Investment Thesis

It is extraordinary for an emerging biotechnology company to have just received in the last year FDA approval for two products that address major market opportunities. The most medically important is AndexXa which reverse the anti-coagulant activity of the Factor Xa antithrombotic agents Xarelto and Eliquis. The mode of action of these drugs is reduce clotting activity and thereby prevent heart attacks and strokes. These are life saving drugs but their mode of action can overly reduce the ability to clot and result in dangerous, life threateting bleeding. AndexXa is the only approved drug that can reverse the anti-coagulat activity of Xarelto and Eliquis when this occurs. In addion, patients on these drugs who suffer trauma or are to undergo major surgery must have their anti-coagulant activity reversed are also targeted patient f groups. AndexXa is a very significant medical advance. Portola management estimates that the above conditions result in xx,00 bleeds each year and that AndexXa is crucial to treating xx% or xx,000 of these patients. At a price of $27,500 per dose this is an addressablre market of $xx.

Why then has the stock done so poorly. In aa, prior to the approcal of betrixaban in xx, the stock was selling at xx. AndexXa was then approved on May x, 2018. Yesterday, it closed. So what is going on? I think that the major issue in the poor stock price performance is stock manipulation techniques that are used ubiquitously against emerging biotechnology and emerging companies in other industries. Using well coordinated legal and naked shorting. A broad and very powerful coalition of hedge funds and market makerds

Portola at Goldman

Two lead drugs in thrombosis approved in 12 month period. Third drug moving along. Bill Lis will retire as of August 1, 2018.Why now. He has a commercial background.

AndexXa was not a factor.

On the betrixaban launch they have learned a lot more about how hospital formularies work. The launch of betrixaban is going as expected and the launch of AndexXa is going extremely well. The drug was available on May 23. They were approved on May 4. Orders in the 30 to 40 hospitals they have targeted with Gen 1. Other requests are coming in which they will tee up with generation 2. Generation 2 is moving along very well. The FDA is aware of it. They reviewed the initial data package and gave the green light to move ahead into the ANNEXA 4 study. They have now treated over 100 patients with Gen 2. The drug has been very well behaved and well tolerated. Continues to show same exciting activity as with Gen 1.Thye are optimistic about GEN 2 going through the PAS process, but they cannot speak for FDA. Hey recognize the possibility that as they pour through the document that they may find some things that they will want to pursue in more depth.

To highlight some of the milestones on Andexamet. They will submit the PAS package later this summer. There will probably be a six month reviews time with the FDA. This leads them to expect GEN 2 approval in 1Q, 2019. They also have Europe and the CHMP opinion is schedules for 4Q, 2018. That is after a positive trend vote in the oral explanation. All of this and they will have ample GEN2 inventory upon approval. Nothing has changed here.

On betrixaban, the launch will be similar to what has been seen with other thrombotics. When they launch into the hospital, there will be period of a burn in laying the groundwork at the hospital and the formularies. There are two step with the pharmacists at the hospitals. They start with the Drug and Therapeutics committees to get the drug on the formulary and then they need to go back and get on the electronic order set. It is a twp. step process. This has taken longer than they originally anticipated. It is a sequential process and 2018 is laying the groundwork for an inflection point in 2019 that will pull through sales.

AndexXa is being sold into many of the same hospital that were involved in the ANEXXA-4 study. It is early as they just launched on May 23. The decision on which hospital to target was based on selecting some of the more robust Annexa-4 sites. Portola is of course very familiar with them and they know a lot about the drug. Thy expect level of use to parallel what was seen in the ANNEXA-4 study. With regard to the other hospitals the level 1 trauma centers and the stroke centers which have not used it before; the data is too small to extrapolate. However, the demand is outstripping the amount of drug that is available. Two years ago there were 116,000 hospital admissions for bleeding on apixaban and rivaroxaban. Perhaps 20% will be suitable for AndexXa-intracranial bleeds, unstable compartment bleeds. Portola must work carefully with the hospitals to make sure that they target with the hospitals to make sure that they are targeting the patients who will benefit the most. The experience so far is that hospitals in a very short period of time are seeing patients that they are treating. There are many hospital inquiring about the drug which they are not going to be able to supply until they get GEN-2 approval. These are large trauma centers and stroke centers. These will be prepared for when GEN2 inventory becomes available. They will expeditiously get them up to speed. They have manufactured enough GEN2 drug to treat thousands of patients.

The level of stocking will vary at each hospital depending on their size. Right now Portola is controlling how much they can stock. This will change significantly when GEN 2 becomes available. In general, the hospitals have enough to treat two patients. Then as they treat, they will supply the next dose. With the larger hospitals they will stock in accordance with their needs. Smaller hospitals might see a patient per month and will stock accordingly.

The first 30 to 40 sites were handpicked by Portola and half participated in the ANEEXA-4 trial. These are characterized by high factor Xa usage. Their use of the drug is almost exactly what Portola predicted. The next 600 hospitals they will be going after with GEN2. These are hospitals that see a lot of intracranial bleeds, gastrointestinal bleeds and compartment bleeds. They will then broaden out to level three and community hospitals. It will be harder to get on formulary and there will need to be extensive education.

Major bleeds are associated with about 2-3% of factor Xa usage. Also the unit growth of factor Xa drugs is about 20% per year. There are also about 1% of factor Xa users who need major surgery. A major hospital in say Florida might have 8 to 10 major bleeds per month.

In their current hospital base price has not been an issue, they are getting a lot n incoming interest. The 600 hospitals that are level one or two trauma centers are also anxious to get the drug.

AndexXa will be part of the DRG. There are multiple DRGs that exist for patients who are coming in with major bleeds and these will cover a portion of the cost of the drug. In addition there is a mechanism available to the hospital called outlier payments. This allows CMS to increase reimbursement amounts taking into account the drug cost in the DRG treatment. The hospital has to explain the rationale for the drug there is also another mechanism that is a new technology add on payment NTAP in which CMs will reimburse for 50% of the drug. The cost of AndexXa is $27,500 per dose so that if NTAP picks up $13,750 it is much easier for the hospital to absorb the cost into the DRG plus the add on mechanism. In the high treating hospitals they are seeing no resistance on price but at they broaden usage NTAP will be more important.

NTAP is CMS and is part of the Medicare part a program. They have been heavily involved in going through this with medical reviewers and there are multiple steps in which they presented data to them and there was then a town hall in February that was open for public comment. The comments they got back were very reasonable and were targeted to their first data set that was published two years ago. Just had an opportunity to meet with them again. They are now updated on the latest data presented at the American College of Cardiology. The CMS reviewers can’t comment on their views but the process is moving long well and they should get the official word on NTAP in August.

For the other two classes of anti-coagulants such as the vitamin K antagonists and warfarin. They gave an NTAP to Kcentra. For the antagonist for direct thrombin inhibitors they gave an NTAP to Praxbind. This is a strong precedent for acceptance of NTAP to get new reversal in place,

GEN 2 manufacturing and what needs to be done to get PAS resubmitted. With GEN 2 they tried to improve the overall yield of the process n but also to not change the molecule which would trigger a brand new BLA. They used the same CHO cell line. Mammalian cell production. Exactly the same cell line. They provided a different set of nutrients in the media to help the cells grow better, Increase the overall titer of the drug. They made sure along the way that any new feeding they did not change the molecule. They are analyzing the molecule as they f go along. The second big change was that in the purification, here they simply added a purification simplification step as is commonly used in monoclonal antibodies to purify the first step. This increased the downstream yield. This does not have an effect on the general properties of the molecule. The whole document is based on bioanalytics. What is the comparability between GEN 1 and GEN 2? They are quite comparable despite the difference in how they fed the cells. The rest of the data package is how GEN 2 behaves in healthy c volunteers and patients. This is the rest of the data package. The PAS will be comprised of crunching of the numbers and writing the report. Management says that results are encouraging that the molecules are comparable in efficacy and safety. It has been tested in 120 healthy volunteers and 100 patients. Very encouraged by the data but regulators often have their own set of questions. Hopefully approval early next year.

In Europe are looking for a final decision later this year. What was the EMA looking for? What the EMA is looking for is not that dissimilar from what the FDA. The EMA has shifted their focus from GEN1 to GEN2 after the oral explanation meeting in February and March. They are focused on the GEN 2 and have asked for a package of data on the GEN2 manufacturing and analytics. It is essentially the same package they are giving the FDA. In addition, they would like to see the updated clinical data comparing GEN1 to GEN2. They also want to look at the healthy volunteers pharmacokinetics and pharmacodynamics. The only different thing they are requesting is an updated PK/PD. Parts of this data will be submitted this simmer and parts in the fall. They will review it all in October and render an opinion in November. This is a special one off timeline reflecting the interest in AndexXa.

They are doing a lot of work in Europe trying to figure out what their strategy should be. Haven’t made a decision on whether to go it alone or with collaborators in targeted countries. Need to put infrastructure in place a year or so before launch. Europe has been at the forefront of treating thrombosis and there are probably twice as many patients on Xa inhibitors as in the US. Pricing is about one-third of what it is in the US. Xarelto and Eliquis have about the same revenues. There is much greater Xa use in the UK, Germany and France and less in Spain and Italy. There is also opportunity in Austria, Switzerland and the Scandinavian countries. Will be dependent on price and factor Xa usage.

Betrixaban estimates have been coming down. Will it really ramp in 2019.Are learning a lot about how hospital view a prophylactic drug. Requires a lot of education. They are encouraged because they know that the patients are there and that the data package is good. In this population, 50% of clots that do occur happen outside of the hospital. Know the patients are there and that the data is good. There are 5 million patients in the US at high risk and patients are at high risk for clots when they leave the hospital. There are 15 different publications that support the data that shows that it reduces the risk of clots without increasing the risk of major bleeds. Also data on rehospitilization, stroke etc. Finally are seeing wins in high profile hospital systems like Stanford, Harvard under the, PNC, Cleveland Clinic. They often are followers in adoption, but are seeing them as leaders in this case. They underestimated that they have to go back to the pharmacist twice, once after the PTC committee and then again. First get on formulary and then push through an electronic order set. This is done sequentially and is taking longer than original thought. Goal is to see an inflection point for revenues in 2019.

The Mariner study will readout later this year. If it is successful and they had to change some aspects of that trial. Does it change the go to market strategy? It doesn’t alter their commercial strategy. They believe that oral inpatient and outpatient is the way to treat these patients. With mariner the patients will have first been given enoxaparin in the hospital and then must be transferred to Xarelto outside the hospital. Hence there will be a time when these patients are between drugs. They believe it is much superior to put patients on the drug in the hospital and continue into the outpatient setting with the same drug. The studies are not comparable. Xarelto has the advantage of being a very well known drug. They started out at 10mg QD and dropped down to 7.5 mg QD. In Magellan there was significant bleeding.

Syk Kinase program. Talked at ASCO about potentially pursuing a strategy for ace; rated approval. They have now treated 150 patients in phase 1 and phase 2a. It has broad activity in B cell leukemias and lymphomas. T cell lymphoma, both cutaneous and peripheral. They have decided to focus on the T-cell lymphomas. ASCO data showed that in a subset of peripheral T-cell lymphomas that there were 5CRs out of 7 patients treated. They have also seen CRs in two follicular lymphoma patients. There is written communication with FDA on a path forward on a registrational study in peripheral T-cell lymphoma. The plan is to return to the FDA in 4Q, 2018 and end of phase 2. Will have more patient data that 7 current and some durability data. The plan then is to begin a registrational study early next year.

This will then be followed by discussions on cutaneous T cell lymphoma. Will have a similar set of discussions as with peripheral T cell lymphoma. And perhaps followed by discussions on follicular lymphoma. These are small indications that they can do on their own. Are always looking at ways to expand the reach of the drug to more patients.