MTSL Issue 1022

March 14, 2024

UPDATES: ACAD, INCY, MDGL, SGMO, SKYE, VKTX

IN THIS ISSUE: MDGL's Rezdiffra for NASH is Next Biotech Blockbuster

Since Last Issue: BTK: 0.36%; NBI: -1.63%; XBI: -4.03%; Model Portfolio: -10.47%

BIOTECH SECTOR ANALYSIS

SENTIMENT — Healthy Pullback for XBI

The biotech rally has fizzled of late as a combination of no M&A and President Biden rattling his saber over expanding the Medicare negotiations has kept a lid on the sector. At the State of the Union address, President Biden was vocally critical of pharmaceutical companies, touting the price negotiation efforts of the IRA as in important win, after noting earlier in the week that the administration's goal is to further expand the scope of negotiations (50 drugs a year vs. current 20). Pharma is already adapting by focusing more on biologics which offer 13 years before negotiation

TECHNICALS – Healthy Pullback Before The Madrigal Launch, M&A Dearth

The XBI (95) closed at a neutral level (RSI=53/54), having experienced a very healthy pullback since the last issue. The recent decline can be attributed to several factors – the stubbornness of interest rates/inflation, a lack of takeovers since early February, an oversupply of new issues and secondary offerings and profit-taking after a stellar two months of 2024 before entering March. While the euphoria of the weight-loss/GLP continues (although VKTX has come back to earth after the early NVO oral data surprised many), the sector is awaiting the FDA approval of MTSL Recommendation MDGL's resmetirom in MASH (due 3/14 – or press time) – see both VKTX and MDGL

which his much better than nine years for small molecules (see Pfizer below).

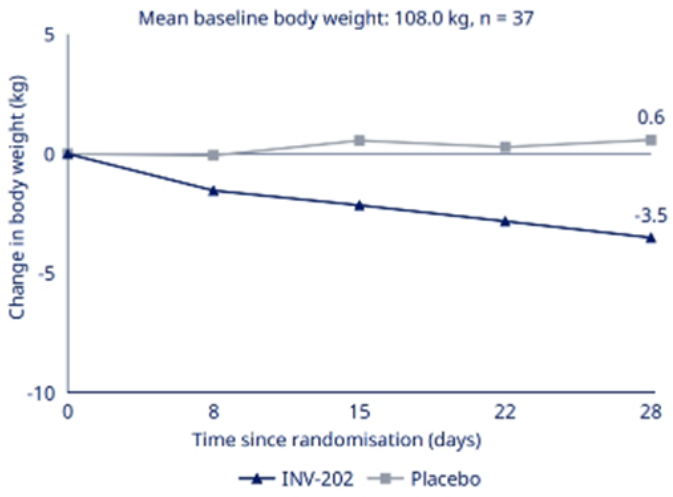
Novo unveils impressive weight loss data from their oral amycretin

During Novo Nordisk's Capital Markets Day, management unveiled the first data from their oral amycretin NN9487, showing an impressive 13.1% weight loss at 12 weeks with a safety profile in line with that of GLP-1s and CagriSema. This more than doubles the average weight loss of ~6% seen in the same timeframe with subcutaneous semaglutide in pivotal trials, and reinforces the synergy of amylin and GLP-1 agonism that CagriSema has previously shown. Novo also discussed their once-monthly subcutaneous GLP-1/GIP molecule, NN9650, for which Phase 1 data are expected in 2025, and their CB1R inverse agonist INV-347 that demonstrated body weight loss of 35%+ in mice at the highest doses. Other obesity updates included expected Phase 1 initiations of a new amylin molecule and a tri-agonist in the next 12 months. With the amycretin data and multiple new molecules entering the clinic in the near term, Novo is clearly focused on remaining the 800 pound gorilla in obesity. The following from *LifeSci Capital* high lights the CB1 space and mentions new *MTSL* recommendation SKYE:

CB1R is coming back as a potential target in obesity. During their capital markets day, Novo also shared data from their cannabinoid 1 receptor (CB1R) inverse agonist, monlunabant (INV-202), an asset they picked up in their $1.1 B acquisition of Inversago in 2023. The results demonstrated in **Figure 8,** show that after four weeks of treatment with INV-202, patients saw a mean change in body mass of 3.5 kg (-3.2% from baseline). d their CB1R inverse agonist INV-347 that demonstrated body weight loss of 35%+ in mice at the highest doses. More importantly, Novo noted that monlunabant had a safe and well-tolerated profile. As a reminder, below. While the sector's heightened volatility is always present, the ultimate end game for every independent biotech firm is the FDA approval and subsequent commercial success of a new blockbuster. We have recommended MDGL since the beginning, back in 2016 at $17, before the strong Phase II results took the stock over $300 per share back then! And while its taken a little longer than expected – the experienced management team led by Paul Friedman and Becky Taub – has delivered the deepest and most consistent regulatory package in MASH to date (used to be called NASH) – and as a result, we expect full FDA approval, the first MASH drug and the next biotech blockbuster. Even though the stock has recovered a bit from 2021, we believe there is still a lot more to go. Yes, there are many other NASH and GLP drugs being developed, but we believe none have the safety profile of a long-term use pill that chronic NASH needs and that resmetirom provides – remember the staying power on the GLPs is way less than a year.

There have not been a lot of M&A deals over the past month, hence some of the speculation has been removed while the NASDAQ folks rotate back to Big Tech and AI names – for now. On the charts, the XBI has filled the gap from the February 27 stock pop of another MTSL Recommendation – VKTX's subcutaneous GLP results that at first glance, look as good if not better than LLY's blockbuster Monjaruo looked at the same stage of development. In addition, yet a third MTSL Recommendation – CLDX – delivered an exceptional update on its urticaria drug at the AAAAI meeting. So we've given some back, but that's OK. There are many more events happening daily and yes, a big premium M&A deal would help. But seasonally biotechs do this – strong start to the New Year, bunch of short squeezes, some funds flowing in and then the classic funding round leading to the pullback. We got the gap filled now – so we believe it is only a matter of time that the group or at least select stocks – resume their upward momentum. The 200-day MA is rising slightly – now it sits at 82 and the 50-day is at

safety is key to watch with small molecule CB1R targeting molecules as CB1R antagonism resulted in safety and tolerability concerns due to CNS side effects that caused rimonabant (which was approved as an anti-obesity treatment in Europe) to get pulled from European markets in the late 2000s.



Read through to other companies targeting CB1R. Novo announced that there are Phase 2 studies ongoing with monlunabant in diabetic kidney disease and obesity and that the next-gen INV-347 has now entered a Phase 1 trial. We think that the positive data for INV-202 may bring renewed interest to CB1R as a target and note the following companies in Figure 9 that are similarly targeting this receptor for the treatment of weight loss.

Company	Asset	Mechanism	Stage
Novo Nordisk (NYSE: NOVO)	Monlunabant (INV-202)	CB1R inverse agonist	Phase 2
	INV-347	CB1R blocker	Phase 1
Skye Bioscience (OTCQB: SKYE)	Nimacimab	CB1R allosteric modulator antibody	Phase 2
Corbus Pharma (Nasdaq: CRBP)	CRB-913	CB1R inverse agonist	Preclinical

13 Years For Biologics is Better Than 9 Years For Small Molecules

Pfizer is doing an about face and will build out their cancer pipeline with a portfolio focused more on biologics than small molecules. Pfizer executives said the company's change in business strategy is motivated in part by the disparity in how the Inflation Reduction Act treats biologics versus small molecule drugs. Biologics are free from negotiation

92. That would be the near-term support for the group. SMID caps have led the way, while small caps have given back a decent amount.

The important long-term 200-week moving average (101) was exceeded at the end of February. And while the XBI has pulled back under that level since, it has been almost 3+ years since the index was this high. The weekly RSI of 65 has been steady – exhibiting the group's solid fundamentals and performance since November. Support is far below at 82 – the 50-week MA and maybe resistance still at that 101 level. First quarter earnings calls are occurring now, providing new clinical updates and timelines for all our names. The ACC (cardiovascular) meetings are coming soon (https://accscientificsession.acc.org/?gad_source=1), as is the PDUFA date for MTSL Rec ESPR (3/31) – right in time for the Company to put the expected outcomes label expansion to work. The VKTX oral GLP data is also due by Q1, although expectations are low as we see the orals as complementary to the SC injectables. Good things overall.

for 13 years following approval, while the grace period for small molecules is only nine years. This four-year difference figured prominently in Pfizer's oncology business strategy going forward. By 2030, Pfizer expects biologics such as antibody-drug conjugates (ADCs) and bispecific antibodies to contribute approximately 65% of its oncology revenues—up from 6% in 2023. Biologics represent a more durable revenue potential based on a number of factors, including differentiated access and affordability to the patient, IRA considerations and patent expiration timelines. The company's strong emphasis on ADCs going forward is not surprising given its recently completed buyout of SGEN for $43 billion, an industry leader in the ADCs.

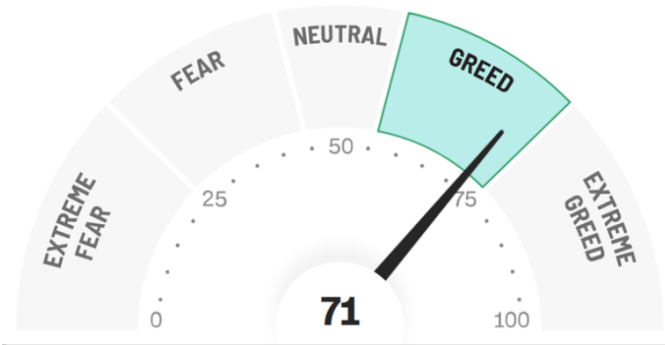
Currently, Pfizer's oncology portfolio includes 11 FDA-approved ADCs—five of which are company products and two others use licensed Seagen technology. Pfizer Oncology, told investors last week that the Seagen acquisition will enable the pharma giant to combine their respective expertise and technologies to discover and develop next-generation cancer therapies. Pfizer will also be incorporating its deep expertise in small molecule drug discovery into legacy Seagen's ADC platform to advance next-generation ADCs with differentiated payloads with new mechanisms of action.

FEAR & GREED-Back To Greed

The FEAR & GREED Index has pulled back into GREED at 71 after closing at 77, Extreme Greed in the last Issue. Extreme greed is clearly unsustainable, and we are probably better off to have let a little of the steam out of the current market.

MTSL Events Due Near-Term:

- VKTX Q1-Phase I Data from Oral Formulation for VK2735 Expected in Q1
- ESPR Q1 – CLEAR Outcomes Label Expansion PDUFA March 31
- CLDX Q1 – Initiate Phase II study of barzolvilumab in prurigo nodularis (PN)
- BCYC Q2 – American Association for Cancer Research (AACR) in San Diego on April 5-10, Three Abstracts:
  - Bicycle Toxin Conjugates for the treatment of solid tumors, Tuesday, April 9, at 1:30 p.m. PT
  - Modulation of the natural killer cell immune response to tumor with a synthetic tumor-immune cell agonist, NK-TICA, Monday, April 8, at 9 a.m. PT
  - Tumor-targeted activation of CD137 using *Bicycles:* New insights into mechanism of action and discovery of BT7455, a clinical candidate for the treatment of EphA2-expressing cancers, Tuesday, April 9, at 1:30 p.m. PT
- PGEN Q2 – Pivotal Phase II RRP data for PRGN-2012 in Q2 which will lead to an FDA filing



Clinical Trials Watch

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

AMGN – A Study Assessing Repatha® in Combination With Standard of Care (SOC) Compared With SOC on Major
Participants With Atherosclerotic Cardiovascular Disease

AMGN – A Study Assessing Rocatinlimab on Vaccine Antibody Response in Moderate-to-severe Atopic Dermatiti
(ROCKET-VOYAGER)

AMGN – A Study Assessing Rocatinlimab in Combination With Topical Corticosteroid and/ or Topical Calcineurin
Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-SHUTTLE)

GILD – Study of GS-1427 in Participants With Moderately to Severely Active Ulcerative Colitis

INCY/BI – Pemigatinib + Afatinib in Advanced Refractory Solid Tumors

INCY – A Study to Evaluate the Efficacy and Safety of INCB054707 in Participants With Prurigo Nodularis

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

PCRX – Efficacy and Safety of Liposomal Bupivacaine Under ERAS Concept for Postoperative Analgesia of Ultras
Laparoscopic Patients: A Randomized, Single-blind, Active-Controlled Clinical Study

REGN – Dupilumab for the Treatment of Chronic Inducible Cold Urticaria in Patients Who Remain Symptomatic
(LIBERTY-CINDU CUrIADS)

REGN – A Study to Test if Trevogrumab or Trevogrumab With Garetosmab When Taken With Semaglutide is Safe
Patients With Obesity for Weight Loss and Fat Loss

SNY/REGN – A Study to Investigate the Pharmacokinetics and Safety of Dupilumab in Participants ≥6 Months to Nodularis

Company Updates

UPDATES: ACAD, IONS, INCY, MDGL, SGMO, SKYE, VKTX

ACAD — ACAD Comes Up Short In ADVANCE-2

ACAD came up short in the Phase III ADVANCE-2 trial of pimavanserin in schizophrenia negative symptoms (SNS) which missed its primary endpoint of NSA-16 score change at 26 weeks. This is a disappointment for pimavanserin as it joins many other treatment candidates that failed in SNS. ADVANCE-2 was a well-controlled study of 454 patients across multiple international sites. It appears that a high placebo response rate contributed to the missed primary endpoint as pimavanserin showed -11.8pts vs. -11.1 for placebo (p=0.4825). ACAD plans no further development of pimavanserin and will focus on execution of the Daybue launch, continue the ADP and PWS trials, and pursue more business development deals.

We also expect ACAD to continue pursuing the clinical potential of next-generation ACP-204 for ADP. ACP-204 is a next-generation compound designed to eliminate QT prolongation, enable more efficacious dosing, and improve onset of activity. The Phase I data showed clean safety, and ACAD recently initiated a Phase II with seamless enrollment into two subsequent Phase III trials. In our view, ACAD is an M&A target for Big Pharma given the stronger-than-expected Daybue uptake in Rett syndrome.

RECOMMENDATION

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

INCY — INCY Derm Portfolio Has Two Positive Phase II Readouts; Povorcitnib in PN and Opzelura in HS

INCY recently presented multiple data updates from its dermatology portfolio and hosted an investor event at the American Academy of Dermatology (AAD) Annual Meeting, highlighting a Phase II trial

INCY also announced results from a Phase II trial evaluating the efficacy and safety of twice-daily Opzelura in adult patients with Hurley stage 1 or 2 (mild-to-moderate) hidradenitis suppurativa (HS).

evaluating the efficacy and safety of povorcitinib, an oral JAK1 inhibitor, in adult patients with prurigo nodularis (PN). The Phase II met its primary endpoint with a ≥4-point improvement in itch Numerical Rating Scale (NRS4) score achieved by significantly more patients who received povorcitinib across all dosing groups than those who received placebo (8.1%) at Week 16. Median times to itch NRS4 were 58, 35 and 17 days for patients who received 15, 45 and 75 mg of povorcitinib, respectively. We note that this placebo-adjusted rate of 42% at the 75mg dose (week 16) is in-line with the ~43% placebo-adjusted rates achieved by Dupixent. The KOL highlighted the difficult-to-treat patient population in this Phase II trial and the Dupixent study had a large Asian population with generally high eosinophil counts (which correlate with Dupixent response).

The study met its primary endpoint, demonstrating a significantly greater reduction in abscess and inflammatory nodule (AN) count in patients treated with Opzelura, compared to those who applied the vehicle control (least squares mean change of -3.61 for Opzelura vs. -2.42 for vehicle control; P value .05 at 16 weeks. According to INCY Phase III planning is ongoing, pending FDA discussions. Importantly, the Phase II HS data appear competitive vs. SoC Humira and Cosentyx. In our view, INCY is doing a good job of expanding their derm portfolio and both programs are under appreciated by Wall Street.

RECOMMENDATION

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

MDGL — (3/15/24 Update) FDA Approves First NASH Drug, MDGL's Rezdiffra (resmetirom) for NASH (F2 to F3 fibrosis), No Biopsy Required, Priced at $47 K, Launch in April

MDGL had great news yesterday afternoon when they announced the FDA has granted accelerated approval for Rezdiffra (resmetirom) in conjunction with diet and exercise for the treatment of adults with noncirrhotic NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). Importantly the drug's label is clean with no contraindications, no boxed warnings, and no monitoring requirements beyond standard of care. MDGL plans to launch within weeks and Rezdiffra is expected to be available to patients in the U.S. in April.

The company has done a phenomenal job of developing the first drug ever approved for NASH and we applaud the management team. In our view, Rezdiffra which will be priced at $47 K, is poised for a strong launch with a huge back load of NASH patients who have been waiting for the first NASH drug and a very clean label to allay any concerns regarding safety or a liver biopsy requirement.

RECOMMENDATION

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

SGMO — SGMO Reports New Delivery Technology, Pfizer Hem A Data Mid-Year

SGMO reported on their next generation delivery technology with data that demonstrated industry-leading blood brain barrier (BBB) penetration and brain transduction in NHPs, with capsid enabled delivery of zinc finger payloads targeting prion disease and tauopathies resulting in potent and widespread repression of target genes. STAC-BBB capsid demonstrated robust penetration of BBB with 700-fold higher transgene expression in neurons compared to the benchmark capsid AAV9 and outperformed all other known published capsid variants evaluated in the study.

SGMO's partner Pfizer expects to report a pivotal readout mid-2024 for the Phase III AFFINE trial of giroctocogene fitelparvovec, an investigational gene therapy for patients with moderately severe to severe hemophilia A. Pfizer anticipates BLA and MAA submissions by early 2025 if the pivotal readout is supportive. Pfizer will pay SGMO $220 million in milestone payments upon the achievement of certain regulatory and commercial milestones for giroctocogene fitelparvovec and a strong royalty rate of 14% – 20%.

While we expect the Hem A data to be positive it will not come in time to address SGMO's cash crunch. The company has $81 million in cash which will only last into Q3. SGMO will need to either execute a partnership or receive a cash infusion from a private equity firm like VXRT did with RA Capital relatively quickly to maintain their current development goals. Importantly, STAC-BBB delivers robust expression of zinc fingers, demonstrating the potential for modification of disease progression in prion disease and various tauopathies. These could be interesting new programs, however, SGMO needs to aggressively address their cash situation to provide transparency on how they will be funded.

RECOMMENDATION

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

VKTX / SKYE — (Update 3/7/24) VKTX & SKYE Selloff on Novo Phase I Oral Obesity Data, Both Stocks BUYS on Overreaction

VKTX and SKYE were under significant pressure today in response to strong Novo Nordisk results from a 16-patient Phase I trial of oral amycretin, a dual GLP-1 and amylin receptor agonist. At 12 weeks, the placebo-adjusted weight loss was 12.0%, 13.3% for amycretin and 1.1% for placebo. This is excellent efficacy for an oral and may be another big GLP-1 winner for Novo. With that being said this is very early data and we would emphasize that the trial provides only a glimpse into the clinical profile of amycretin given the small sizel, the short follow-up and the undisclosed patient baseline characteristics. As for safety, Novo said amycretin was safe and well-tolerated overall and its adverse effects were in line with Novo's prior studies of GLP-1 receptor agonists. That does not tell us much as previous GLP-1s trials and real world use point out significant problems with nausea for the class, hence our continued emphasis on the potentially better safety profile for VK2735 which could position the drug to be best in class. Today's selloff in both stocks was an overreaction just like the GGG data from Lilly was last June and the recent Lilly MASH data three plus weeks ago.

According to some Wall Street investor feedback the efficacy bar for the upcoming oral VK2735 data readout has increased to 4%-5% (at week 4, amycretin appears to show a placebo-adjusted weight loss within this range) from 2%-3%. In our view, there is a chance that the oral will get close to the 4%-5% range but 2%-3% will not be a disappointment. '2735 subQ has shown a very good safety profile to date and we expect the oral safety data to be as good or better. SKYE sold off as their recent move up was based on the positive VKTX subQ data.

We acknowledge that Lilly and Novo are the undisputed Kings of GLP-1 weight loss, however we do not think Big Pharma will sit back and let the world's largest drug market, easily in excess of $100 billion annually, be dominated by just two players. Today's selloff in both stocks was an overreaction just like the GGG data from Lilly was last June and the recent Lilly MASH data three plus weeks ago. In our view, the net present value from an M&A valuation went up today as VKTX represents a truly scarce asset that may be able to compete with the GLP-1 Kings.

RECOMMENDATION

VKTX is a BUY under 100 with a TARGET PRICE of 145

RECOMMENDATION

SKYE is a BUY under 24 with a TARGET PRICE of 40

The Back Page

Symbol	Company	Orig.Rec.	Current	Target	Recommendation

ACAD	Acadia	33.79	18.73	45	BUY under $28
ALKS	Alkermes	10.13	28.88	55	BUY under $35
BCYC	Bicycle	43.92	22.94	75	BUY under $50
BMRN	BioMarin	12.68	84.39	150	BUY under $100
CLDX	Celldex	10.50	42.52	100	BUY under $75
ESPR	Esperion	24.42	2.05	25	BUY under $10
INCY	Incyte	5.88	58.54	108	BUY under $85
IONS	Ionis	7.63	42.18	65	BUY under $50
MDGL	Madrigal	17.00	243.57	400	BUY under $300
PCRX	Pacira	15.78	29.26	100	BUY under $80
PGEN	Precigen	34.42	1.43	12	BUY under $5
SGMO	Sangamo	4.77	0.78	5	BUY under $2
SKYE*	Skye*	17.00*	12.90	40*	BUY under $24*
TCRT	Alaunos	8.00	1.64	5	HOLD
VKTX	Viking	16.83	65.05	145	BUY under $100
VXRT	Vaxart	8.00	1.10	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	88,968
Alkermes (ALKS)	3,800	88,690	109,744
Bicycle (BCYC)	2,400	105,408	55,056
Celldex (CLDX)	15,832	174,993	608,971
Esperion (ESPR)	3,316	105,316	6,798
Incyte (INCY)	1,229	34,817	71,946
Ionis (IONS)	3,087	49,123	130,210
Madrigal (MDGL)	3,127	69,980	700,751
Pacira (PCRX)	2,375	63,887	69,493
Precigen (PGEN)	9,690	76,510	13,857
Sangamo (SGMO)	19,456	253,596	15,176
Skye (SKYE)	13,500	229,500	174,150
Alaunos (TCRT)	26,125	166,100	42,845

Viking (VKTX)	12,000	201,960	780,600
Vaxart (VXRT)	29,687	250,000	32,656
(03/14/24)		**Equities:**	**$2,901,219**
		Cash:	**$ 8,384**
		PORTFOLIO VALUE:	**$2,909,602**

**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.*

**Model Portfolio Update: Purchased $229,500 of SKYE.*

BENCHMARKS

	NASDAQ	S&P 500	MODEL
Last 2 Weeks	0.2%	1.1%	-10.5%
2024 YTD	7.2%	6.8%	23.3%
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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