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Spotlight on NACFC 2017: Hot Topics and Abstracts of Interest

The Annual North American Cystic Fibrosis Conference (NACFC) is scheduled to take place on November 2-4 in Indianapolis, IN. In line with our annual tradition, herein we highlight, partition and dissect some of the most interesting work and themes emerging from the abstract book, which was recently released (contact us for a copy).

The big picture. It seems like the NACFC is running on bi-yearly cycles with respect to significant data reporting from companies. Last year was a relatively quiet year with few studies reporting and no major announcements. In contrast, this year is loaded with data from key trials as several studies have either just completed or are in the position to provide more details after completing their data mining efforts. With that being said, we are somewhat surprised that none of the recent studies are poised to make a significant impact. Here's what to look for: (1) The cola wars continue as Vertex (VRTX; Neutral) and Galapagos (GLPG; not rated) are the only major players with correctors/potentiators in clinical trials. Vertex continues to lead but stumbles with 2 trials that fail to hit the primary endpoint; (2) Gene Therapy remains interesting with PRoQR (PRQR; Buy) showing modest success and entry of a new candidate, Ionis Pharmaceuticals (IONS; not rated); (3) We believe that ENaC inhibition is still a relevant target, but with the failure of the Vertex/Parion (private) trial, it's now left up to Spyryx (private) to validate this target for rehydrating the CF airway; (4) At last an anti-inflammatory candidate has progressed far enough for us to gain a meaningful insight into its activity. The Corbus (CRBP; not rated) anti-inflammatory agent, Anabasum, should be the subject of 3 separate presentations; and (5) we highlight early work in the field of mucolytics. Dissolving and breaking up the mucus barrier may serve to not only allow for more efficient entry of other compounds (including gene therapy), but it may itself serve to clear and improve lung function.

In the field of CFTR modulators, Vertex still holds a significant lead over Galapagos. Vertex continues to be the track leader in this therapeutic modality. We have recently seen the Phase 2 of the triple combination. Although the patient numbers are small, the data looks solid, and if it holds up, it would give Vertex a significant advantage beyond Orkambi alone. Most KOLs are predicting that due to the better safety and tolerability profile, Tezacaftor and Ivacaftor will ultimately replace Orkambi. If that does unfold, we will have to wait for follow-up studies with this combination and the eventual selected 2nd generation corrector to determine if they have similar efficacy and safety profiles. Although we may gain some insight into this during NACFC2017, please recall that safety issues for Orkambi really didn't become apparent until after the trials when real life conditions lead to significant subject withdrawal, presumably mostly due to the Broncho-constrictive effects. We will be looking for management guidance regarding the development plan since the Phase 3 trial of Tezacaftor/Ivacaftor in patients with 1 copy of F508del and a gating mutation on the other allele, failed to meet its primary endpoint. Vertex does have a history of providing new data, and we point to a late-breaking abstract that should be presented in workshop 18 (Nov 3, afternoon) titled "Preliminary Safety and Efficacy of Triple Combination Modulator Regimens in CF." We think this will be particularly important since to our knowledge, management has yet to explain the questionable safety profile of VX-440 and VX-152. Other important abstracts from Vertex include the Phase 3 extension report (abstract 278) and the prospect part B trial describing long-term effectiveness of lumacaftor/ivacaftor (abstract 437 in workshop 13). Regarding the competitive landscape for modulators, we note that Galapagos also have a presentation during workshop 18 and we hope to garner insight into their recent progress. The majority of the KOL's we have contacted have routinely been impressed with the GLPG data set; however, the considerable time lag to the clinic has us wonder (again) how readily available and willing patients will be to jump off the Vertex ship that appears to be providing solid benefits? To that point, GLPG has several outstanding abstracts (specifically abstracts 46 and 198 characterizing their generation 2 correctors) describing preclinical evaluation of their molecules but relatively few descriptors of their clinical program. Although Galapagos continues to demonstrate excellent safety and PK profiles for many of their modulators, we do believe it is time to accelerate their program and dive with both feet into several Phase 2 programs in an attempt to make up some ground on the Vertex stronghold. We look forward to guidance from GLPG on their path forward and competitive strategy.

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Where have all the third-party candidates gone? With the untimely demise of Nivalis last year, it appears that Proteostasis (PTI; Buy) remains as the lead candidate that can provide a novel mechanism (amplifier) to the standard treatment path of correctors and potentiators. If there is going to be a shift from the purple-brick road, we believe that deviation could come from an amplifier molecule that would obviate the need for the Generation 2 correctors. We point you to workshop 18 abstract 196, which should provide more insight into this program. Another interesting although very early program comes from Enterprise Therapeutics (private), which is pursuing a modulator of TMEM-16a, the Ca-activated Cl channel (abstract 218). It seems like a decade ago (because it was) that INSPIRE Pharmaceuticals (acquired) was targeting this pathway for CF lung disease, perhaps Enterprise will have more success since it now has an ion channel to target. Any long-term forecast involving the CF modulator field must take into account an eventual second and possibly third competitor to the Vertex platform. Simply from consideration of the financial burden on CF patients and their families, we expect that the CFF is actively pursuing strategies to provide that competition.

Gene therapy (gene editing approaches), that may ultimately obviate the need for pharmacotherapy. Certainly, the leader in this category is ProQR. It recently presented top-line data from their Phase 1B trial in homozygous F508del patients and demonstrated a modest level of clinical performance. As we noted previously, although there are still questions to be addressed, in our opinion this program is still worthy of further development. We expect to hear further examination of the data from the Phase 1B as well as a more developed strategy from ProQR, especially since Dr. David Rodman has now had a few months to put his fingerprints on the program. Dr. Stuart Elborn is expected to present the data during workshop 29, abstract 206 on Nov 4th. We would also highlight Ionis Pharmaceuticals, which is using anti-sense approaches to target both CFTR as well as ENaC. It is focusing on CFTR by using ASO to inhibit regulatory elements that block efficient CFTR transcription; this work is scheduled to first be described during workshop 12 on November 3rd. Then followed by a poster presentation describing the Ionis technology to target stop mutations, specifically w1282x using a mini-gene correction approach (abstract 29). As mentioned, Ionis is also developing an anti-sense oligomer to block the sodium channel ENaC. Thus far, it has provided data successfully blocking ENaC expression and function in the β-ENaC mouse model (abstract 95). Please note that Ionis recently received the Prix Galien Best Biotechnology Product in 2017 for SPINRAZA for the treatment of Spinal Muscular Atrophy, clearly demonstrating that anti-sense oligomer therapy has an interesting future. The concern for CF however, is not the efficacy of any of these technologies but rather, if any effective mechanisms are available to mediate entry in to the hostile environment of the CF lung.

ENaC inhibitors alter the airway fluid balance. From our vantage point, it is clear that ENaC has a significant impact on lung fluid homeostasis and that regulation of ENaC activity should have an impact on CF lung disease. The questions have really been around, the dose-response relationship for the inhibitors, as well as the mechanism for delivery and ensuring a formulation that avoids any renal toxicity. Spyryx Biosciences (private) appears to have addressed most of these issues and although there may have been an early lack of clarity around MOA, we believe those issues have mostly been resolved and have been discussed in a recent American Journal of Respiratory and Critical Care Medicine publication (May 2017). In this manuscript, the compound, SPX-101 demonstrates a reduction in Isc from 22 to 8 μA as well as having an effect on neutrophils in the β-ENaC mouse. Finally, as just announced, SPYRYX has initiated their Phase 2 study and has reported that they have completed first patient-first dose for SPX-101. We expect to see further details of this program as Spyryx should be joining Vertex and GLPG in workshop 18, abstract 199 (Nov 3). Supporting characterization of the Spyryx program can be found in abstracts 117, 291. Recently, we learned that the Vertex/Parion partnership combining an ENaC inhibitor (VX-371) with Orkambi failed to achieve efficacy in the Phase 2 trial, and expect that this will also be a significant topic of discussion this year.

When will we see an anti-inflammatory agent for CF? This is a clear need and one that could be present for at least three decades regardless of the pharmacotherapy that is developed. Even if patients are able to improve mucociliary clearance from this stage forward, there is still a significant degree of lung damage and remodeling that occurs along with concomitant inflammation. The key is that any anti-inflammatory therapy must first be safe, as inflammation is valuable, but is only problematic when left unchecked. Of secondary importance is that it has been difficult to effectively identify a meaningful endpoint for anti-inflammatories as FEV1 alone is unlikely to be changed significantly by this MOA. Thus, this category has consistently shown up as an area of great need, but also an area of great difficulty. Two companies, Corbus and Celtaxsys (private), have continued to lead the charge in developing anti-inflammatory therapy for CF patients. First, Corbus continues to develop Anabasum, which is a novel agonist of the CB2 receptor. CB2 is part of the endocannabinoid system and has a role in mediating the resolution of chronic inflammation and fibrosis. Corbus has 3 abstracts at the meeting, but importantly, Dr. Jim Chimel is scheduled to be summarizing the work they have completed including data from their Phase 2 trial in a Symposium presentation on

Friday, November 3, 2017, at 11:35 AM (Symposium 14). This MOA is very intriguing to us, because unlike previous efforts to inhibit the inflammatory system, Anabasum is designed to stimulate the resolution arm of inflammation. Celtaxsys does not have an abstract at this year's meeting, but we are reminded that their Phase 2 trial of once-daily oral acebilustat is expected to readout in the first half of 2018. Acebilustat is designed to re-establish the LTB4-LXA4 inflammation-recovery balance, without completely abolishing the inflammatory response. Together these two programs are providing the greatest recent hope for resolving inflammation in the CF airways.

Where could the next interesting add-on come from? Mucolytics remain highly attractive, although at the rate with which modulators are progressing, it could be argued that they won't be necessary if modulators are truly successful. The MOA for mucolytics has always been interesting, and we have seen efficacy previously with compounds such as NAC or cysteamine. One of the more interesting programs we have been watching is the development of Oligo G, which inhibits alginate, from Algipharma AS (private) (abstract 241). Last year, we were intrigued by the presentation of two compounds developed by Synedgen (private) that target both disruption of biofilm formation and provide anti-bacterial activity. This year, we look forward to assessing the development of their program in poster 207.

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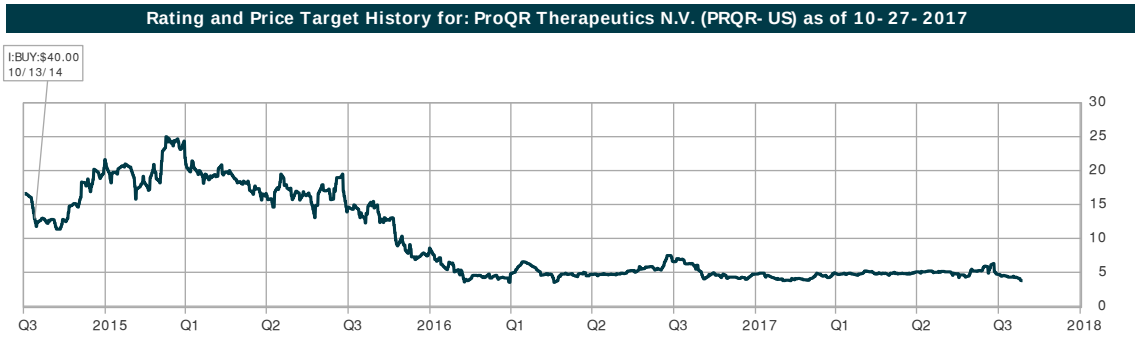

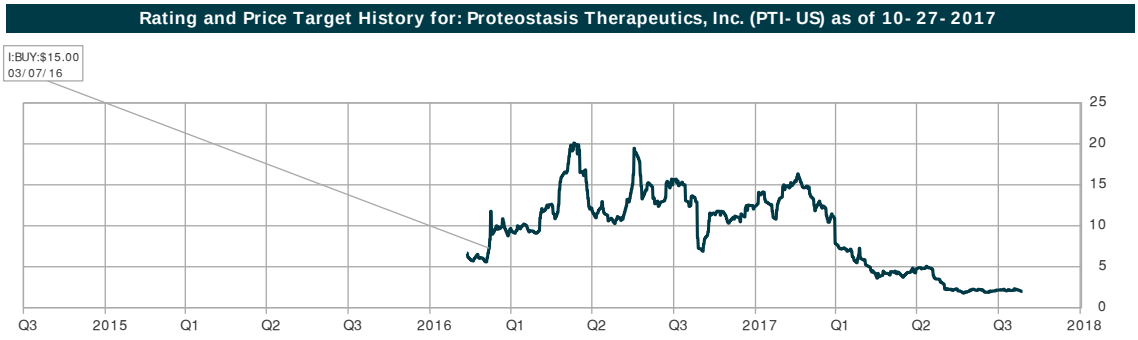

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Proteostasis Therapeutics, Inc.	PTI	Buy	$15.00	$1.98	$50
Vertex Pharmaceuticals Inc.	VRTX	Neutral	$85.00	$150.11	$37930

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