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Osteoporosis

In young healthy people, a constant resorption (removal of old bone) and formation of bone (creation of new bone) takes place. This process is called remodeling. However, with age, chronic disorders, hormones and some nutrient deficiencies, this process could become unbalanced leading to bone resorption outpacing bone formation. This leads to osteoporosis which is progressive decline in bone mineral density (BMD), loss of bone strength leading to increased incidence of fracture primarily in spine, forearm and hip.

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, which increases the risk of bone fracture. Both men and women are affected by osteoporosis; however, women experience the fastest bone loss in the first few years after menopause and continue through the menopausal years. According to the National Osteoporosis Foundation, more than 50 million people over age 50 are affected by osteoporosis and low bone mass in the U.S., of which 10 million have osteoporosis.

Treatment Overview

The treatment for osteoporosis consists of lifestyle changes as well as pharmacologic therapy. Risk for developing osteoporosis increases with age, being a woman and/or; Caucasian/Asian, in addition to having a petite body type and a family history of bone fractures. Recommended lifestyle changes for patients with osteoporosis include changes in diet, exercise, smoking cessation, among other healthy lifestyle habits. Typically, pharmacologic therapy is recommended to reduce bone loss in postmenopausal women with BMD T-score of -2.5 or lower. Women who are in the first five years post menopause are most susceptible to a rapid decline in BMD.

Two ways of restoring this imbalance: reduce resorption or increase formation. As above mentioned, osteoporosis is nothing but bone decay faster than new for-

mation. Therefore, this can typically be managed via reducing the decay or increasing the bone formation.

Anti-resorptives are fine but may be insufficient for very high risk patients. Drugs such as oral bisphosphonates and denosumab (Amgen's Prolia) fall under anti-resorptives, selective estrogen receptor modulators (SERMs), calcitonin, and estrogen. These are the most widely prescribed medicines. These drugs effectively slow bone loss due to osteoporosis and result in relative increase or stabilization in BMD. Oral bisphosphonates are associated with GI side effects, rare (but frightening) risk of osteonecrosis of the jaw, and several years ago also came under scrutiny for risk of rare atypical femur fractures. IV-administered bisphosphonate (zoledronic acid) is an alternative therapy for patients who experience gastrointestinal intolerance to oral bisphosphonates and is administered via IV once a year. Prolia is an anti-RANKL monoclonal antibody administered subcutaneously twice a year. SERMs, such as raloxifene, have been shown to reduce risk of breast cancer in post-menopausal women as well as inhibiting bone resorption, reducing the risk of vertebral facture. However, for fragile patients with severe osteoporosis fracture risk is generally very high. Stabilization alone may not be sufficient to protect against fracture and a more effective agent may be needed.

Forteo (teriparatide) is a bone formation agent used in high risk patients. Eli Lilly's drug Forteo is the only drug approved for bone formation. Forteo is an anabolic for the treatment of osteoporosis. It is a recombinant form of endogenous human parathyroid hormone (PTH) that stimulates bone formation and activates bone remodeling. PTH plays a key role in regulating calcium-phosphate metabolism. Research shows evidence of anabolic properties of PTH – when administered in low doses and intermittently, this hormone seems to be able to exert positive effects on bone volume and microstructure. The connection between parathyroid hormone and bone has been well recognized and Forteo was the first drug to be approved. Due to its cost and subcutaneous administration, in addition to availability of other options, Forteo is not used as a first-line therapy but typically used in cases of severe osteoporosis and/or as a follow-up therapy when bisphosphonates fail to reduce bone loss. Despite its effectiveness in fracture reduction, only a fraction of patients eligible for Forteo take Forteo.

Forteo Background

In a double-blind multicenter, placebo-controlled clinical study in postmenopausal women (1,637) with osteoporosis, the cumulative percentage of women who sustained new nonvertebral fractures was lower in the Forteo-treated group than in placebo -treated patients. However, this benefit did not show up until ~9 months after the start of therapy. The study also showed an increased lumbar spine BMD in women treated with Forteo compared to placebo.

Regarding safety, incidence of serious adverse events was 16% compared to 19% in placebo and discontinuation due to adverse events occurred in 7% compared to 6% in in placebo.

Osteoporosis Treatment Options in Development

Romosozumab is a monoclonal antibody that binds sclerostin in Phase 3 development by Amgen/UCB. Positive top-line Phase 3 BMD data from the STRUCTURE study vs. Forteo was recently announced for the product. Detailed results of this study to be presented at a medical meeting until 2016. The STRUCTURE data bodes well for positive fracture data in the other Phase 3 trials, FRAME and ARCH, which compare romosozumab to Prolia and Merck's Fosamax, respectively.

A key event for romosozumab will be the 2-year FRAME vertebral fracture study expected in the first half of 2016, in which patients (6,000) are treated with 12 months of romosozumab or placebo followed by 12 months of Prolia for all patients. If positive, this trial will likely represent the basis for a U.S. filing.

Romosozumab is also being studied in the ARCH study evaluating 12 months of romosozumab vs. 12 months of Fosamax followed by 12 months of Fosamax for all patients on vertebral fractures. This trial is expected to readout in late 2016. ARCH and FRAME will likely both be needed for the product's EU filing.

In a Phase 2, multicenter, international, randomized, placebo-controlled, parallel group, eight-group study, efficacy and safety of romosozumab compared to placebo, Fosamax and Forteo was assessed over a year. Romosozumab increased BMD at the lumber spine, total hip and femoral neck from patients receiving romosozumab compared to placebo, Forteo and Fosamax. Romosozumab was shown to significantly increase BMD at the lumber spine by 11.3% compared to 4.1% with alendronate and 7.1% with Forteo. So far, the data point to good bone formation profile and with the convenience of a once monthly injection.

Regarding safety, incidence of serious adverse events was 7% across of all romosozumab groups compared to 14% in the placebo group, 8% in the Fosamax group and 9% in Forteo treated group. No notable changes from baseline in vital signs, laboratory values or electrocardiographic variables were reported.

Sclerostin is an important regulator of bone formation. Sclerostin interferes with osteoblast proliferation leading to reduction in bone formation. Romosozumab inhibits sclerotin to increase bone formation mediated by osteoblast. This target has been genetically validated as the patients who lack this exhibit bone overgrowth.

Radius' abaloparatide is a novel synthetic peptide analog of parathyroid hormone-related protein (PTHrP), a member of the parathyroid hormone family. Abaloparatide works in a similar mechanism as Forteo and is expected to compete in the same market. Abaloparatide as a highly effective potential therapy for those who have had a fracture, for those intolerant to bisphosphonates due to gastrointestinal issues and/or for patients with severe to moderate osteoporosis.

Abaloparatide-SC for osteoporosis, MAA was filed on November 17, 2015, but NDA filing is delayed to the of the first quarter of 2016 (vs. yearend 2015) to allow more time to complete the 12 month stability analysis, samples for which should be ready in December. With a strong Phase 3 data set from both ACTIVE and ACTIVExtend, a very high probability of approval.

In the ongoing ACTIVExtend extension study (24-month extension trial of ACTIVE), both the placebo and the abaloparatide groups from ACTIVE received Fosamax for the extension phase after a once-month washout. During the first 6 months of the extension study, patients treated with Fosamax after abaloparatide had no vertebral fractures (0/544) vs. 1.2% (7/568) for those who went on alendronate after placebo. In addition, abaloparatide/Fosamax treated patients had a lower rate of non-vertebral fractures in that six month period – 0.5% (3/558) vs. 1.2% (7/581) for placebo/Fosamax, and for major osteoporotic fractures the rate was also lower at 0.4% (2/558) vs. 0.7% (4/581) with placebo/Fosamax.

From a safety standpoint, over the six months of extension data both groups had similar rates of AEs with no new safety or tolerability signals observed. Over a 25-month period, patients treated with abaloparatide/Fosamax achieved an average increase in BMD of 12.8%, 5.5%, and 4.5% at the lumbar spine, total hip, and the femoral neck, respectively compared to 3.5% at the lumbar spine, 1.4% at total hip, and 0.5% at the femoral neck with placebo/Fosamax.

Also, abaloparatide achieved a statistically significant reduction the incidence of major osteoporotic fractures by 70% compared to placebo in the ACTIVE study and a 55% reduction in these fractures relative to Forteo.

Abaloparatide has a compelling profile compared to Forteo in high risk patients. In Phase 3, 18-month results, ACTIVE demonstrated an 86% reduction for the primary endpoint of new vertebral fractures as compared to the placebo-treated group, which compares to an 80% reduction reported in the Forteo-treated group. In non-vertebral fractures, abaloparatide particularly stands out, demonstrating a statistically significant 43% reduction vs. placebo, while a 29% reduction in the Forteo-treated patients was not statistically significant. Abaloparatide-treated patients also experienced greater improvements in BMD compared to Forteo.

Zosano's ZP-PTH is rapid delivery patch for the treatment of severe osteoporosis is being developed as an alternative to daily injections. The product delivers PTH 1-34, Forteo (PTH), a compound that stimulates formation of new bone and reduces the risk of fractures. The ZP PTH product has also demonstrated greater than 36 month shelf-life without the need for refrigeration.

A weekly PTH product, Teribone, has already been successfully marketed in Japan. Weekly ZP-PTH provides further dosing convenience vs. daily ZP-PTH, and could potentially extend the two-year usage limit of daily Forteo (the ZP-PTH API), as the

study of Teribone demonstrated an absence of a carcinogenicity signal for weekly Forteo injection in rats after two years of treatment. Zosano completed a Phase 1 study for the weekly ZP-PTH program in Australia in early 2014. The Phase 1 results showed an enhanced pulsatile PK profile of weekly ZP-PTH compared to Teribone or Forteo injection, and demonstrated dose proportionality and high bioavailability with no serious adverse events. Zosano had met FDA in July 2014 for discussion of a planned Phase 2 and Phase 3 trial of the weekly ZP-PTH. Zosano plans to initiate a Phase 2 trial of weekly ZP-PTH in the first half of 2016.

Forteo biosimilars

Exclusivity for Forteo's earliest patents expire in December 2018, and at some point it is possible biosimilar products could enter the market.

Corium is developing a MicroCor formulation of PTH (1-34), the active ingredient in the currently marketed product, Forteo for the treatment of osteoporosis. With a simple one-step application process, short wear time, and a favorable pharmacokinetic profile, MicroCor PTH (1-34) addresses the needs for improved anabolic therapies and increased patient compliance in the osteoporosis market. MicroCor PTH (1-34) has shown an excellent safety profile in multiple nonclinical biocompatibility and microbial studies. The product has also shown excellent room temperature stability.

Corium has completed a Phase 1 safety and pharmacokinetic study of MicroCor PTH (1-34) in healthy women. In this study, MicroCor PTH (1-34) was shown to be safe and well tolerated with equivalent exposure to that achieved with the commercially available subcutaneous injections. The product achieved rapid systemic delivery of PTH with a short wear time. On the basis on these results, planning is underway for further clinical development of MicroCor PTH (1-34) under a 505(b)(2) regulatory pathway.

Corium has in place pilot facilities for GMP manufacture of MicroCor products for early clinical testing. Corium's extensive experience with transdermal products and process development through commercial scale provides reduced downstream technical risk for the manufacture of MicroCor PTH (1-34). Corium has designed the manufacturing process for MicroCor systems to be streamlined, robust, and cost effective.

Phase 2a suggest the PK profile is acceptable and that usage is tolerable to the skin. Corium conducted a two-stage program designed primarily to assess the PK performance of MicroCor PTH. The first trial arm (18 patients) measured the comparability of a single dose of MicroCor PTH vs Forteo whereas the second stage (21 patients) evaluated the PK profile of MicroCor PTH relative to Forteo over a 28-day period. The safety and tolerability of the MicroCor PTH patch was also evaluated in the second stage. Importantly, MicroCor PTH was safe and well-tolerated in both study arms, and according to Corium, the PK profiles demonstrated by its novel patch technology closely mimicked the performance of Forteo across several key biomarkers throughout the 28-day study period. MicroCor PTH was rapidly delivered (5 minute application time), demonstrated dose proportionality across the 16mcg and 38mcg doses, and did not demonstrate any evidence of drug accumulation over the 28-day window – all very positive signals. Corium expects to reveal the full dataset at a future scientific meeting.

Next Step for MicroCor PTH is to conduct a Phase 2b trial in 150-200 patients likely in late 2016. The trial will evaluate the safety and efficacy of 3 separate doses of MicroCor PTH vs Forteo and the primary endpoint will be the change in BMD at lumbar spine at 6 months. Of interest, Corium is amenable to partnerships either before or after Phase 2b trial initiation and anticipates identifying a strategic partner rather than solely seeking a source of financing.

Pfenex's generic version of Forteo will benefit from the simpler ANDA pathway as well as potentially first-to-file exclusivity since, as a peptide of just 34 amino acids, still qualifies as a small molecule.

While many products in Pfenex's pipeline are true biosimilar candidates, PF708 (Reference product: Forteo) is in fact a peptide. In February 2012, the FDA issued draft guidance to add "protein (except any chemically synthesized polypeptide)" to the definition of a biological product. The guidance further specified a protein to be "any alpha amino acid polymer with a specific

defined sequence that is greater than 40 amino acids in size". Forteo falls into the "peptide" bucket, as it is only 34 amino acids. The importance of this differentiation is that Pfenex's PF708 will only require the ANDA pathway to gain approval, which should not only be faster but simpler in terms of establishing bioequivalence.

With Pfenex initiating the ANDA-enabling PK study by the end of 2015, the company is that much closer to disrupting the $1.2 billion Forteo market. The company believes this could a first-to-file opportunity, potentially offering 180-day of exclusivity. Generic Forteo will prove to be a durable long-term asset given the high likelihood of limited competition.

Final Words

Osteoporosis is a huge market with data indicating ~10 million patients in the U.S. living with the disease. ~8 million of them are postmenopausal women. According to a prevalence study published in the journal of bone and mineral research, in 2005 there were 2 million osteoporotic fractures in the U.S. and the number is expected to grow to 3 million by 2025. Current treatment is focused on the use of bisphosphonates as the first-line approach; however, these agents provide only anti-resorptive activity and are associated with significant GI side effects and other adverse outcomes. Treatment with exogenous PTH is the only anabolic treatment modality currently available for the treatment of osteoporosis. 2014 sales of Forteo were ~$1.3 billion, despite significant patient compliance and convenience challenges (daily sc injection, refrigerated storage). The PTH market segment is expected to maintain sales of approximately $1 billion through 2018 with increased diagnoses and earlier treatment. $$

Radius Health

Radius Health is focused on the development and commercialization of medications for the treatment of patients with osteoporosis and other endocrine-mediated diseases, including metastatic breast cancer. Radius's pipeline includes the company's lead product and main value driver abaloparatide, RAD1901, and a preclinical asset, RAD140.

Abaloparatide is directly tied to its mechanism as a regulator of bone formation and its selectivity for receptor conformation (R0, RG), suggesting it has the ability to activate the parathyroid hormone receptor but with less downstream signaling than Forteo, a 34 N-terminal amino acid sequence of human parathyroid hormone. Forteo is able to stimulate new bone formation, but in addition to binding with high affinity to osteoblast receptors in bone, also binds to cell surface receptors in the kidney. Forteo is able to build bone but is also associated with hypercalcemia, a condition in which excess calcium remains in the bloodstream. In the top-line Phase 3 ACTIVE trial results, hypercalcemia rates were lower in the abaloparatide arm compared to the Forteo arm (6.0% vs. 10.8%).

Abaloparatide is currently in development for the treatment of postmenopausal osteoporosis in two formulations: abaloparatide-SC (Phase 3) sub-cutaneous injection, and abaloparatide-TD (Phase 2), a transdermal patch. Radius has shown bioequivalence between abaloparatide-SC and its patch formulation preclinically in primates, and the next step will be to show bioequivalence in a PK study humans. Such a trial could start by year-end 2015.

Radius's value to date has largely been driven by the Phase 3 success of abaloparatide for osteoporosis.

The abaloparatide Phase 3 trial included Forteo as an active comparator, demonstrated a meaningfully better profile both on prevention of non-vertebral/clinical fractures and BMD increases. This profile should drive a conversion to abaloparatide over time and has potential to expand the market.

While the osteoporosis competitive landscape evolving with the potential for new entrants such as Forteo biosimilars and Amgen's romosozumab, abaloparatide remains differentiated from these products, multiple branded agents can coexist in a market this size, including romosozumab. Romosozumab works through a different mechanism of action compared to abaloparatide, and romosozumab represents another offering in the space (expect its potential approvals in mid-2017 (U.S.) and 2018 (EU)), nonetheless there is an ample market opportunity for abaloparatide.

Radius is also evaluating a transdermal patch for abaloparatide, which could significantly expand the market opportunity. Transdermal delivery could significantly expand the commercial opportunity for abaloparatide by providing a convenient route of administration. Abaloparatide-TD could add substantial upside to the abaloparatide opportunity.

Beyond abaloparatide, Radius has an emerging oncology asset in RAD1901, a selective estrogen receptor degrader or SERD, currently being studied in a Phase 1 multicenter, open-label, dose-escalation trial in postmenopausal women with advanced estrogen receptor positive and HER2 negative breast cancer. This product has also demonstrated a reduction in the frequency and severity of vasomotor symptoms such as hot flashes in a Phase 2 proof-of-concept trial.

Radius presented early data from the Phase 1b RAD1901 trial in ER+ advanced breast cancer presented at the San Antonio Breast Cancer Symposium. Eight advanced breast cancer patients have been treated (four in the 200 mg cohort and four in the 400 mg cohort) in the dose-escalation portion of the Phase 1b study. Seven of the patients were evaluable for response and three patients remain on the study. RAD1901 was associated with two cases of stable disease. RAD1901's safety data looks to be tracking favorably. There was one case of Grade 3 constipation observed, which occurred in the 200 mg dose cohort. No dose limiting toxicity has been reached.

Based on the favorable healthy volunteer data, Radius intends to dose-escalate through the full range and up to 1,000 mg in the breast cancer patients.

While early stage, updates thus far suggest a clean safety profile, and Phase 1 data in patients will likely been presented at ASCO 2016.

$71 price target is based on U.S. revenues of abaloparatide-SC and RAD1901. $$

BioTech Stock Updates

This section is to update and inform our readers of significant news about those stocks that are in our BioPortfolio, and to provide insight on market conditions that will influence the biotech sector.

Alnylam/NASDAQ: **ALNY** (*BSR* #170: Rare Diseases) continues to advance the Phase 3 APOLLO trial of patisiran and ENDEAVOUR trial of revusiran. Alnylam also presented detail data at ASH on fitusiran (ALN-AT3) in hemophilia and ALN-CC5 for complement-mediated diseases.

Alnylam recently updated an 18-month Phase 2 OLE (open-label extension) data on 0.3mg/kg q3W intravenous patisiran showing stabilization of mNIS+7 at +1.7 points at 18 months vs. expected +22.9 points based on natural history. Patisiran increased sweat gland nerve fiber density in the distal thigh at 12 and 18 months supporting mechanism of action. Alnylam expects to complete enrollment in the Phase 3 APOLLO trial soon with NDA/MAA filings in 2017, although the company is discussing an interim efficacy analysis with regulatory agencies.

Alnylam also updated 6-month Phase 2 OLE data on 500mg weekly subcutaneous revusiran in familial amyloidotic cardiomyopathy (FAC) and Senile Systemic Amyloidosis (SSA). Injection site reactions occurred in 11/25 (44%) patients, although there were no further discontinuations beyond the 3 announced this summer. Revusiran showed a modest decline in 6-minute walk distance at 6 months (-20M FAC, -24M SSA), which appeared in line with natural history, potentially indicating that longer drug exposure is needed to see cardio-pulmonary benefits. The Phase 3 ENDEAVOUR trial of revusiran in FAC is on-going and Alnylam intends to advance ALN-TTRsc02 into the clinic next year with Phase 3 trials in 2017.

At ASH, ALN-AT3 in hemophilia demonstrated an ideal response profile around 70-85% antithrombin (AT) knockdown, considered to be clinically meaningful for reduction of pathological bleeds, but also not likely to trigger thrombotic events. Subcutaneous monthly dosing of AT3 led to robust, dose dependent AT lowering from ~70% to up to 88% in hemophilia patients. Part C (225, 450, 900 mcg/kg qM) showed a median Annual Bleed Rates (ABR) of 4.3 in the observation period, an 85% reduction relative to historical bleed rate. In the 450 and 900 mcg/kg cohorts, the ABR was 2.2, a 92% reduction vs the median historical ABR. These data are a promising indication of AT3's dose dependent, dose response profile and therapeutic effect.

Also at ASH, ALN-CC5 key updates from the MAD (multiple ascending dosing study portion included a mean maximum C5 knockdown of 98% and hemolysis inhibition of 84% at the highest dose tested of 400mg QW. In the SAD (single ascending dosing) data, mean maximum at the highest 900mg dose was ~71%. Currently the dose that will be moved forward in PNH patients has not been disclosed. In general, the biomarker data for ALN-CC5 are encouraging (CAP, CCP, C5 knockdown, etc.). That said, in the MAD data, the hemolysis reduction did not meet what the general investor expectations of ~80% hemolysis reduction. Overall, the ALN-CC5 safety profile was clean, with no SAEs or discontinuations observed in the MAD cohorts, and reported AEs being mild to moderate. ALN-CC5 data in PNH patients are expected mid-2016.

On November 25, 2015, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee met to discuss **BioMarin**'s/**NASDAQ**: **BMRN** (*BSR* #170*:* Rare Diseases) drisapersen (Kyndrisa). In April, BioMarin completed the rolling submission of an NDA for drisapersen for the treatment of exon 51-skip amendable Duchenne Muscular Dystrophy (DMD). Drisapersen has been granted Orphan, Fast Track status, and Breakthrough Therapy designation by the FDA, with a December 27th PDUFA. The FDA AdCom provided with little new evidence to help understand how the FDA is likely to act. While the compa-

ny did provide compelling rebuttals to many of FDA's concerns, and public commentary went a long way towards making the case for approval, many of the underlying issues identified by FDA were also discussed at length (and not resolved). Overall, the discussion and voting questions appeared to skew against approval.

The FDA's Ad. Com. found drisapersen's efficacy data generally unconvincing. While no formal vote on approval was taken, the discussion appears unlikely to persuade the FDA to approve drisapersen. Then on December 18th, the FDA said it was not finish with its review and would render a decision in early January. Hence, approval may require a new pivotal trial. Most investors seem likely to have already come to the conclusion that drisapersen is unlikely to be on the market in 2016. While drisapersen will continue to be an overhang and point of focus for investors, BioMarin still has an overall robust pipeline, with supportive read-outs expected near-term.

Over the next 12-18 months, late-stage candidates; cerliponase (CLN2), pegvaliase (PKU), reveglucosidase (Pompe) and BMN-111 (achondroplasia) will complete their clinical development, and it is expected all are likely to succeed. Moreover, over the next year, additional data from early programs, such as BMN 270 (hemophilia A gene therapy).

Celgene's/**NASDAQ**: **CELG** (*BSR* #86: ASH) core business had three franchises, hematologic malignancy, solid tumors and inflammation and immunology with each franchise anchored by a key product, REVLIMID, ABRAXANE and OTEZLA respectively. REVLIMID built on thalidomide, a storied drug that laid the foundation for a revolution in treating multiple myeloma. ABRAXANE is the latest iteration of the taxane class of drugs that is a cornerstone for treating solid tumors and currently ABRAXANE is the only branded taxane on the market. Moving away from oncology, OTEZLA is a first in class p38 MAP kinase inhibitor that is approved to treat psoriasis and psoriatic arthritis. OTEZLA is the only recently approved disease modifying oral agent for psoriasis and is positioned between the inexpensive low efficacy generic drugs and the injectable biologic agents.

On this backdrop, Celgene has established a broad collection of collaborations, many if which include cutting edge science to reinforce its leadership in these core areas as well as expand into allied fields such as inflammatory bowel disease with the recent acquisition of Receptos. The combination of oral antisense GED-0301 and ozanimod in Crohn's and ulcerative colitis could add another $4-6 billion in opportunity. Most under-appreciated is Celgene's emerging immuno-oncology platform, with potential best-in-class antibodies from Sutro and best-in-class bi-specifics from Zymeworks.

Chimerex/**NASDAQ**: **CMRX** (*BSR* #200*:* Newbies) will release Phase 3 SUPPRESS trial (brincidofovir for the prevention of CMV infection) early next year. While many investors expect success on the primary endpoint, analysis of the entire dataset will ultimately be critical to define the clinical relevance of the dataset and differentiation from generic valganciclovir. Chimerex will look beyond the topline readout of the SUPPRESS trial, and focus on the clinical meaningfulness of the data in respect to the primary endpoint and the secondary endpoints given the accepted limitations of valganciclovir. That said, Chimerex emphasized that prophylactic brincidofovir is expected to show substantial benefit beyond CMV on other double stranded DNA viruses which are a major problem as well as side effects such as neutropenia and nephrotoxicity, though improvements on key secondary endpoints will help speed adoption and the value of its share price.

In the second half of 2016, AdVise will provide a full top-line data read-out including 12 weeks of dosing followed by 24 weeks of followup complete with matched historical controls.

Beyond these lead indications, brincidofovir continues to advance with enrollment in kidney transplant trials SUSTAIN and SURPASS ongoing and discussions with BARDA about stockpiling in smallpox proceeding as well, though timing for contracting remains dependent on congressional budgetary legislation.

Gilead/**NASDAQ**: **GILD** (*BSR* #2: AIDs-related) continues its dominance in HCV and HIV spaces. Gilead, remains as a

solid large-cap opportunity for investors, although much of its outlook will depend on the company's ability to maintain its strong track record of transformation growth-driving M&A.

The approval of Genvoya (E/C/F/TAF) represents a major milestone for Gilead as the company is building multiple TAF-related products going forward. With strong dateset in the label (92% viral suppression rate and attractive safety profile), Gilead believes Genovya will be the first choice of treatment for new patients (50,000 in the U.S. and 50,000 in the E.U. every year) as well as taking share from Atripla, Stribild, and Viread. In addition, TAF-containing regimens (potential alternative to Complera and Truvada) are under review by the FDA and should come out next year. F/TAF + GS-9883 (non-boosted integrase inhibitor) regimen is currently studied in Phase 3 while JNJ is coordinating registration for a darunavir (a protease inhibitor) + C/F/TAF regimen. Generic multi-tablet HIV drugs have gained little traction since they entered the market and the first single-tablet HIV drug (generic atripla) won't enter the market until 2021. But with Atripla on the decline, the company seems well positioned to maintain its presence with other single drug regimens well into the next decade.

As of the end of September, Gilead had treated 190,000 HCV patients in the U.S., which represents less than 10% of U.S. HCV population (north of 4 million). The company continues to dominate the HCV space, maintaining north of 90% (close to 95%) of the market share in the U.S. The recent approval of indication expansion for Harvoni (GTs 4, 5 and 6 and HIV/HCV confection; Harvoni + ribavirin 12-week regimen for GT1 with cirrhosis) further solidifies the company's leading position in HCV. The company has applied for approval of a pan-genotypic combination of sofosbuvir + velpatasvir, which is a 12-week regimen and is highly effective across all genotypes. Phase 3 studies are underway for a pan-GT triple combo which may be positioned for refractory patients. These new regimens, if approved, will give a very important option for patients around the world where non-GT1 or -GT2 patients are predominant. While many investors believe 2015 will be the peak of HCV sales for Gilead, the company isn't so sure that will prove to be accurate.

On Dec. 17, 2016, **Intercept**'s/**NASDAQ**: **ICPT** (*BSR* #212 NASH) announced the FDA has extended the PDUFA date for obeticholic acid (OCA) for the treatment of primary biliary cirrhosis (PBC) to May 29, 2016. In response to an information request from the FDA, additional clinical data analyses have been submitted and the additional three months will provide time for a full review of the submission**.** The FDA has also notified Intercept of a planned advisory committee meeting date of April 7, 2016. Despite the delay, near-term focus is on a potential FDA panel review of OCA; it is viewed with certainty and that some risk could emerge from FDA review and panel scrutiny of the biochemical composite endpoint, degree of unmet need, adverse events like pruritus and adverse effects on lipids seen in NASH development.

Ultimately, the true value driver for Intercept is expected to be development of OCA for NASH following positive Phase 2b FLINT data and with ongoing Phase 3 development in the REGENERATE study. With focus on fibrosis reversal underlying the company's primary Phase 3 endpoint and supporting breakthrough therapy designation, recent failure to confirm a benefit in a Japanese study introduces incremental risk to ultimate success in REGENERATE.

While success is still more likely than failure, that the likelihood of success at the 2018 interim analysis is much less likely and have pushed out NASH estimates to 2020 to reflect more reasonable expectations for NASH development. Overall, fibrosis reversal has been a difficult endpoint to achieve in NASH drug development, and feedback from hepatologists in the area suggests that a combination drug approach may be required.

Intercept is fairly valued given extended time lines for OCA development in NASH, mixed data on fibrosis reversal between FLINT and Japanese studies, and given relatively high expectations for OCA approval nearer term in the smaller opportunity of PBC.

Isis/NASDAQ: ISIS (*BSR* #141: Chin Up) has two approved antisense drugs already on the market, two high-profile phase

3 programs approaching data in blockbuster indications, high-value partnerships with Biogen, GlaxoSmithKline, Bayer, Roche, and others, multiple Phase 2 proof-of-concept data points emerging, and an ever expanding pipeline of close to 40 antisense candidates, Isis is poised to enter an inflection of value creation.

The primary focus remains on ISIS's 9-drug neuromuscular disease partnership with Biogen and approaching Phase 3 data for ISIS-SMN-Rx in newborns and children with spinal muscular atrophy; Phase 2 data suggesting extended survival and recovery of function in newborns and motor function improvement in children will be replicated and support approval and commercial success.

With antisense therapeutics having demonstrated unprecedented predictability and potency of effect across diverse indications, including Factor XI for clotting disorders, ApoC3 for triglyceride abnormalities, and transthyretin (TTR) for familial amyloid polyneuropathy (FAP), there is the likelihood of success for these programs. At present, current valuation attaches partial value to the most advanced indications of SMA, TTR, and ApoC3, but potential upside on fuller recognition of value for these programs when Phase 3 data emerge, and visibility of earlier pipeline opportunities. $$

BioPortfolio

BIOPORTFOLIO is a list of companies that lead in their application. Companies on this list are selected only for their technology leadership, without consideration of their current share price or the appropriate timing of an investment decision. The presence of a company on the list is not a recommendation to buy shares at the current price. Reference Price is the company's closing price on the Reference Date, the day the company was added to the table, typically the Thursday of the month prior to publication.

Updates are italicized. Key new flows and dates can cause a company's valuation to go up or down dramatically.

Company	Date	Reference Price	12-21 Price	% 1-mo	% YTD	% Inception	Institutional % Ownership:+/-
Aggressive Growth							
Aimmune (AIMT)	10-29-15	15.44	18.87	-11.16	22.22	22.22	51:NC
AIMT plans to initiate PALISADE Phase 3 trial for AR101 for peanut allergies at the beginning of 2016. **Target Price**: $25 **Rating**: Buy below $18.							
Alnylam (ALNY)	6-24-10	15.45	88.01	-16.38	-9.98	469.64	77:NC
On Dec. 21, 2015, ALNY filed a CTA with the U.K. regulatory agency for ALN-GO1 to initiate Phase 1 study in early 2016 and to report initial clinical data in late 2016 for primary hyperoxaluria type 1. On Dec. 7, 2015, ALNY reported positive interim Phase 1/2 clinical trial for ALN-CC5, in development for the treatment of complement-mediated diseases that knockdown of serum C5 of up to 99% and inhibition of serum complement activity of up to 98%. Initial results from Phase 1/2 study of ALN-CC5 as a treatment for PNH is expected in mid-2016 with final data at the end of 2016 and initiate Phase 3 studies in 2017. ALNY will initiate the Phase 1/2 study of ALN-AAT for the treatment of alpha-1 antitrypsin deficiency-associated liver disease in late 2015, with initial data expected to be reported in early 2016. See current and December 2015 BioTech Updates **Target Price**: $130 **Rating**: Buy below $90.							
BioMarin (BMRN)	3-23-11	23.57	104.14	8.41	12.99	341.83	99:NC
On Nov. 20, 2015, FDA briefing documents said drisaperin's data showed evidence of efficacy is inconsistent and in some cases contradictory as well as safety is a concern. As such, it is suggested the efficacy of the drug was inconclusive and there was no vote by the FDA committee. BMRN's drisapersen's rolling NDA as a treatment for DMD PDUFA was Dec. 27, 2015, *but the PDUFA has been delayed to early January 2016*. On June 25, 2015, BMRN announced the EMA has validated the MAA, initiating the review process of drisapersen's application as a treatment for DMD. Release Phase 3 results for PEG-PAL as a treatment for PKU in the Q1-16 and submit BLA in mid-2016. Release Phase 1/2 clinical data on BMN 190 for Batten disease in Q4-15. Release BMN 701's Phase 2/3 clinical data as a treatment for Pompe disease in Q4-15 and the second half of 2016. See current BioTech Updates. **Target price:** $148 **Rating**: Change from buy below $110, to hold due to the uncertainty of drisapersen.							
Chimerix (CMRX)	9-26-13	20.30	36.44	-11.77	-12.78	79.51	91:NC
Release brincidofovir's Phase 3 SUPPRESS trial against CMV in adult with HSCT in early 2016 with potential NDA submission in 2016. Report brincidofovir's Phase 3 AdVise data as a treatment of AdV in the first half of 2016. See current and November 2015 BioTech Updates **Target Price**: $52 **Rating**: Buy below $45.							

Company	Date	Reference Price	12-21 Price	% 1-mo	% YTD	% Inception	Institutional % Ownership:+/-
Inceptos (ICPT)	3-25-15	260.64	162.23	-11.71	-37.76	-37.76	77:NC
On Dec. 7, 2015, ICPT initiated Phase 2 clinical trial to evaluate the effect of the combo OCA and statins for monitoring of lipid metabolism in patients with NASH. On June 29, 2015, ICPT filed the NDA and MAA for OCA as a treatment for PBC. *To provide time for a full review of the submission, dates have been revised. Advisory committee on Jan. 13, 2016 is changed to April 7, 2016 and a new PDUFA date of May 29, 2016. A delay of 3 months*. See current, December and November 2015 BioTech Updates **Target price**: $300 **Rating**: Change from buy below $175 to hold.							
Incyte (INCY)	9-24-09	6.88	112.9	-2.17	53.06	1540.99	93:NC
Baricitinib's NDA as a treatment for rheumatoid arthritis to be filed at the end of 2015. Data from the pivotal Phase 3 Janus 1 and Janus 2 studies of Jakafi (ruxolitinib) in second line metastatic pancreatic cancer is expected in 2016. Results from three Phase 3 trials of Jakafi in colorectal, breast and NSCLC patients, are expected in 2016. See current and November 2015 BioTech Updates **Target Price**: $127 **Rating**: Buy below $110.							
Ionis (IONS) formerly known as Isis (ISIS)	12-18-08	13.34	57.56	-7.80	-6.51	331.48	88:+2
On Dec. 11, 2015, IONS reported that partner Biogen has initiated a Phase 1/2 clinical study of ISIS-SOD1 in patients with ALS. ISIS-SMN data to be reported in the first half of 2017 as a treatment for SMA. ISIS-APOCIII's Phase 3 top-line results in Q1-17 for FCS as well as a treatment for FPL in late 2017. *On Dec. 17, 2015, IONS initiated a Phase 2 study of ISIS-TTR Rx in patients with TTR cardiomyopathy amyloidosis.* Report Phase 2/3 ISIS-TTR as a treatment for FAP in the first half of 2017. Report ISIS-APOCIII's Phase 3 top-line results in Q1-17 for FCS as well as a treatment for FPL in late 2017. See current, December and November 2015 BioTech Updates. **Target Price:** $60 **Rating**: Hold, met target price.							
Medivation (MDVN)	10-27-11	8.92	46.27	12.39	-9.10	937.44	91:NC
On Dec. 21, 2015, MDVN announced the initiation of the Phase 2 clinical trial of MDV9300 in DLBCL. Talazoparib is currently in a Phase 3 study for the treatments of patients with deleterious germline BRCA 1 or BRCA 2 mutations and locally advanced and/or metastatic breast cancer. See November 2015 BioTech Stock Updates **Target Price:** $67 **Rating:** Buy below $43.							
Merrimack (MACK)	7-19-12	7.25	7.75	-15.12	-32.20	3.06	67:NC
Results from the Phase 2 clinical study of MM-121 in patients with advanced or metastatic NSCLC in the second half of 2016. See December 2015 BioTech Stock Updates. **Target Price:** $14 **Rating:** Buy below $9.							
Regeneron (REGN)	6-28-07	17.95	532.55	-5.19	29.84	2866.85	72:NC
Release dupilumab's Phase 2 clinical data as treatment for atopic dermatitis at the end of 2015/2016. Release REGN88's Phase 3 clinical as a treatment for rheumatoid arthritis at the end of 2015 with the potential BLA filing. See November 2015 BioTech Updates. **Target Price**: $530 **Rating**: Take some money off the table.							

Company	Date	Reference Price	12-21 Price	% 1-mo	% YTD	% Inception	Institutional % Ownership:+/-
Sangamo BioSciences (SGMO)	6-26-14	15.40	9.31	22.82	-39.03	-39.55	75:NC
On Dec. 11, 2015, SGMO presented Phase 2 clinical data from two SB–728-T HIV studies, suggest that adenoviral delivery of zinc finger nucleases to T-cells may be uniquely immune-stimulatory for both acute control of infection, and importantly, HIV reservoir reduction. More data will be released in 2016. On Dec. 1, 2015, SGMO announced FDA clearance of SB-FIX for treatment of hemophilia B; study scheduled to begin in 2016. SGMO on track to file an IND for MPS I by the end of 2015 and IND application for Hunter syndrome in the first half of 2016. SGMO also expects to file three more IND applications in the second half of 2016 for hemophilia A, Gaucher disease, and one other LSD target. See December 2015 BioTech Updates **Target Price:** $17. **Rating:** Change from buy below $7 to buy below $9							
Seattle Genetics (SGEN)	6-25-09	9.27	42.11	-.24	29.41	354.26	100:NC
On Dec. 10, 2015, at the SABCS, SGEN presented Phase 1 data from SGN-LIV1A that showed ORR was 12%, disease control rate was 65% and clinical benefit rate of 24% in metastatic breast cancer patients. At ASH 2015, SGEN presented data on several of its therapies that demonstrated potential. Release Adcetris' Phase 3 data from ALCANZA trial for relapsed CTCL in 2016. **Target Price**: $47 **Rating:** Buy below $40.							
Trevena (TRVN)	5-28-15	7.00	9.76	-22.97	39.43	39.43	73:NC
Potential initiation of Phase 3 clinical trial of TRV130 for soft tissue pain in 2016. Release Phase 2b study of TRV027 in Q1-16 as a treatment for acute heart failure. See December 2015 BioTech Updates **Target Price**: $15 Rating: Buy below $10.							
Vertex (VRTX)	6-23-05	15.52	120.56	-8.65	-2.04	676.80	96:NC
Kalydeco's sNDA as a treatment for cystic fibrosis, PDFUA date is Feb. 6, 2016. Release Phase 3 clinical data for VX-661/Kalydeco as a treatment for homozygous and heterozygous cystic fibrosis in 2016. See November 2015 BioTech Stock Updates. **Target Price**: $140 **Rating:** Change from hold to buy below $115.							
Intermediate Growth							
Alexion (ALXN)	1-29-09	36.57	182.24	3.57	95.33	282.71	100:NC
Kanuma was approved as a treatment for lysosomal acid lipase deficiency on Dec. 8, 2015. The release of updated Phase 2 clinical data for Soliris in recipients of kidneys from deceased-donors in the second half of 2015. Release Soliris' Phase 3 clinical data for kidney transplant and MG in 2016 *and NMO in 2017*. See November 2015 BioTech Updates **Target Price**: $200 **Rating**: Buy below $170.							

Company	Date	Reference Price	12-21 Price	% 1-mo	% YTD	% Inception	Institutional % Ownership:+/-
Celgene (CELG)	4-28-00	23.53	110.84	-1.34	-2.36	842.12	82:NC

On Dec. 21, 2015, CELG announced Revlimid was granted marketing authorization by Japan's Ministry of Health, Labour and Welfare to be used in combo with dexamethasone as a treatment for patients with newly diagnosed with multiple myeloma. At the December 2015 ASH, CELG reported study of bortezomib added to Revlimid and dexamethason, significantly improved progression-free survival compared to lenalidomide and dexamethasone in patients newly-diagnosed with multiple myeloma, 43 months compared to 30 months. On Dec. 7, 2015, CELG and Acceleron announced the FDA has granted fast track designation to luspatercept for the treatment of anemia in patients with MDS. On Dec. 7, 2015, CELG and AstraZeneca announced the initiation of the FUSION clinical development of durvalumab across a range of blood cancers. The program will initially include four studies. On Dec. 10, 2015, CELG and Inception IBD entered exclusive, strategic collaboration to discover and develop novel therapeutics for ulcerative colitis and Crohn's disease. See current BioTech Updates. **Target Price:** $137 **Rating**: Buy below $115.

Gilead Sciences (GILD)	3-27-97	3.11	102.63	-4.78	8.13	6501.33	82:+1

On Dec. 17, 2015, GILD and Galapagos has signed a deal potentially worth more than $2 bil to develop a drug, filgotinib targeting inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Filgotinib may start Phase 3 clinical trials in 2016. On Dec. 8, 2015, GILD announced results from a prespecified interim analysis of a Phase 3 study evaluating Zydelig in combo with bendamustine and rituximab; achieved statistical significance in all secondary endpoints for patients with previously treated CLL. On Nov. 16, 2015, GILD announced that its Phase 3 study evaluating Zydelig added to standard therapy in previously-treated CLL recommended by the DMC to be unblinded in early 2016. PDUFA date for R/F/TAF as a treatment for HIV, March 1, 2016 and the PDUFA date for F/TAF also for HIV is April 7, 2016. On Oct. 29, 2015, GILD submitted an NDA to the FDA for a fixed-dose combo of Sofosbuvir/Velpatasvir for the treatment of all 6 genotypes of hep C. *On Dec. 4, 2015, GILD received EMA validation for the marketing application for Sofosbuvir/Velpatasvir to treat HCV*. Release top-line data from Phase 2 study of GS-4774 in hepatitis B in 2015. Data from Phase 2 study of simtuzumab in NASH in 2016. See current BioTech Updates. **Target Price**: $125 **Rating**: Buy below $102.

Stable Growth							
Amgen (AMGN)	3-27-97	14.44	163.95	-2.85	-.38	1003.24	81:NC

On Dec. 21, 2015, AMGN announced it acquired Catherex for $10.5 mil, a clinical state immunotherapy company focusing on the development of T-cell therapy platforms for the treatment of cancer. On Dec. 18, 2015, AMGN announced that the EC has approved the use of IMLYGIC for the treatment of metastatic melanoma. On Dec. 14, 2015, AMGN entered into a definitive agreement with GSK to reacquire all of its remaining rights to Prolia, Xgeva and Vectibix in 48 countries in Asia, South America, Europe and Australia; AMGN anticipates this transaction to be accretive to adjusted 2017 EPS. On Dec. 7, 2015, AMGN announced at ASH new data from three Phase 2 trials of BLINCYTO. In a confirmatory multicenter single-arm trial, adult patients with B-cell precursor ALL who received BLINCYTO monotherapy demonstrated clinically meaningful relapse-free survival. Other presentations demonstrated BLINCYTO's potential in a high risk subpopulation. On Dec. 4, 2015, AMGN and Merck entered a cancer immunotherapy collaboration to support a Phase 1b/3 study investigating BLINCYTO in combo with KEYTRUDA in patients with DLBCL. This study to evaluate safety and efficacy in patients with DLBCL. On Nov. 25, 2015, AMGN filed with the FDA ABP 501, its biosimilar to Humira as a treatment for rheumatoid arthritis and plaque psoriasis. On Aug. 25, 2015, AMGN announced it filed the BLA for etelcalcetide as a treatment for secondary hyperparathyroidism, a condition that cause fragile bones, pain, and organ damage, PDFUA date is May 1, 2016. On July 23, 2015, AMGN submitted Kyprolis's NDA Kyprolis for the treatment of patients with relapsed multiple myeloma who have received at least one prior therapy. PDUFA date is Jan. 22, 2016. Release Phase 3 clinical results of blinatumomab in R/R B-precursor ALL in Q3-16. See November 2015 BioTech Updates. **Target Price:** $170 **Rating**: Buy below $160.

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Performance Indicators

BioPortfolio YTD Performance	7.94
YTD NASDAQ Biotech Index	9.37
YTD Dow Jones Industrials	-3.21
YTD Nasdaq Composite	4.92
Since Inception Performance	959.57

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