

BioTech Stock Report

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The Clot Thickens: Hemophilia

Hemophilia is a rare genetic disorder that causes bleeding or hemorrhage, due to a deficiency in blood coagulant that promotes blood clotting. It is an X-chromosome-linked genetic disease meaning the disease-causing gene is located on the X chromosome. Because males carry only one X chromosome compared to females with two X chromosomes, if males have a mutation on the X chromosome, the male would only have the mutant gene and would likely have the disease; in contrast, females with a single X chromosome mutation still have another X chromosome with a normal copy of the gene. Thus, males are significantly more susceptible to inheriting an X-chromosome-linked genetic disease compared to females. Prevalence of these rare diseases is estimated at approximately 1 in about 5,000 male births for hemophilia A, patients lack factor IX (FIX) and 1 in about 30,000 male births for hemophilia B, patients lack factor VIII (FVIII). Factor VIII and IX genes are a recessive trait and are located on the X-chromosome, explaining why hemophilia occurs in males who carry a single X-chromosome. Besides hemophilia A and B, there are several other rare bleeding disorders, such as factor X deficiency and parahemophilia, which, similar to hemophilia A and B, are due to deficiencies in clotting factors.

Hemophilia A and B are diseases characterized by a deficiency in clotting such that if the patient sustains an injury that leads to bleeding or undergoes spontaneous bleeding, the intensity of the bleeding is similar to a normal individual, but the duration of the bleeding is longer. This can lead to serious injury that can be fatal or cause permanent damage. For hemophilia A and B the severity of the disease is characterized based on the percentage of factor present in the patient compared to nonhemophilic individuals, which ranges from 50-150%. Mild hemophilia is defined as between 5-40% normal factor levels, and moderate hemophilia is defined as between 1-5%. Spontaneous bleeding is rare for individuals classified as having mild or moderate hemophilia. Severe hemophilia is defined as <1% of normal factor levels, putting these individuals at high risk for spontaneous bleeding in the absence

of an injury.

The extrinsic pathway is activated upon blood vessel damage caused by either physical injury or spontaneously. This vessel damage leads to the activating conversion of factor VII to activated factor VIIa by tissue factor. Meanwhile, clotting factors in the intrinsic pathway undergo a sequential reaction wherein the factors undergo conversion to an activated state (for example, conversion of factor IX to activated factor IXa). Both the extrinsic and intrinsic pathways feed into the common pathway where factor X is activated to factor Xa. The activated form of factor V, factor Va, and factor Xa are required to convert prothrombin to activated thrombin. Activated thrombin promotes the conversion of fibrinogen to fibrin. Finally, the production of fibrin allows for stabilization of the platelets localized to the damaged vessels, leading to blood clot formation.

Initially, hemophilia was treated through the administration of whole blood products, or plasma at professional infusion centers. Starting in the 1970s, home-based infusions became possible and are now the predominant standard of care, with 90% of patients using home therapy. Higher purity plasma-derived products became a necessity in the 1970s and 1980s due to a better appreciation of the risks of blood-transmitted viruses such as HBV and HCV and then later HIV. The development of recombinant factors eliminated the need for blood-based products, allowing for safer treatments for patients. Current treatment of hemophilia A and B typically involves regular prophylactic intravenous infusion of the deficient clotting factor as frequently as two to three times per week. This need for intravenous infusions multiple times per week has negatively impacted patient compliance, and adherence to prophylaxis in studies ranges from 17% to 100%, with an average of around 63%. Consequently, more advanced, long-lasting recombinant factor products, based on biochemical modification of existing recombinant factors, have reduced treatment down to once weekly for some patients.

In spite of their efficacy in hemophilia A and B, the use of prophylactic recombinant factors faces the difficulty of the development of antibodies against the recombinant factors; these antibodies are referred to as inhibitors. Inhibitors neutralize the activity of the replacement factor by binding to the regions of factor VIII or X required for activity in the coagulation cascade, effectively blocking replacement factor function. Because inhibitors can dramatically impact the efficacy of therapy, they are considered to be a serious complication in the treatment of hemophilia. Approximately 30% and 6.5% of severe and mild/moderate hemophilia A patients develop factor VIII inhibitors, while the frequency of inhibitors in all severities of hemophilia B patients is lower at approximately 2.5%. Those less frequent, inhibitors in hemophilia B are of particular concern, as such blocking antibodies have been known to generate an anaphylactic response, creating severe medical emergencies if unresolved. If the concentration, or titer, of inhibitors is low, replacement factor therapy concentrations can be substantially escalated alone or in combination with various immune suppressive therapies like chemotherapy or anti-B cell therapies like Rituxan to overcome the inhibitors, a process known as immune tolerance induction. However, if the inhibitor titer is high, bypassing agents, such as activated prothrombin complex conjugates, activated factor VII, or FVIII inhibitor bypassing activity (FEIBA), are necessary. Several novel therapeutics that may overcome the limitations of inhibitors are currently in clinical development.

Current hemophilia treatments help to control and prevent bleeding

To mitigate bleeding, available treatments offer two solutions: 1) on demand treatment, with the frequency of injection determined by bleeding severity and 2) prophylaxis treatment, which entails scheduled infusions of around twice per week. Treatments entail factor replacement products, which include plasma-derived factor concentrates, recombinant factor concentrates, and extended half-life recombinant (EHL) factor. EHL factor IX molecules aim to reduce the use of prophylaxis infusions. However, considering the issues associated with factor replacement (e.g. inhibitor development, patient compliance with regards to patient dosing frequency), an emergence of innovative treatments that is bispecific antibodies, RNA silencing and anti-TFPI, as well as next-generation investigational therapies like gene-therapy drugs are in development for the treatment of hemophilia A and B. These next-generation therapies in hemophilia are targeting various components of the coagulation cascade.

A novel approach for the treatment of hemophilia A is the use of bispecific antibodies, such as ACE910 (emicizumab) by **Roche** (through its subsidiary **Chugai**) and an unnamed program from the **Biogen** spinoff **Bioverativ**. ACE910 is an engineered recombinant humanized bispecific antibody that mimics the activity of FVIII by bringing FIXa in proximity to FX through

each of its two antigen-binding regions (one for FIXa and one for FX). As the activation of FX through the recruitment of FIXa by FVIII is a crucial control point in the coagulation pathway, ACE910 is thus theoretically capable of restoring hemostasis specifically in hemophilia A patients.

Preclinical efficacy for ACE910 was initially tested in a non-human primate model of acquired hemophilia A. In this model, weekly ACE910 treatment demonstrated a striking ability to ameliorate joint bleeds in 3 out of 4 animals, a key morbidity in hemophilia A. Notably, 1 out of 4 of the ACE910-treated animals had significant traumatic oral bleeding preceded by loss of ACE910 in plasma and the concomitant detection of anti-ACE910 alloantibodies. Taken together, while these results were promising in terms of preventing hemophilic bleeds, the data raise the issue of neutralizing anti-drug antibodies (ADAs) against ACE910 similar to but distinct from inhibitors against coagulation factors in hemophilia.

In Phase 1 studies in healthy volunteers, s.c. delivery of ACE910 demonstrated reasonable pharmacokinetic durability, with a half-life of around 30 days. However, ADAs against ACE910 emerged in the clinical setting, with 2 out of 48 subjects developing antibodies against the drug. More importantly, in one patient, ADAs developed 12 weeks after ACE910 treatment and were at least partly neutralizing, reducing ACE910 half-life to around 9 days and minimizing coagulation activity in terms of both activated partial thromboplastin time and peak thrombin generation. Taken together, while demonstrating durability in human subjects, the issue of ADAs remains for ACE910.

Following from the Phase 1 trial, ACE910 was tested by weekly s.c. administration at three different doses for 12 weeks in an open-label Phase 1/2 study in 18 patients with severe hemophilia A either with or without inhibitors. Median annualized bleed rates (ABRs) went from 32.5 to 4.4, from 18.3 to 0.0, and from 15.2 to 0.0 at the 0.3, 1, and 3 mg/kg doses, respectively. These findings, along with data from the open-label extension study presented on July 27, 2016 at World Federation of Hemophilia (WFH) 2016 Congress, are promising, with efficacy comparable to approved FVIII therapies. Of particular interest is the reduced ABRs in inhibitor-positive patients, for whom existing bypassing agents have marginal efficacy and long acting factor and gene therapy are likely to be ineffective. Moreover, the ability for ACE910 to be administered s.c. on a weekly basis is of notable benefit to hemophilia patients as a more convenient means of treatment compared to multi-weekly i.v. infusion. However, several important issues remain.

On November 2, 2016, Roche announced that four patients (118 trial patients, due to conclude at end-2016; two instances of thromboembolism, two of thrombotic microangiopathy) have experienced serious adverse events (SAEs) in the Phase 3 trial of ACE910 in inhibitor-positive patients. These SAEs relate to thrombotic events (two thromboembolisms and two thrombotic microangiopathies) in patients with breakthrough bleeds being treated with bypass agents FEIBA from Shire or NovoSeven from Novo Nordisk. While Roche notes that both bypass agents have thrombosis warnings as part of their respective labels, thrombosis adverse events are exceptionally rare for both drugs, with incidences of 8.24 per 105 infusions for FEIBA and 24.6 per 105 infusions for NovoSeven. Considering that the Phase 3 trial for ACE910 has an estimated enrollment of only 118 patients, four occurrences of thrombotic SAEs, is unlikely to be explained by the bypass agents alone. Clinical trials have not been halted (the independent data monitoring committee has issued a 'dear investigator letter' notifying participating physicians). ACE910 had been thought to carry some risk of blood clotting by nature of the mechanism, but this has not been an issue so far. Taken together, while visibility is lacking on the SAEs, such events could pose a safety and efficacy risk for ACE910 moving forward.

Nonetheless, additional Phase 3 studies to begin in 2016 will test longer dosing intervals, such as every four weeks. The most advanced Phase 3 study in adolescents and adults with inhibitors has an estimated primary completion date of February 2017.

In contrast with potentially disruptive therapies that function primarily in the intrinsic pathway (e.g. long acting factors, adeno-associated virus (AAV) -based gene therapies, ex vivo gene therapies, and gene editing) or in the common pathway (e.g. ACE910, fitusiran), anti-tissue factor pathway inhibitor (TFPI) antibodies (e.g. concizumab from **Novo Nordisk**) function primarily through the extrinsic pathway. In particular, upon blood vessel damage, the tissue factor becomes active, triggering the activation of FVII, which then activates FX to promote coagulation. To counter the extrinsic pathway, TFPI operates to block both the activation of FVII and the ability of activated FVII to subsequently activate FX.

Concizumab is a monoclonal antibody that binds and sequesters TFPI that can be used for both hemophilia A and B. In pre-

clinical studies, i.v. treatment with concizumab (also known as mAb 2021) demonstrates durable suppression of bleeding in an animal model of hemophilia comparable to recombinant activated FVII. Subsequent Phase 1 results indicate that concizumab, administered either by i.v. or s.c., achieves TFPI suppression for at least one week, with a correlation between the extent of TFPI inhibition and both concizumab concentration and bleed frequency; subsequent Phase 1 studies are underway for s.c. administration of concizumab in hemophilia A patients. However, earlier TFPI blockers, such as the anti-TFPI aptamer BAX499 from Baxter International, in spite of promising preclinical results, were discontinued clinically due to an elevated bleed rate in BAX499-treated patients after treatment. Moreover, Novo Nordisk began development of anti-TFPI antibodies in the 1990s, with clinical trials starting in 2010. Thus, taken together, while anti-TFPI antibodies like concizumab have promise as an alternative therapeutic in hemophilia A, there are substantial challenges for the approach.

A further novel approach for the treatment of both hemophilia A and B is the use of RNA interference (RNAi) molecules, such as fitusiran (ALN-AT3) by **Alnylam**. Fitusiran is a short interfering RNA (siRNA) that targets antithrombin (AT), a key negative regulator of multiple points of the coagulation cascade for which mutations have been shown to be associated with milder clinical presentation. In particular, for fitusiran the siRNA is chemically linked to N-acetylgalactosamine, which directs the siRNA to the liver for efficient uptake via binding to the asialoglycoprotein receptor.

In ongoing Phase 1/2 studies, fitusiran has shown efficacy equal to or better than current therapies. A serious adverse event (non-cardiac chest pain associated with transient increases in liver enzymes) was reported in the Phase 1/2 study which poses a potential safety risk. However, Alnylam recently presented compelling Phase 1 and Phase 1/2 open label extension (OLE) results of fitusiran for the treatment of hemophilia A and B patients with and without inhibitors at ASH. The Phase 1/2 OLE results demonstrated that once-monthly, subcutaneous fitusiran administration achieved a median annualized ABR of 1.0 with a median observation period of 5.7 months. These low ABRs represent a compelling target product profile. On the strength of the positive safety and efficacy data, Alnylam remains on track to initiate a Phase 3 study of fitusiran in early 2017. Fitusiran was generally well tolerated in hemophilia A and B patients with inhibitors. No SAEs related to study drug and no thromboembolic events were reported. All AEs were mild or moderate in severity. As of the data cut-off date, seven inhibitor patients had transitioned to the Phase 2 OLE study and continued dosing with fitusiran for up to seven months.

Like ACE910, monthly s.c. administration would provide a substantial convenience advantage to fitusiran over factor replacement by weekly or multi-weekly i.v. infusion. Overall, results provide a positive signal for antithrombin blockade by RNAi for the treatment of hemophilia, but uncertainties about long-term efficacy remain.

Beyond hemophilia, fitusiran can potentially be used not only in both hemophilia A and B, but also in various other rare bleeding disorders, as fitusiran potentially restores thrombin activation downstream of many of these conditions. Such disorders include deficiencies in other clotting factors and potentially additional platelet function conditions, such as von Willebrand disease, an autosomal dominant genetic disorder in which loss of VWF reduces FVIII levels, and Glanzmann thrombasthenia, an autosomal recessive genetic disorder in which loss of the fibrinogen receptor on platelets can be treated through induction of thrombin by bypassing agents like FVII. Taken together, these additional indications allow for further label expansion for fitusiran, which would constitute additional potential for upside for fitusiran and for Alnylam.

In line with traditional factor therapy, various gene therapy approaches (including AAV gene therapy, lentiviral gene therapy, and gene editing) function through restoration of the deficient coagulation that could result in long acting factors.

Gene therapy offers a new solution to “cure” hemophilia

In gene therapy, external genes are inserted using a transportation vehicle known as a vector. Vectors deliver functional genes into living cells, which then use the functional genes to produce healthy proteins. As such, gene therapy helps to reduce or eliminate disease symptoms and restore physiological function.

AAV is a small DNA virus that infects humans and other species, but the virus does not appear to cause any harm. AAV can infect dividing and quiescent cells without integrating into the genome of the host cell. In addition, AAVs lack immunogenicity

and generate mild and manageable immune responses (although the associated antibody production could limit the use of the vectors in certain applications). The safety profile and the feature to infect quiescent cells make AAV an attractive candidate for human gene therapy. AAV vectors have been widely tested in clinical trials around the world in a number of diseases, including Leber congenital amaurosis, hemophilia, congestive heart failure and Parkinson's disease.

Benefits of using gene therapy in hemophilia:

- Since hemophilia is a single gene disorder, use of gene therapy has a clear cause and effect relationship
- Gene therapy could potentially eliminate the requirement of repeated replacement administration (e.g. one-time infusion vs 3x weekly IV injection over a lifetime)
- Gene therapy allows for a wide therapeutic window
- Efficacy is easy to assess in the clinic and laboratory
- High potential for consistent expression without abrupt peaks and troughs

Disadvantages and challenges of gene therapy in hemophilia:

- Typical AAV vectors are limited to less than 5 kb (kilobases) in length, which present a challenge for hemophilia A gene therapy. Full-length FIX can be packaged into the vector since it is usually 461 amino acids (or ~1.4kb), while full-length FVIII must be truncated since it is a relatively large protein with 2,351 amino acids (or ~7.1kb)
- Clinical scale manufacturing feasibility is limiting and result in low manufacturing yields of AAV vectors
- While the FIX gene accommodates nicely in AAV vector, early data indicate that not all gene therapies have the same behavior for hemophilia B

As such, compared to hemophilia B, progress in gene therapy for hemophilia A has been slower due to the size of the gene. However, companies like BioMarin, Spark and Baxalta look to truncate the FVIII gene cassette protein by cutting out certain domains that do not play a role in clotting.

There are multiple ongoing programs for the development of AAV-based gene therapies for the treatment of hemophilia A and B, respectively. For hemophilia A, the lead gene therapy program is BMN270 from **BioMarin**.

Back in April 2016, BioMarin reported positive Phase 1/2 data of BMN-270 in hemophilia A patients. Specifically, the data looked much better than expected. BioMarin said data was very encouraging and preliminary results suggested that gene therapy was going to be part of the future at BioMarin. In high dose cohort, two patients reached FVIII levels of up to 60-66% production at 8-16 weeks. One patient reached 66% by week 14 and was at 57% at week 16, while a second patient was only at week 8 and was already at 60% factor VIII levels. Safety looked good, there were some expected ALT (liver) elevation but the use of prophylaxis steroids prevented any safety issues from arising. There were no interruptions, discontinuations of infusions, and serious adverse events.

In July 2016, BioMarin provided additional follow up data at WFH, noting that 6 of 7 patients in 'high dose' cohort achieved FVIII levels above 50%. Post treatment follow-up ranged from 12 to 28 weeks. 6 of 7 patients achieved much higher FVIII levels at 50-271% production (extremely high). Last patient had FVIII levels just above 10% (but he has fallen to just above 5% since then). Four patients that were followed up the longest had a mean FVIII level of 146% at their 20 week visit. There were no new updates on safety or disclosures since the July cut-off, but BioMarin will provide an update in early 2017.

Since then, patients have all come off the steroid protocol and thus it will be important to see if patients maintain high efficacy and are not really declining, thus showing continued strong durability of effect and patients do not have any liver signals after removing the steroid. Data should continue to look good given the UK just allowed dosing of more patients with a higher bar to trigger any need for steroid and thus suggesting patients look good so far. While BioMarin BMN270's Phase 1/2 results did show robust FVIII induction at the highest dose, there is potential safety risks from liver enzyme elevations in the presence of steroids. Moreover, as the high dose generated a broad range of FVIII levels, with the restarted Phase 1/2 trial and upcoming Phase 2b

study scheduled to begin in the second half of 2017 will likely require significant dose finding trial and error.

Beyond BMN270, several other companies have AAV-based gene therapy programs for hemophilia A, all of which are currently preclinical. **Sangamo** has SB-525, an AAV vector using the AAV6 capsid and a B-domain deleted form of FVIII, with preclinical data presented at WFH 2016. Sangamo plans to file an IND for SB-525 in 2016. Comparable to the hemophilia B therapy, SPK-9001, **Spark** has developed SPK-8001, an AAV vector using a novel bioengineered capsid, Spark200 and a B-domain deleted form of FVIII. Preclinical data were presented at the American Society of Gene and Cell Therapy 2016. A Phase 1/2 trial is expected to start, with initial results expected in the first half of 2017. Beyond Sangamo and Spark, **Dimension** has DTX201 (an AAV vector using the AAVrh10 capsid licensed from **REGENXBIO**). Dimension has guided starting IND-enabling studies in 2017, and is partnered with **Bayer**. While **uniQure** has an unnamed programs in hemophilia A. All are pre-clinical.

The lead hemophilia B gene therapy programs are Spark's SPK-9001 and uniQure's AMT-060, both of which have presented interim results from ongoing Phase 1/2 studies; the remaining programs include DTX101 from Dimension, which is in an early Phase 1/2 study.

SPK-9001 is an AAV-based gene therapy for the treatment of hemophilia B that Spark has partnered with Pfizer. Currently in Phase 1/2 studies led by Spark, Pfizer will lead later stages of clinical development and commercialization, providing both milestone payments and a low-teen percentage of net product sale royalty to Spark. At WFH 2016 (and previously at the European Hematology Association 2016 Annual Meeting), presented Phase 1/2 data for i.v. administration of SPK-9001, a bioengineered AAV vector (named Spark100) expressing a codon-optimized FIX variant expressing the Padua transgene variant (arginine 388 to leucine, or R388L), a naturally-occurring FIX mutation shown to have roughly seven-fold higher FIX activity than normal, for the treatment of moderate to severe hemophilia B. Data was presented for four patients dosed at the initial low dose. Intriguingly, in these four patients, SPK-9001 was able to achieve significant inductions in FIX activity (21-42%, which represents the mild to normal range), leading to near-complete (> 99%) suppression of FIX infusion. Moreover, among these initial four patients, there was little to no activation of T cells against the virus (as measured by induction of interferon-gamma, a key biomarker of T-cell activation). This is important as, according to a recent review, preclinical and clinical studies of AAV based gene therapy support the view that "capsid-specific T cell responses were responsible for clearance of transduced cells." The lack of T cell responses beyond 12 weeks is associated with durability of response for AAV based gene therapies. Taken together, while relatively early, SPK-9001 has achieved striking induction of FIX activity, substantially reducing FIX use in hemophilia B patients.

On November 3, 2016, Spark presented additional data from the SPK-9001 Phase 1/2 reflecting seven patients treated at the low dose. While the seven patients continued to achieve significant levels of current FIX activity (11-36%, continuing to represent the mild to normal range and near-complete (> 99%) suppression of FIX infusion, the company announced, "one participant, who had not reached 12 weeks post-vector administration, manifested an immune response to the AAV capsid, accompanied by a drop in factor IX activity level, and was put on a tapering course of corticosteroids." An immune response in one hemophilia B patient following SPK-9001 treatment caused Spark shares to drop 20+%.

At ASH, updated results for the Phase 1/2 study of SPK-9001 show sustained FIX activity levels, but another patient develops immune response to capsid with steroid treatment reducing FIX levels. Spark believes it has identified factors that predict immune response, which already appears to be improving outcomes in the second patient. It highlighted that learnings from the first patient allowed for more rapid identification of a problem/initiation of steroids in the second. This led to a relatively incremental decrease in factor levels (71% to 68%) vs. a steeper decline in the first patient who was started on steroids later in the immune response (and FIX decline from 32% to a still clinical relevant 15%). Currently, the first and second patients have continue to taper and are at 10mg/day and 40mg/day, respectively, while achieving liver enzyme levels within normal range. The two patient immune responses and demonstrated encouraging understanding surrounding potential prevention, monitoring and management of a future response.

Following presentation of the Phase 1/2 SPK-9001 data in hemophilia B at ASH, Spark is on track to enroll the final patient in the trial before the end of the year, and Pfizer is have a meeting scheduled with the FDA in the first quarter of 2017.

Another hemophilia B AAV-based gene therapy program with clinical results is AMT-060 from **uniQure**. AMT-060 uses an AAV5 vector to express codon-optimized FIX from a liver-specific promoter and is currently being tested in a Phase 1/2 trial by i.v. administration at two doses: a low dose and a high dose. At WFH 2016, low dose results were presented from the Phase 1/2 trial for the treatment of moderate to severe hemophilia B in five patients through up to 9 months of follow-up (data as of July 22). The effect of AMT-060 on FIX activity, while currently longer in duration than SPK-9001 (39 weeks for AMT-060 vs. at most 26 weeks for SPK-9001), was more modest in magnitude, with a presented range of 3.1-6.7% normal FIX. In line with these effects, AMT-060 achieved a modest (75%) reduction of FIX infusion. Moreover, while no patient experienced sustained AAV5-specific T-cell activation (one patient had a transient T-cell activation at one time point), all patients developed antibodies to AAV5, suggesting there could be issues re-dosing these patients with AMT-060 or another AAV5 gene therapy. Taken together, while an absolute improvement in FIX levels, low dose AMT-060's effects are currently more modest than SPK-9001.

In July 2016 at WFH, uniQure presented low-dose data in five patients through up to 9 months of follow-up (data as of July 22). At up to 9 months, all five patients saw improvements in disease phenotype and reached a median FIX activity increase of 5.4% (range was 3.1% - 6.7%). Four of five patients were prophylactic-free. All five patients developed anti-AAV5 antibodies, none had developed inhibitory antibodies against FIX, and two SAEs occurred. One patient had a mild elevation of liver enzymes that disappeared after administration of prednisolone. The Phase 1/2 study is now investigating the high-dose cohort, with data presented at ASH 2016.

Data from 5 hemophilia B patients in the high-dose data showed FIX expression of ~7% (vs. ~5% on 4x low dose previously), a minimal improvement. Overall, 3 patients had mild, asymptomatic ALT elevation (2 in high-dose and 1 in low-dose); these patients received tapering corticosteroids with no loss of FIX activity or T-cell response. uniQure expects to begin discussions with regulators about the design of a pivotal trial in the first quarter of 2017. AMT-060 leads to disease severity improvement (e.g., no spontaneous bleeding); however given the competition from SPK-9001 and availability of long-acting rFIX replacement tx (yielding ~20% FIX expression with ~weekly prophylactic dosing) this may not be sufficient for wide adoption, if approved.

Dimension Therapeutics which focuses on liver-directed gene therapy treatments for severe and rare genetic diseases. While Dimension's hemophilia candidates use the AAV10 construct, the company has an exclusive worldwide license to certain REGENXBIO AAV vector technology, enabling the company to in-license various serotypes except AAV8.

In January 2016, the company initiated a Phase 1/2 study of DTX101 in hemophilia B patients, and in the following month, the company received approval to initiate Phase 1/2 hemophilia B trials in the UK. In the May 2016 ASGCT meeting, Dimension reported preclinical hemophilia B data (90 days) that demonstrated dose-dependent response in FIX levels and sustained FIX expression levels after a single dose administration in mice's tail vein.

In contrast to traditional AAV-based gene therapy approaches, in which the AAV vector produces the deficient transgene from a chromosome distinct from the genome of the target cell, gene editing approaches work by permanently introducing a change into the genome of the target cell. In particular, gene editing begins with a nuclease inducing a break in the DNA sequence of the genome, leading to DNA repair. This DNA break can generate either a random length mutation through deletions or insertions of various lengths, or a precisely engineered mutation through introduction of a specific sequence by a donor DNA sequence template co-introduced with the nuclease.

The main gene editing approach in development for the treatment of hemophilia is SB-FIX from **Sangamo BioSciences**. SB-FIX is comprised of an AAV containing a zinc finger nuclease (ZFN) targeting the human albumin gene, and a second AAV containing a donor FIX gene template. Because albumin is a highly-expressed liver gene, the break-mediated introduction of

human FIX into the “safe harbor” albumin locus has the potential to elicit production of reasonably high levels of FIX. Sangamo’s technology inserts a correct copy of FIX gene into the Albumin locus in hepatocytes. In preclinical studies, animals that received the combination of the albumin-targeted ZFN with the FIX template achieved nearly 70% normal FIX activity, with FIX levels increasing in a ZFN AAV dose-dependent manner.

The company initiated a Phase 1 hemophilia B study of SB-FIX in 12 adult hemophilia B patients in June 2016 and expects to initiate a Phase 1 hemophilia A trial of SB-525 in late 2016.

Final Words

The standard of care in hemophilia has revolved around the use of recombinant factor replacement. While longer-acting/extended half-life recombinant factors have led to "incremental" improvement for patient quality of life and compliance, these therapies are not transformational for patient care, as patients still require multiple weekly injections. On a relative basis, longer-acting Factor IX therapies have had more of a beneficial impact on patient care than longer-acting Factor VIII therapies. Lowered treatment burden associated with longer-acting factors has encouraged more patients to utilize prophylactic treatment. [Therefore](#), treatments with novel mechanisms (gene therapy, RNAi, factor mimetics including bi-specific antibodies) will have a place within the current treatment paradigm. These treatments could represent substantially lower treatment burdens compared to factor, with far less frequent and far less invasive administration and longer duration, thus can have significant appeal.

Positive data presented at ASH from Alnylam in inhibitor and non-inhibitor hemophilia B settings suggests RNAi drug fitusiran (which may also have utility in hemophilia A) can transform hemophilia therapy. Early data from RNAi drug, givosiran, in acute intermittent porphyria look promising, however a patient death is a concern. Also at ASH, uniQure may have a first-mover advantage in hemophilia B AAV GT and has the potential to treat the ~30-40% of patients with neutralizing antibodies to the SPK-9001 capsid. However, the combination of more modest FIX activity, relative to SPK-9001, raises potentially surmountable concerns for AMT-060. Then there is Spark Therapeutics, while the efficacy data on SPK-9001 favorably, there are concerns over immune responses against the bioengineered capsid, the potential for delays due to manufacturing, and an uncertain IP situation given that Spark's vector might be derived from AAV8 from REGENXBIO. Sangamo BioSciences presented preclinical and manufacturing data for its AAV GT program in hemophilia A at ASH. The company remains on track to file an IND by the end of 2016. In regards to BioMarin and Dimensions, more data will be released in 2017 to determine potential. \$\$

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.

Aimmune/NASDAQ: AIMT (BSR #225: Picking through the Rubble) completed enrollment in the Phase 3 PALISADE trial of AR101 which randomized ~540 peanut-allergic patients ages 4-55 years, evaluating efficacy via a primary endpoint of tolerating a cumulative amount of 1,043 mg of peanut protein at 12 months. The results are expected in the fourth quarter of 2017 and if positive, support both a US and EU BLA submission during 2018. Separately, the company also announced the European ARTEMIS pediatric trial, which will begin in mid-2017, employing a higher efficacy hurdle than PALISADE. Specifically, the trial will enroll 120-160 peanut-allergic children and adolescents ages 4-17 years with a primary efficacy endpoint of tolerating a cumulative amount of 2,043 mg of peanut protein at nine months. Aimmune expects to include the data in its MAA submission. ARTEMIS can highlight the higher level of protection possible with AR101 in a broader group of children and teens. These results as important to supporting approval, commercial reimbursement and adoption in the EU market. Additionally, ARTEMIS is a complementary strategy to that in the US. In the US, recall the placebo-controlled RAMSES trial will enroll 400 children and adults without an introduction food challenge and provide important results on predictive biomarkers, TEAEs, and a broad set of patient-centric outcomes.

Alnylam/NASDAQ: ALNY (BSR #170: Rare Diseases) presented promising initial Phase 1 results for givosiran (ALN-AS1) for the treatment of patients with acute intermittent porphyria (AIP) at ASH. The presentation of efficacy and safety results establishes givosiran as potentially the first therapeutic agent for AIP. From Part C of its study in AIP patients, as with Parts A & B in asymptomatic high excreter patients, the administration of givosiran appears to contribute to material declines in key toxic intermediaries (ALA & PBG). Importantly, the reductions in these intermediaries led to a lowering of the annual attack rate by 74% (when compared to run-in) and the annual hemin usage rate by 75%. As a reduction in attacks would likely be a key endpoint in any pivotal program, this is meaningful. On the strength of the positive safety and efficacy data, Alnylam plans to meet with regulatory authorities in an effort to initiate a Phase 3 givosiran trial by late 2017. The company stated that it will next update investors regarding the next data read-out in June 2017 at a conference in France, pending abstract acceptance.

In recent months concern regarding safety issues has arisen on multiple occasions and has kept pressure on its shares. The givosiran study presented at ASH had no drug-related SAEs and there were no discontinuations. However, there was one patient death post the data transfer date due to acute pancreatitis complicated by a pulmonary embolism. This SAE was determined as likely related to gallbladder sludge and is not believed to be drug related. Moreover, given recent concerns regarding RNAi therapies following the discontinuation of revusiran, the decision to move to second generation ALN-AAT02, and--though also considered drug unrelated--a death in the Phase 2 ORION-1 trial for inclisiran (for hypercholesterolemia), investors should expect concerns regarding safety are likely to persist until clean data from the patisiran Phase 3 in hATTR-PN is presented next year.

In mid-December, a jury voted that **Gilead Sciences** (NASDAQ: BSR #2: Aids-related) sofosbuvir (a key component in its HCV regimens) violates a Merck patent (that originated with Idenix which was acquired by Merck in 2014 for nearly \$4B), and that Gilead owes \$2.54B (10% royalty on sales as a result). The jury rejected Gilead's argument that the Merck patent is invalid due to lack of enablement. This is a different patent than the one decided earlier this year for which a jury also decided in favor of Merck but was ultimately thrown out by a judge due to "numerous unconscionable acts" (i.e. lies) by a Merck chemist/attorney. Gilead plans to appeal the case which will now move in front of a judge, not a jury, and will likely take 18-24 months for a new decision.

Gilead continues to diversify away from sofosbuvir as part of its HCV regimens and diversify away from HCV as the franchise continues to decline while the HIV business grows and potentially new products are added to the fold through M&A or pipeline success.

GBT-440 is a small molecule 'left-shifter' that increases oxygen affinity of hemoglobin, resulting in increased oxygen binding and less sickled cells in patients with sickle cell disease (SCD). **Global Blood Therapeutics/NASDAQ: GBT (BSR #225: Sickle Cell)** presented updated results for the ongoing Phase 1/2 study of its hemoglobin modifier GBT440 in a poster session at ASH. The presentation included new data from the 900 mg dose cohort (in Part C), in which 7 patients were dosed for at least 90 days, including 5 patients dosed for more than 90 days and up to 6 months. Efficacy results were consistent with the 700 mg, 90-day dosing cohort reported previously.

Furthermore, unconjugated bilirubin (arguably the most important biomarker in SCD after hemoglobin [Hb]) decreased dose dependently 42.9% (900mg cohort) versus a 2% increase in the placebo, reticulocytes decreased 15% (900mg cohort) versus a 9% increase in placebo, and LDH decreased 51.4% (900 mg cohort) versus a 2.9% decrease in placebo. All of these biomarkers of hemolysis (red blood cell destruction) still suggest a profound and durable reduction. There were no serious adverse events related to study drug and no sickle cell crises events while on study drug.

These results are consistent with earlier dosing data and suggest significant reduction in red cell destruction. Absence of veno-occlusive crises (VOC) in any patient on GBT440 is highly encouraging and provides further confidence in prospects for Phase 3 HOPE study success. Further confidence in Phase 3 success stems from expectation that at the highest dose of 1500mg, 20% hemoglobin modification will be maintained at trough blood levels, for full 24 sickling prevention.

In a new high-dose cohort, GBT440 elicited a significant and clinically meaningful improvement in Hb levels compared to placebo, a key endpoint in the company's HOPE study. Global Blood Therapeutics has begun to initiate clinical trial sites for the Phase 3 HOPE study. These updated results showed that GBT440 can meet its primary endpoint in the pivotal HOPE trial. The first segment of the study will assess the six month outcomes for patients treated at either 900 mg or 1,500 mg daily GBT440. To succeed, the trial must show an increased proportion of patients achieving a greater than or equal to 1 g/dL improvement in Hb, and improvement in a non-hematological endpoint, such as patient reported pain, fatigue, or VOC.

These results were not the only good news at ASH for patients with hemoglobinopathies; several presentations were devoted to new early stage drugs for SCA, with an emphasis on preventing clinical manifestations of the disease.

Global Blood Therapeutics also announced the initiation of a second trial of GBT440 in patients with idiopathic pulmonary fibrosis (IPF). The Phase 2a study, dubbed ZEPHYR, is designed to test the drug in patients who require supplemental oxygen at rest, unlike the company's ongoing study (NCT02846324) in patients with less severe disease. Given GBT440's unique mechanism of action and tolerability demonstrated thus far, the drug has potential to treat a wide spectrum of hypoxemic disorders. ZEPHYR is an open label study that could enroll approximately 18 patients with severe IPF symptoms requiring supplemental oxygen at rest. Per the study protocol, these patients will be treated with 900 mg of GBT440 daily for 90 days. The primary endpoint is to evaluate GBT440's effect on oxygen saturation. Secondary endpoints include improvements in quality of life scores, such as the six-minute walk test and reductions in the use of supplemental oxygen. Interim results for the open-label study could be available in the second half of 2017.

There is another Phase 2a study of GBT440 in IPF, the GBT440-006 study in mildly hypoxemic IPF patients who do not require oxygen at rest but become hypoxemic with exercise, has been initiated in mid-2016, with data expected no later than the second half of 2017.

With preclinical data from three different animal models suggesting increased oxygen delivery to tissues with GBT440, including improved tolerance to 5% oxygen hypoxia and survival in an acute lung injury model and improved arterial oxygen saturation in a chronic lung injury model, there is strong preclinical evidence supporting potential clinical activity in IPF with potential clinical benefit in reducing the need for supplemental oxygen.

On December 12, 2016, Ophthotech announced that Fovista failed to meet the primary endpoint of mean change in visual acuity at 12 months in two pivotal Phase 3 studies. Importantly, the Ophthotech announcement removes potential product competition for **Regeneron's/NASDAQ: REGN (BSR #124: Small but Significant) EYLEA** and reinforces the high benefit of the anti-VEGF mechanism in wet-AMD. In September, Regeneron reported a Phase 2 study of co-formulated EYLEA and anti-PDGFR- β antibody showing no benefit over EYLEA monotherapy in neovascular AMD. EYLEA remains the market leader for wet-AMD with \$854 million in 2016 third quarter sales, Lucentis generated \$456 million in third quarter 2016 sales. Regeneron management has guided 2016 EYLEA sales growth of 23-25%. Meanwhile, it is anticipated FDA approval for Dupixent in atop-

ic dermatitis by the March 29 PDUFA date and late 2017 in the EU. It is assumed Sanofi will rectify sarilumab manufacturing issues that resulted in the CRL ultimately resulting in approval in rheumatoid arthritis

Seattle Genetics/NASDAQ: SGEN (BSR #147: ADC) is viewed probably as a best-in-class oncology pipeline, therefore, the stock as fairly valued following its ~+30% run following the US presidential elections. Following the elections, the Street discounting drug pricing concerns, and anticipating potential for M&A if large biotech/pharma can repatriate cash during a tax holiday granted by the new US presidential administration. Despite this, investors await healthcare and tax policy guidance from the Trump administration prior to becoming more bullish on these opportunities. There is the potential for downside from Street expectations if political pricing concerns emerge or if increased M&A is not realized.

The upcoming ECHELON-1 trial readout (in frontline Hodgkin Lymphoma [HL]) in 2017 is the largest near-term catalyst for the stock. Adcetris for HL represents future expansion into the frontline setting on the back of ECHELON-1. Adcetris has demonstrated compelling efficacy in ECHELON-1 in line with what was observed in its Phase 1 run-in trial (96% CR rate), and see rapid uptake in higher risk patients in this setting.

Trevena's/NASDAQ: TRVN (BSR #219: Fixing a Broken Heart) oliceridine is in two ongoing Phase 3 studies for moderate to severe acute pain - APOLLO-1 following bunionectomy and APOLLO-2 following abdominoplasty. Overall, pivotal data should be similar to what has been seen in Phase 2, with oliceridine significantly better than placebo and differentiated from morphine. The APOLLO pivotal studies test oliceridine in a bunionectomy (hard tissue) and abdominoplasty (soft tissue) post-operative setting, just as in Phase 2. Therefore, the chance of success as high.

In Phase 2, the bunionectomy study used bolus dosing of oliceridine and morphine. To better capture how opioids are used in the “real world”, Trevena is running both pivotal studies with an “as needed” patient controlled analgesia (PCA) dosing paradigm. The abdominoplasty PCA Phase 2 study was first of its kind. Trevena is using a responder index for its primary endpoint, incorporating a safety component into an efficacy measure. In Phase 2, Trevena used PCA doses of 0.1 mg and 0.35 mg after a 1.5 mg loading dose; it has added a 0.5 mg dose in the pivotal studies. The addition of this dose allows for a more comprehensive understanding of the safety profile of the compound and it may also lead to faster onset and less rescue medication, opening up the potential for superiority on efficacy.

ATHENA data is complementary to the pivotal trials, such as bolus dosing, longer dosing durations or different post-operative/medical settings. The study is on target for enrollment of 900 patients; it is the rate limiting step in NDA filing in the second half of 2017. The three studies should support a broad label for pain management. ATHENA can also provide real world data to inform physicians of how to use the drug and could provide data to supplement the understanding of the value of oliceridine.

Vertex/NASDAQ: VRTX (BSR #101: Life after ASCO) has been volatile lately due to lingering concerns regarding profiles of their next-generation correctors, its key for significant cystic fibrosis market expansion, namely potential teratogenic risk of VX-440.

Embryo fetal development studies, conducted in parallel with Phase 1s, are standardized, testing a drug in 2 species (e.g., rat & rabbit); Vertex noted they observed some fetal abnormalities in rabbits. Certain anatomical variants frequently seen in rabbits (aortic arch change, absent gall bladder or lung lobe) and rates/patterns (e.g., malformations in 1-2 fetuses across litters) may not necessarily translate to humans, though such findings are reported out of abundance of caution.

Despite the findings, regulators typically do not require any additional preclinical work beyond standard studies. As such, it would not be expected any potential limitations on VX-440's future use in children with cystic fibrosis, nor translatability to Vertex's other next-generation correctors. Lastly in embryo fetal development studies do not typically prevent a drug's approval, just the label. Given cystic fibrosis' limits on both life quality and expectancy, it is not expected of such labeling, and need for contraception in women of childbearing age, to significantly hamper potential future uptake of VX-440 if it offered the best efficacy/tolerability in a 3x-combo. \$\$

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	21.01	-15.64	36.27	36.27	62:-11
Release AR101's topline data in Q4-17 with regulatory filing in 2018 as a treatment for peanut allergies. File IND for egg allergy at the end of 2016/Q1-17. See current BioTech Stock Updates. Target Price: \$25 Rating: Change from hold, to buy below \$20.							
Alnylam (ALNY)	6-24-10	15.45	40.48	-11.33	-56.49	162.01	91:NC
<i>On Dec. 16, 2016, ALNY announced preliminary clinical data from its Phase 1 study of ALN-TTRsc02 for the treatment of ATTR amyloidosis. New results of 48 patients showed a single subcutaneous doses of ALN-TTRsc02 achieved robust TTR knockdown of up to 98.4%, with durability well over four months. On July 7, 2016, ALNY initiated a Phase 1/2 clinical trial with ALN-HBV for the treatment of chronic hepatitis B virus infection with initial clinical data to be reported in mid-2017. Release Patisiran's Phase 3 APOLLO data in mid-2017 as a treatment for TTR-mediated amyloidosis. ALNY's Phase 1/2 study of ALN-AAT for the treatment of alpha-1 antitrypsin deficiency-associated liver disease, initial data expected to be reported in late 2016. On Dec. 4, ALNY announced new positive results from its ongoing Phase 2 fitusiran study in patients with hemophilia A or B without inhibitors. The clinical data showed that once-monthly subcutaneous administration of fitusiran achieved consistent lowering of AT and increases in thrombin generation, resulting in a median estimated annualized bleeding ate of 1.0 patients. Initiate Phase 3 trial of Fitusiran as a treatment for hemophilia in the first half of 2017. See current and November 2016 BioTech Stock Updates</i> Target Price: \$65. Rating: Buy below \$36.							
BioMarin (BMRN)	3-23-11	23.57	85.05	-.44	-18.94	260.84	98:NC
On Sept. 1, 2016, BMRN announced the BLA's PDUFA date of Jan. 27, 2017 for cerliponase 1 in CLN2 disorder has been extended to April 27, 2017, due to the FDA's request for additional data. BMRN plans to initiate a Phase 3 study over 12 months in children with dwarfism, ages 4-14 at the first half of 2017. BMRN to submit PEG-PAL's BLA in Q1-17 as a treatment for PKU subject with FDA. Release BMN 701's Phase 2/3 clinical data as a treatment for Pompe disease in the second half of 2016. See November 2016 BioTech Stock Updates. Target price: \$114 Rating: Buy below \$90.							
Global Blood Therapeutics (GBT)	8-25-16	18.05	15.15	-11.66	-16.07	-16.07	57:NC
<i>On Dec. 4, 2016, GBT reported at ASH new long-term clinical data from ongoing Phase 1/2 trial of GBT440; showed treatment led to reduction in hemolysis and sickled cell in all patients treated for up to 6 months. On Nov. 30, 2016, GBT announced the European Commission has designated GBT440 as an orphan medicinal product for the treatment of sickle cell disease. See current and December 2016 BioTech Stock Updates. Target price \$45 Rating: Buy below \$20.</i>							
Intercept (ICPT)	3-25-15	260.64	104.40	-6.54	-29.37	-59.94	83:NC
<i>On Dec. 14, 2016, ICPT announced the EC has granted conditional approval for Ocaliva for the treatment of PBC in the EU. Release Phase 2 CONTROL data in NASH in 2017. Ocaliva's Phase 3 REGENERATE trial enrollment completion for interim analysis expected in the first half of 2017 as a treatment for NASH. Ocaliva's top-line results from the Phase 2 AESOP trial anticipated in 2017 as a treatment for PSC. Release Phase 1 clinical data of INT-767 as a treatment for fibrosis end of 2016. See December 2016 BioTech Stock Updates. Target price: Adjust from \$204 to \$190 Rating: Hold.</i>							

Company	Date	Reference Price	12-21 Price	% 1-mo	% YTD	% Inception	Institutional % Ownership: +/-
Incyte (INCY)	9-24-09	6.88	99.76	-6.59	-3.45	1350.0	93:NC
<p>On Dec. 21, 2016, INCY entered into a global collaboration and license agreement with Merus that gives INCY the exclusive rights for up to 11 bispecific antibody research programs. INCY has agreed to pay Merus an upfront payment of \$120 mil. On Dec. 4, 2016, INCY reported 5-year follow-up of the Phase 3 COMFORT-I and COMFORT-II trials; long-term treatment with Jakafi prolonged survival compared to controls in patients with intermediate or high-risk myelofibrosis. Median overall survival for Jakafi was 5.3 years compared with 3.8 years for the control group. On Dec. 16, 2016, INCY and Eli Lilly confirmed that the EMA's CHMP has issued positive opinion recommending the approval of baricitinib as a treatment for rheumatoid arthritis. On Jan. 19, 2016, INCY and its partner Eli Lilly submitted baricitinib's NDA as a treatment for rheumatoid arthritis with an expected approval in Q1-17. See December 2016 BioTech Stock</p>							
Ionis (IONS)	12-18-08	13.34	52.15	19.58	-15.45	290.93	90:NC
<p>On Sept. 27, 2016, IONS and partner BIIB have completed IONIS-SMN's NDA as a treatment for spinal muscular atrophy. IONIS-APOCIII's Phase 3 top-line results in Q1-17 for FCS as well as a treatment for FPL in the first half of 2018. Report Phase 2/3 IONIS-TTR as a treatment for FAP in the first half of 2017. Report IONIS-FXI's Phase 2 clinical data as a treatment in atrial fibrillation for end-stage kidney disease patient study at the end of 2016. Release Phase 2 results of IONIS-ARrx as a treatment for prostate cancer in the second half of 2016. Release GCGR's Phase 2 data in patients with type 2 diabetes at the end of 2016. Release DMPK-2.5's Phase 1/2 data in patients with Myotonic Dystrophy Type 1 at the beginning of 2017. Release STAT3-2.5 Phase 2 in patients with head and neck cancer at the end of 2016. Release AR-2.5's Phase 2 data with advanced tumors at the end of 2016. See November 2016 BioTech Stock Updates Target Price: \$42 Rating: Hold, met target price.</p>							
Merrimack (MACK)	7-19-12	7.25	4.38	-28.08	-43.41	-41.76	74:NC
<p>Results from the Phase 2 clinical study of Onivyde in previously untreated patients in front-line metastatic pancreatic cancer in the first half of 2017. On Dec. 21, 2016, MACK stops the Phase 2 study of HERMIONE, the clinical study of MM-302 in patients with HER2-positive metastatic breast cancer. The decision to stop the trial was made following the Data and Safety Monitoring Board's opinion that the continuing would be unlikely to demonstrate benefit over the comparator treatments. MACK will provide further details in January. Results in 2018 from the Phase 2 clinical study of MM-141 in patients with front-line metastatic pancreatic cancer. Results in 2018 from the Phase 2 clinical study of MM-121 in patients with locally advanced or metastatic NSCLC. Target Price: \$9 Rating: Hold.</p>							
Regeneron (REGN)	6-28-07	17.95	365.06	-8.50	-29.33	1933.76	70:NC
<p>On Oct. 31, 2016, REGN received a complete response letter (CRL) from the FDA citing manufacturing deficiencies at its rheumatoid arthritis drug, sarilumab. As a result, approval of sarilumab has been delayed and its partner Sanofi said it will submit a corrective plan to the FDA to address any concerns. The CRL does not identify any concerns relating to the safety or efficacy of sarilumab. Praluent's monthly dosing regimen as a treatment for high cholesterol, PDUFA date of Jan. 24, 2017. REGN filed Dupixent's BLA as a treatment for atopic dermatitis with a PDUFA date of March 29, 2017. On Dec. 8, 2016, REGN and Sanofi announced that the EMA has accepted for review the MAA for Dupixent for the treatment of adults with moderate-to-severe atopic dermatitis. Release Dupixent's Phase 2 clinical data as a treatment for eosinophilic esophagitis and chronic sinusitis/nasal polyposis in 2016. Release Dupixent's Phase 3 clinical data for asthma in mid-second half of 2017. Release Phase 3 data for REGN2222 as a treatment for RSV in the first half of 2017. See current and November 2016 BioTech Stock Updates. Target Price: \$466 Rating: Buy below \$400.</p>							

Company	Date	Reference Price	12-21 Price	% 1-mo	% YTD	% Inception	Institutional % Ownership:+/-
Sangamo BioSciences (SGMO)	6-26-14	15.40	3.25	-12.16	-63.69	-78.90	62:NC
<p>On Dec. 11, 2015, SGMO presented Phase 2 clinical data from two SB-728-T HIV studies, suggested 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 the second half of 2017. File gene therapy IND treatment for hemophilia A in Q4-16. File IND for sickle cell disease in 2017. SGMO expects to file two IND applications in 2017 for Hunter syndrome and beta-thalassemia. See December and November 2016 BioTech Stock Updates Target Price: \$7. Rating: Hold.</p>							
Seattle Genetics (SGEN)	6-25-09	9.27	61.38	-11.20	46.42	562.14	99:NC
<p>On Dec. 5, 2016, SGEN and BMY highlighted first reported data from an ongoing Phase 1/2 clinical trial evaluating Adcetris in combo with Opdivo in relapsed or refractory classical Hodgkin lymphoma; it showed 90% objective response rate and 62% complete response rate. On Dec. 4, 2016, SGEN presented Phase 1 data on SGN33A in combo with HMAs in newly diagnosed older AML patients. Key findings include of 49 patients evaluable for response, complete response was observed in 36 patients, remissions were observed in higher-risk patients and 18 of the 36 patients who achieved remission were negative for minimal residual disease. File Adcetris' sBLA for relapsed CTCL in first half of 2017. Report Adcetris Phase 2 data in 2016 and define next steps in frontline and relapsed DLBCL. See current and December 2016 BioTech Stock Updates Target Price: Adjust from \$53 to \$60 Rating: Hold, met target price.</p>							
Trevena (TRVN)	5-28-15	7.00	5.59	-9.11	-20.14	-20.14	74:NC
<p>Report top-line APOLLO data from these studies in Q1-17 as a treatment for pain. Potential to file an NDA in the second half of 2017. See current and November 2016 BioTech Stock Updates Target Price: \$13 Rating: Buy below \$8.</p>							
Vertex (VRTX)	6-23-05	15.52	72.60	-15.78	-40.92	367.78	96:NC
<p>File ORKAMBI's MAA as a treatment for in children with cystic fibrosis ages 6 through 11 who have two copies of F508del mutation in the first half of 2017. The Phase 2 study is to evaluate the safety and efficacy of 4-week dosing of VX-440 in combo with VX-661 and Kalydeco. Data is expected in the second half of 2017 with the intention to support Phase 3 development. The Phase 2 study of VX-152 will evaluate 2 weeks of triple combo and data will be released in the second half of 2017 with the hopes to initiate a Phase 2b study. Release VX-150's Phase 2 clinical data at the end of 2016 for osteoarthritis pain. See current and December 2016 BioTech Stock Updates Target Price: \$110 Rating: Hold, until share price stabilizes.</p>							
Intermediate Growth							
Alexion (ALXN)	1-29-09	36.57	118.99	1.68	28.80	550.75	96:NC
<p>On Dec. 4, 2016, ALXN presented new data from ALXN121 Phase 1/2 dose-escalation study in patients with PNH showed rapid and sustained reductions in lactate dehydrogenase, a direct marker of hemolysis, in patients treated with once-monthly dosing. On Dec. 21, 2016, ALXN released Soliris' Phase 2/3 clinical data for DGF after kidney transplant that did not its primary endpoints. Target Price: \$175 Rating: Hold until prize stabilizes.</p>							

Company	Date	Reference Price	12-21 Price	% 1-mo	% YTD	% Inception	Institutional % Ownership: +/-
Celgene (CELG)	4-28-00	23.53	115.85	-4.23	-1.50	884.70	77:NC
<p>On Dec. 20, 2016, Juno Therapeutics and CELG granted Breakthrough Therapy designation for JCAR017 for the treatment of patients with relapsed/refractory aggressive large B-cell NHL including DLBCL. On Dec. 6, 2016, CELG presented interim results from the ABOUND clinical trial of ABRAXANE; it support safety, efficacy and tolerability in patients with advanced NSCLC. On Dec. 4, 2016, CELG, the Dana-Farber Cancer Institute and the University of Arkansas for Medical Sciences announced the creation of the Myeloma Genome Project, a collaborative initiative aimed at developing clinically relevant tests for multiple myeloma patients. Release ozanimod's Phase 3 clinical in RRMS in 2017. Release CC-220's Phase 2 clinical data in SLE in the second half of 2016. Release CC-122's Phase 2 clinical data as a treatment for NHL in late 2016. Release RPC4045's Phase 2 esophagitis data in the second half of 2016. See November 2016 BioTech Stock Updates. Target Price: \$137 Rating: Change from buy below \$100 to below \$110.</p>							
Gilead Sciences (GILD)	3-27-97	3.11	73.96	-67	-24.54	4657.23	75:NC
<p>GILD reaffirms guidance for FY16 revs of \$29.5-30.5 bil vs. consensus estimated of \$30.38 bil. On Dec. 19, 2016, GILD announced the Japanese Ministry of Health, Labour and Welfare has approved Vemlidy as a hepatitis B treatment. On Dec. 8, 2016, GILD submitted the NDA for the single tablet of sofosbuvir, velpatasvir, and voxilaprevir for the treatment of genotype 1-6 chronic HCV. On Nov. 11, 2016, GILD confirmed that the CHMP adopted a positive opinion for Vemlidy for the treatment of chronic HBV. Final marketing authorization from EU commission is expected in Q1-17. Release topline Phase 2 data for GS-9620 in virally suppressed HBV in 2017. Release GS-6615's top-line Phase 3 data in the first half of 2017 as a treatment for LQT-3 syndrome. See current, December and November 2016 BioTech Stock Updates Target Price: \$102 Rating: Continue to hold.</p>							
Stable Growth							
Amgen (AMGN)	3-27-97	14.44	146.17	1.27	-7.98	912.43	79:NC
<p>On Dec. 13, 2016, AMGN and its partner Allergan submitted a MAA to the European Medicines Agency for ABP 215 its biosimilar to Avastin, a cancer drug. AMG 334's Phase 3 clinical data (STRIVE) in 2017 as a treatment for episodic migraine. On July 22, 2016, AMGN and UCB submitted BLA's romosozumab as a treatment of osteoporosis in postmenopausal women at increased risk of fracture. On Dec. 20, 2016, AMGN announced that it has submitted romosozumab's marketing application to the Japanese agency for review as a treatment for osteoporosis. Release romosozumab's Phase 3 ARCH data in the first half of 2017 as a treatment for osteoporosis. See December and November 2016 BioTech Stock Updates Target Price: \$180 Rating: Buy below \$150.</p>							

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