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Reflections From the North American Cystic Fibrosis Conference

NACFC in the rear window. We choose to begin with a few reflections on the comments from the Cystic Fibrosis Foundation's Mike Boyle in the opening Plenary session. Dr. Boyle correctly noted the outstanding progress that has been made in the care and treatment of people with CF this past year, as we have seen the median survival increase from 41 to 47 years old. That alone is a striking and significant impact that is at least in part due to the advent of modulator therapy for CF. He also predicted that the advent of "the triples" of 3 CFTR modulators would increase the number of people that could receive a therapy to nearly 90% of the CF population in as early as 2020. To get to 100% of CF patients being effectively treated, he identified, and we agree, with the next key steps: (1) the triples will need to deliver on their early promise; and (2) people with advanced lung disease will still need improved antibiotics, anti-inflammatories and mucolytics.

Do the triples pack a big punch and is it enough? As presented during the conference, the Vertex (VRTX; Neutral rated) triple combination with Tezacaftor and Ivacaftor and a next generation corrector, (VX-440 or VX-152) generates a pre-clinical level of efficacy that is at least comparable to that observed for Ivacaftor alone. The question that was addressed during NACFC2017 was, do these treatments achieve the same level of efficacy (FEV1 and SwCl) in the clinic? Not surprisingly, the answer is mixed. Regardless of genotype, the Triples appear to generate an improvement in lung function to about 9% absolute FEV1. The SwCl response is a bit more variable ranging from a 20 to 40 mmol/l drop compared to baseline. There is no denying that these are excellent responses for CF patients. There are, however, several important questions that remain unanswered. First, is this magnitude of an improvement in FEV1 sufficient in the more seriously affected F508del/F508del CF patient? When speaking with KOL's during the meeting, we have heard that G551D patients routinely experience a significant benefit with Ivacaftor initially and some even get removed from the lung transplant list. But now, with 3-4 years of data after starting on Ivacaftor, some of those same patients have not sustained the lung improvements and have had to return to the lung transplant list. Thus, if the improvement is mediated predominantly by enhanced mucociliary clearance, but there is little to no repair of the airway and lung decline is slowed but not stopped, this mechanism alone may not be sufficient. Second, there does not appear to be the same correlation between lung function and SwCl that was observed for Ivacaftor in G551D, begging the question, is this due to some differential tissue distribution of the correctors or is there simply no correlation between these measures? Although it is becoming clear that a correlation to SwCl and lung function is shaky at best, we need to be clear which outcomes are key for efficacy. We still believe that some measure of chloride transport, e.g., SwCl, is an important indicator of target engagement and efficacy. Third, if we are using Ivacaftor correction in G551D patients as a bar, and we now believe that those patients may not be sustaining their initial improvements, we have to ask, is this treatment sufficient or do we need to address inflammation or another as yet unknown mechanism (e.g., stability)?

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Has Vertex lapped the field? Although it is very clear that Vertex is the front runner and the triple data as provided is solid, we did notice that other companies are closing with their own triple combinations. Although Proteostasis (PTI; Buy rated) has all three of their molecules in the clinic, we only saw data from the amplifier PTI-428 in a MAD Phase 1 on top of Orkambi. In this early trial, the amplifier had no safety concerns, a linear PK profile and no DDi issues with either lumacaftor or Ivacaftor. Perhaps most interestingly, functional CFTR (Band C) was "amplified" 8-fold by the addition of PTI-428. If this level of protein expression translates to a functional increase in a Phase 2 trial and beyond, we would expect this novel modulator to perhaps start gaining ground. Galapagos (GLPG; not rated) continues to provide a wealth of data on numerous molecules. They currently have 2 potentiators, 2 C1 correctors and 2 C2 correctors and are launching 3 different Triple combinations. With this many options, we expect that they are likely to find a combination that provides a competitive advantage, for example their first potentiator, 2451, has a significantly extended PK profile so 1x daily dosing will be ideal for this molecule and it may even be possible to extend that to less frequent dosing. All of the preclinical data generated thus far has suggested that these molecules should match the level of efficacy observed in the Vertex trials, although several trials are projected to read-out in the next 12-18 months we wonder if they have left their homestretch kick a little too late and without a significant difference it may be difficult to catch the leader.

Are there any anti-inflammatories better than high-dose Ibuprofen? As we mentioned above, inflammation is again getting significant attention, as CF modulators are unlikely to reverse lung disease. But we've seen this level of interest before and as 1 KOL asked, if the 3 companies currently leading the charge: Corbus (CRBP; not rated), Celtaxsys (private), and Laurent (private), aren't successful, then what? Could this be the last legitimate chance to address CF related inflammation? The Corbus approach feels like a fresh new strategy for CF inflammation. With Anabasum, Corbus is attempting to stimulate the resolution phase rather than inhibiting or down-regulating the inflammatory stimuli. Data from the Phase 2 study was solid, and demonstrated a strong safety signature, with only dry mouth being consistently mentioned, a finding that the CEO of Corbus continues to find amusing for this endocannabinoid-mimetic drug. The efficacy data were suggestive towards an impact on pulmonary exacerbations; although, we do caution that these were relatively few patients and only treated for a short time period. This study clearly piques our interest as we await a Phase 2B trial with a primary endpoint of pulmonary exacerbations. Not only will this be important for Corbus, but it may also have value for the community in setting a bar of what the regulators will need to see to advance anti-inflammatory therapy in CF. Laurent pharmaceuticals has a similar feel to Corbus in that they are also targeting the resolution phase of inflammation. In this case, they are addressing the ceramide and lipid imbalance that is present in lung inflammation. Although Laurent is at an earlier stage of development, we note that the similarities in approach, goals and philosophy between Corbus and Laurent might lead to further shared corporate discussions. The final member of this triumvirate that we will mention is Celtaxsys. We had an opportunity to sit down and chat with management during NACFC2017, even though they did not present data at the meeting. Celtaxsys is targeting inhibition of inflammatory stimuli in a clever manner by seeking to balance the interplay between LTB4 and LXA4. So again, it's not simply attempting to shut off the inflammatory response; been there, done that and not doing it again. The approach with Acebulistat, appears to be safe, dosing at 50-100 mg is at least 2-4 times below the level where LTB4 begins to shut down. All patients have been on drug or placebo for 24 weeks as of this time, and the DTSMB has continued to give approval to move forward. We expect to see data readout from this pivotal Phase 2B by middle of 2018. This could be the longest anti-inflammatory trial with the most patients that we have seen in CF, and we believe this will be an important water-shed moment for anti-inflammatory therapies. We anticipate that the anti-inflammatory field could follow a similar approach to modulators where we need to use both an inhibitor of stimulation as well as an activator of resolution. But, alas, we are getting ahead of ourselves, let's cross that inflammatory bridge once we have successful treatments for both arms.

Three novel ideas that caught our eye. First, even if the GSNO-R pathway didn't prove out in the last iteration from Nivalis, we and others still see the value in enhancing CFTR activity by: (1) amplification; or (2) stabilization. We've already discussed amplification mediated by PTI-428. Both Flatley Discovery labs (private) and Pfizer (PFE; not rated) have molecules in development that address stability. Specifically abstracts 2 and 54 from the University of Pittsburgh group, supported by Pfizer, discuss the MOA of inhibiting Ubiquitination as a strategy to maintain CFTR stability and residence time at the cell surface. This remains an attractive approach as maintaining CFTR activity for a longer period of time might have a more pronounced effect on difficult to remove mucus. Second, abstract 39 by UNC investigators Carla Ribeiro and Martina Gentzsch and colleagues represents the next step in a long line of experimentation by these investigators. Drs. Ribeiro and Gentzsch have been working to improve the HAE model system by examining the effect of adding supernatant from mucopurulent material (SMM) derived from human CF airways to the HAE cultures. Their data demonstrate that the addition of SMM results in greater

modulator effects mediated by both VX-809 (lumacaftor) and VX-770 (ivacaftor). If these data translate to the clinic it would suggest that at least these two modulators have a better response in the presence of the inflammatory mileu than in its absence. Perhaps this suggests that the DDI effects are greater than expected. It will be interesting to see how other modulators (specifically VX-661) function in the SMM-treated HAE model system. Third, we know that gene therapy works *in vitro*, and has worked for nearly a decade. The limiting feature has consistently been the ability to deliver these agents to a CF airway that is blocked by desiccated mucus. Abstract 202, Kim et.al., describes the use of DNA containing mucus penetrating nanoparticles (DNA-MPP) as a solution for this problem. Dr. Kim and colleagues studied distribution as well as gene transfer efficacy in the b-ENaC mouse model, which demonstrates significant mucus accumulation. The results were impressive, and although it was an animal model and not human data, we do view this as a step forward from in vitro data. It will be interesting to see if Justin Hanes (coauthor, and nanoparticle guru) aligns himself with one of the leading industry participants to further advance these particles.

Hey you didn't say anything about ENaC. It's difficult to carve out a meaningful thesis regarding the likely efficacy of ENaC inhibitors in the CF airway. Its abundantly clear from a wealth of preclinical data that ENaC and CFTR function are in sync with each other to maintain the fluid homeostasis of the airway. It's also clear based on the b-ENaC mouse model that excess sodium absorption through unchecked ENaC activity will lead to mucus accumulation and bacterial colonization reminiscent of CF. What's less clear is why the Vertex compound (VX-371) failed to reach a significant impact. Its possible that the drug was under dosed and simply does not have the margin of dosing where it can reach efficacy without imparting renal toxicity. Or it may simply be that inhibiting ENaC, although it rehydrates the airway is not sufficient to restore mucociliary clearance. So, it appears that the responsibility of proving this hypothesis now rests in the hands of Spyryx (private). Spyryx provided several high-level presentations of the effect of SPX-101 and how it is clearly differentiated from classical ENaC inhibitors. Specifically, that this molecule acts to internalize ENaC and thus results in a longer mediated effect. Moreover, dosing via inhalation eliminates any renal concerns and allows for a higher dose being delivered to the active site in the airway. Ultimately we won't have a clear indication of clinical efficacy until we see what is possible in CF subjects, and we should see that later this year.

With so many studies nearing a boil, we anticipate a robust data producing year in 2018. We expect that several studies will be complete and top-line data should be available and presented at both the European CF basic science meeting (Loutraki, Greece; March 21-24) as well as the European meeting (Belgrade, Serbia; June 6-9). See you there.

Before we could even get this note out. Galapagos released data yesterday regarding their Albatross study with Corrector 2222 in F508del/Class III patients on stable Ivacaftor. Although the number of patients were small, there was a statistically significant improvement in SwCl and a trend to an improvement in FEV1. We believe that the results of this Phase 2 trial confirm what has been seen preclinicaly, that is that the GLPG compounds perform at least as well as the Vertex counterparts. In this case both GLPG-2222 and Vertex Tezacaftor have shown improvement on top of Ivacaftor in gating mutation subjects in Phase 2 studies. The Phase 3 studies should hopefully identify key features that will help us distinguish between these candidates.

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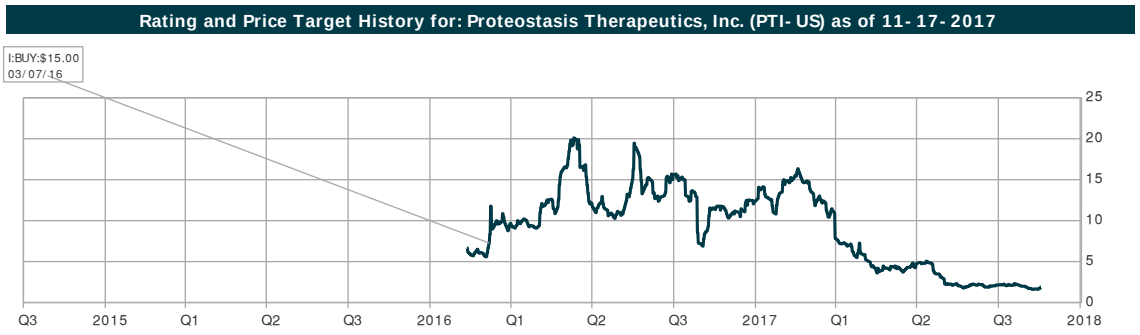

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