacaine Vs. Supraclavicular Liposomal Bupivacaine for Distal Radius Fracture Repair

PCRX – Efficacy of Liposomal Bupivacaine Post Septorhinoplasty

SGMO – A Study to Assess the Safety, Tolerability, and Efficacy of ST-400 for Treatment of Transfusion-Depende

SGMO – Safety & Tolerability Study of Chimeric Antigen Receptor T-Reg Cell Therapy in Living Donor Renal Trar

SNY/REGN – Efficacy and Safety of Subcutaneous Dupilumab in Par-ticipants With Asthma/ Asthmatic Wheeze A
TREKIDS)

Company Updates

UPDATES: ALKS, BCYC, ESPR

ALKS — ALKS Shows Impressive Long-Term LYBALVI Compliance Data

ALKS recently announced impressive topline results from a Phase III open-label extension study assessing the long-term safety, tolerability and durability of treatment effect of LYBALVI (olanzapine and samidorphan) in patients with schizophrenia, schizophreniform disorder or bipolar I disorder for up to four years of treatment, following treatment received in prior LYBALVI studies. This is an impressive result when compared to the average treatment time of less than six months for oral atypical antipsychotics which cause weight gain not seen

Similarly, there were generally minimal changes in lipid and glycemic parameters, including HDL cholesterol, LDL cholesterol, triglycerides, fasting glucose and HbA1c over the measured time period. Overall, 60% of patients reported an adverse event (AE). The most common AEs reported (>5%) were weight gain, headache, anxiety, insomnia, somnolence, nausea and weight decrease; most AEs were mild to moderate in severity.

with LYBALVI. Patient compliance is a huge problem with this group of patients.

In the global, open-label extension study, 523 participants received at least one dose of LYBALVI and 35.9% of participants completed the four-year treatment period. The safety profile of LYBALVI was consistent with previous studies. Patients' symptoms of schizophrenia or bipolar I disorder remained stable with up to four years of treatment with LYBALVI, as measured by the Clinical Global Impression of Severity (CGI-S) scale (mean change from baseline in CGI-S score of -0.28). Long-term treatment with LYBALVI was associated with minimal changes in body weight (mean change from baseline of +1.47 kg) and waist circumference (observed mean change from baseline of +0.61 cm) with up to four years of treatment.

These data, which demonstrated long-term tolerability and symptom control, as well as stability across key weight and metabolic factors, underscore LYBALVI's established safety and efficacy profile in the real world setting. Specifically, the data highlight the potential utility of LYBALVI as a foundational maintenance treatment option for people living with schizophrenia or bipolar I disorder and reinforce the safety profile of LYBALVI established in previous trials. This is an impressive result when compared to the average treatment time of less than six months for oral atypical antipsychotics which cause weight gain not seen with LYBALVI. Patient compliance is a huge problem with this group of patients.

RECOMMENDATION

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

BCYC — BCYC Shows Off Platform/Pipeline at R&D Day

BCYC recently held an R&D day to show off its impressive platform and pipeline of targeted drug development candidates. In our view, the primary value driver at BCYC is BT8009 which has potential to be a best-in-class and safer and more tolerable compound when compared to SGEN's Padcef. Importantly, the FDA has already signed off on the Phase II/III Duravelo-2 registrational trial of BT8009 in patients with mUC in 1Q 2024.

Longer term, BCYC's advantages for delivering cytotoxic payloads are also advantages for delivering radionuclide payloads. In our view, there are multiple opportunities for novel radioligands as BCYC's peptides are well suited for developing novel radiopharmaceuticals (RPTs) targeting solid tumors.

33 patients assigned to receive one of 9 different doses of BT7480, an emerging differentiated safety and tolerability profile with a low number of severe adverse events. The majority of the patients studied had tumors that expressed Nectin-4 and CD137. The data showed two unconfirmed partial responses in heavily pre-treated patients with cervical cancer and three prolonged stable disease (≥7 months) in NSCLC and anal cancer.

Next Steps: BCYC will continue to define the recommended Phase 2 dose (or maximum dose) and dose range for BT7480, with a view to enroll combination cohorts with checkpoint inhibitors in 2024. These data will inform the design of a Phase 2

RPTs are hot as BMY just paid $4.1 billion for RayzeBio a clinical-stage radiopharmaceutical therapeutics company.

Nectin-4 Portfolio: BCYC is advancing two clinical programs, BT8009 and BT7480, targeting Nectin-4, a well-validated tumor antigen with elevated levels of expression in multiple tumor types.

BT8009 is a Nectin-4 Bicycle toxin conjugate (BTC®) designed to overcome the significant toxicity associated with other toxin conjugate approaches. In the ongoing Phase 1/2 Duravelo-1 study involving heavily pre-treated patients, BT8009 showed:

Promising response profile with a 38% objective response rate (ORR) in 26 patients with metastatic urothelial cancer (mUC) receiving 5 mg/m2 weekly and who had not been treated with enfortumab vedotin (EV-naïve), and a median duration of response (mDOR) of 11.1 months in 10 patients with 5 responders still on therapy. This includes 1 complete response, 7 partial responses and 2 unconfirmed responses.

BCYC plans to initiate the Phase II/III Duravelo-2 registrational trial of BT8009 in patients with mUC in 1Q 2024 and intends to complete the Phase I/II Duravelo-1 open-label study across multiple cancers including ovarian, triple-negative breast (TNBC) and non-small cell lung (NSCLC) that support further expansion beyond mUC.

Next Steps

Expect to start Duravelo-2 in 1Q 2024

Expect to receive complete data sets from ongoing open-label expansion cohorts in 2H 2024:

- BT8009 monotherapy in LL mUC
- BT8009 + pembrolizumab in 1L mUC
- BT8009 monotherapy in ovarian, TNBC, NSCLC

trial that could support potential accelerated approval of BT7480.

Ephrin-A2 (EphA2) Portfolio: BCYC is advancing one clinical program, BT5528, and one preclinical program, BT7455, targeting EphA2, a tumor antigen that is widely expressed in many cancers and has historically been difficult to target. BT7455 is an EphA2-targeted CD137 agonist whose Investigational New Drug-enabling work is ongoing.

BT5528 is an EphA2 BTC® designed to overcome the significant toxicity associated with other toxin conjugate approaches that have been unsuccessful. In an ongoing Phase 1/2 clinical trial enrolling patients with various solid tumors, BT5528 showed;

In 109 patients, an acceptable emerging tolerability profile with few severe adverse events. This was also seen in 74 patients receiving 6.5 mg/m2 every other week, the dose being studied in various tumors in the expansion cohorts. Encouraging early activity in mUC with a 39% ORR in 18 patients receiving 6.5 mg/m2, 8.5 mg/m2 or 10 mg/m2 every other week, and an mDOR of 4 months in 7 patients with one responder still on therapy, which includes 6 partial responses and 1 unconfirmed response.

BCYC recently held their R&D day to show off their impressive platform and pipeline of targeted drug development candidates. In our view, the primary value driver at BCYC is BT8009 which has potential to be a best in class when compared to SGEN's Padcef which has significant toxicity. Importantly, the FDA has already signed off on the Phase II/III Duravelo-2 registrational trial of BT8009 in patients with mUC in 1Q 2024. Longer term, BCYC's advantages for delivering cytotoxic payloads are also advantages for delivering radionuclide payloads. In our view, there are multiple opportunities for novel radioligands as BCYC's peptides are well suited for developing novel radiopharmaceuticals (RPTs) targeting solid tumors. RPTs are hot as BMY just paid $4.1 billion for

Expect to start expansion study in combination with checkpoint inhibitors in TNBC and NSCLC in 2024.

BT7480 is a Nectin-4 targeted CD137 agonist designed to overcome immune agonist toxicities and activate the immune system in Nectin-4 expressing tumors. Clinical development has been guided by safety considerations observed with first-generation CD137 agonists, the novelty of the Bicycle® platform technology and the FDA Project Optimus initiative. In a Phase 1 clinical trial, BT7480 showed;

RayzeBio a clinical-stage radiopharmaceutical therapeutics company.

RECOMMENDATION

BCYC is a BUY under 50 with a TARGET PRICE of 75

ESPR — ESPR and DSE Settle for $125 Million, Good But Not Great News

ESPR and Daiichi Sankyo Europe (DSE) have agreed to a $125 million amendment to their collaboration, which includes an amicable resolution to their commercial dispute and certain other adjustments to enhance the long-term value of their products. This is good news, not great news as ESPR will only get $125 million of the potential $500 million milestone payment.

DSE has agreed to pay ESPR $100 million in mid-January ahead of an anticipated Type II(a) variation approval by the European Medicines Agency (EMA) for NILEMDO® (bempedoic acid) Tablet and NUSTENDI® (bempedoic acid and ezetimibe) Tablet. DSE will make an additional $25 million payment to Esperion in the calendar quarter immediately following EMA's decision on the pending application. The legal action pending in the United States District Court for the Southern District of New York will be dismiss

The parties also agreed, as part of the resolution:

- Esperion to transition to DSE manufacturing and supply responsibilities in Europe and
- Expand their collaboration in Europe and other territories, to include the potential development and commercialization of a triple formulation product comprising bempedoic acid, ezetimibe and a statin, which could represent significant long-term value for the collaboration
- DSE to now lead all regulatory communications with the EMA regarding the pending applications

The agreement is good but modestly disappointing as $500 was a substantial sum and more than enough to pay down any existing debt and then some. One could theorize that the Judge warned ESPR that they were in danger of losing and a settlement for less may be in ESPR's best interest. Nevertheless, the $125 million does make a difference for ESPR and the develop of a triple formulation drug comprising bempedoic acid, ezetimibe and a statin could be a substantial winner long-term

RECOMMENDATION

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

other territories, resulting in significant cost savings and efficiencies for both companies

The Back Page

Symbol	Company	Orig.Rec.	Current	Target	Recommendation
ACAD	Acadia	33.79	29.95	45	BUY under $28
ALKS	Alkermes	10.13	28.63	55	BUY under $35
BCYC	Bicycle	43.92	17.46	75	BUY under $50
BMRN	BioMarin	12.68	97.73	150	BUY under $100
CLDX	Celldex	10.50	39.11	100	BUY under $75
ESPR	Esperion	24.42	2.31	25	BUY under $10
INCY	Incyte	5.88	66.59	108	BUY under $85
IONS	Ionis	7.63	51.48	65	BUY under $50
MDGL	Madrigal	17.00	218.21	400	BUY under $300
PCRX	Pacira	15.78	32.42	100	BUY under $80
PGEN	Precigen	34.42	1.31	12	BUY under $5
SGMO	Sangamo	4.77	0.49	15	HOLD
TCRT	Alaunos	8.00	0.13	5	HOLD
VKTX	Viking	16.83	18.58	45	BUY under $28
VXRT	Vaxart	8.00	0.58	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	142,263
Alkermes (ALKS)	3,800	88,690	108,794
Bicycle (BCYC)	2,400	105,408	41,905
Celldex (CLDX)	15,832	174,993	619,190
Esperion (ESPR)	3,316	105,316	7,643
Incyte (INCY)	1,229	34,817	81,839
Ionis (IONS)	3,087	49,123	158,919
Madrigal (MDGL)	3,127	69,980	682,343
Pacira (PCRX)	2,375	63,887	76,998
Precigen (PGEN)	9,690	76,510	12,694
Sangamo (SGMO)	19,456	253,596	9,623

Alaunos (TCRT)	26,125	166,100	3,318
Viking (VKTX)	12,000	201,960	551,584
Vaxart (VXRT)	29,687	250,000	6,930
(01/04/24)		**Equities:**	**$2,504,041**
		Cash:	**$ 237,884**
		PORTFOLIO VALUE:	**$2,741,924**

**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 3 Weeks	-1.7%	1.8%	0.7%
2024 YTD	-3.5%	-1.7%	-2.0%
Calendar Year 2023	43.4%	24.2%	8.9%
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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