INSMED INCORPORATED

(NASDAQ: INSM)

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Biopharma / Rare Diseases

Will ASPEN Send it or Huck and Pray? Previewing Big Brensocatib Binary in 2Q24

January 1, 2024

- **Bottom Line: We conducted a deep dive on the prior data for brensocatib, failures in the NCFB space, and the bull/bear debate on the ASPEN readout. Despite some uncertainties, we maintain a positive outlook and continue to like the setup heading into the readout in 2Q24.** For many months we have been fielding inbounds on the pivotal ASPEN study, which could be one of the biggest binaries in our coverage in 2024. The level of interest we are detecting is reminiscent of the inbounds we received several months ahead of CRNX's (OP) Ph.3 PATHFNDR-1 data last year (LINK). After reporting positive PATHFNDR-1 data, CRNX rallied +63% (vs. +0.2% XBI). Despite INSM having a larger market cap, we believe it could have a similarly sized move on ASPEN result in 2Q24, depending on the strength of the data. Positive ASPEN data could not only unlock an opportunity in non-cystic fibrosis bronchiectasis/NCFB for brensocatib, but also presage even larger markets like chronic rhinosinusitis without nasal polyposis/CRSsNP. For NCFB, INSM estimates there are ~1.7M-6M patients worldwide/WW. If we assume there are ~425K patients in the US, brensocatib is ~ $30K per patient per year, and peak penetration is ~25%, this would mean that brensocatib could be >$3.0B in the US alone in one indication. As discussed within, the prior Ph.2 WILLOW data raised some questions, and numerous failures in the NCFB space make some nervous about ASPEN. We also address several other areas of uncertainty herein, but ultimately come away with a positive outlook and see good rationale for why brensocatib could succeed. We like the risk/reward since we believe that there is a higher likelihood that INSM will prevail and generate significant value in a second untapped respiratory indication (which is why we made INSM one of our top picks for 2024 here). We estimate an up/down move for the stock of +55%/-35% (**Exhibit 1**) on the ASPEN data announcement. Reiterate Outperform and $50 PT.
- ***Our deep dive continues within...***

Reason for report:

PROPRIETARY INSIGHTS

Key Stats

S&P 500 Health Care Index:	**1,590.37**
Price:	**$30.99**
Price Target:	$50.00
52-Week High – Low:	$32.00 - $16.04
Shares Outstanding (mil):	142.9
Market Capitalization (mil):	4,428.5
Book Value/Share:	$2.02
Cash Per Share:	$(2.55)
Net Debt to Total Capital:	116%
Convertibles:	Yes
Dividend (ann):	$0.00
Dividend Yield:	0.0%

	Dec Yr		
	2022A	2023E	2024E
Q1	$53.1	$65.2A	$79.7
Q2	$65.2	$77.2A	$86.2
Q3	$67.7	$79.1A	$89.5
Q4	$59.3	$80.1	$93.5
FY Rev	$245.4	$301.6	$349.0
Q1	($0.80)	($1.17)A	($1.05)
Q2	($0.80)	($1.78)A	($1.03)
Q3	($1.09)	($1.11)A	($1.02)
Q4	($1.21)	($1.06)	($0.97)
FY EPS	($3.91)	($5.11)	($4.06)
P/E	NM	NM	NM

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Source: Company Information and Leerink Partners LLC Research.
Cash Per Share: Net Cash per Share. Net Debt to Total Capital: Total debt to total capital. General: Net cash and shares outstanding are estimated as of end of 3Q23. GAAP; Revenues in $M.

Please refer to page 37 for Important Disclosures, Price Charts and Analyst Certification.

Main Takeaways from our ASPEN Deep Dive

- **Given the importance of the ASPEN data for INSM, we performed a stress test of the most important factors we believe could influence the results.** While we list several factors that may appear to be important potential negatives, we don't necessarily anticipate that any or all of them will conspire to undermine the outcome of the trial. This exercise is reminiscent of the report we published ahead of positive CONVERT data for Arikayce (CONVERT Preview Explores What Could Go Wrong in Phase 3, but Probably Won't), which struck investors as more cautious, but was intended to serve as a similar exercise and ended up previewing a positive Ph.3 which perfectly replicated the Ph.2 — an outcome we believe could occur again with ASPEN. We continue to believe that brensocatib will likely have a favorable efficacy and safety profile that will enable ASPEN to succeed, but we believe it is worthwhile to interrogate issues that INSM may encounter in this treatment setting and need to navigate in order for a trial as large and spread out around the globe as ASPEN to prevail. Overall, we conclude that despite the mixed WILLOW data, prior failures in the space, and several other areas of uncertainty, we come away with a positive outlook and see solid reasoning for brensocatib's potential success in ASPEN (**Exhibit 2**). We acknowledge that the WILLOW data have raised questions for investors about the lack of dose response and concordance between neutrophil elastase/NE reduction and clinical effect. However, we see plausible rationale for why these inconsistencies occurred in WILLOW and believe on the whole the data are positive and de-risk the brensocatib program. We are encouraged that INSM applied learnings from WILLOW, as well as the historical failures in NCFB, to design ASPEN for success without changing the study design significantly. From our deep dive and conversations with MEDACorp KOLs, it seems to us that INSM is controlling for the most obvious and logical variables that could trip up ASPEN.
- **Heading into ASPEN, we believe the biggest investor debates and determinants of success are (Exhibit 4): (1)** the mechanism of action, **(2)** trial design, **(3)** exacerbation definition, **(4)** baseline characteristics, **(5)** disease heterogeneity, **(6)** placebo response, **(7)** trial sites/size, and **(8)** the blended/blinded event rate. After stress testing each of these dynamics with MEDACorp KOLs, we maintain our positive outlook since while the event is certainly poised to drive a major stock move in either direction, we believe there is a higher likelihood that ASPEN will prevail, thereby derisking one or more blockbuster opportunities that can change the character of the company substantially. NCFB could be a blockbuster (or more) opportunity for brensocatib on its own, and INSM is pursuing other indications such as CRSsNP which may be even larger. This could put the company in the crosshairs of strategic interest from larger biopharma companies, which would make our model estimates conservative. Accordingly, we like the risk/reward at this juncture and see an up/down of +55%/-35% on the readout, making ASPEN one of the biggest catalysts in our coverage universe in 2024.

Thinking About the Setup for the Stock Ahead of ASPEN

- **Why is ASPEN expected to be such a big binary for INSM?** NCFB is a large untapped indication with no approved treatment options. INSM estimates there are ~1.7M-6M patients WW, with ~340K-520K in the US, ~350K-500K in EU5, and ~1M-5M in Asia-Pacific. If we simply assume there are ~425K patients in the US, brensocatib is ~$30K per patient per year, and peak penetration is ~25% of the market, this would mean that brensocatib could be >$3.0B in the US alone

in one indication. For reference, we currently only model the opportunity in the US, with gross peak sales of approx. $1.1B (2033E), driven by a peak penetration of approx. 10%. Perhaps more importantly, NCFB could be a gateway indication whereby positive ASPEN data could allow INSM to pursue even larger indications. The company has already highlighted CRSsNP, a condition with no approved treatments that impacts approx. 26M patients in the US alone (the BiRCh study is also ongoing; NCT06013241), while other potential expansion areas include rheumatoid arthritis, lupus nephritis, and hidradenitis suppurativa. Considering the size of the NCFB opportunity (as well as the expansion optionality), we believe the stock could reach prior highs in our base case and make new highs in our bull case. On the other hand, there have been a handful of failures and/or suspended programs in the space, and the Ph.2 WILLOW data have raised some questions with investors; thus the ASPEN readout is expected to be a major binary event that deserves careful consideration in our view.

- **We think the up/down on the readout is +55%/-35% (Exhibit 1) at either extreme.** Investors have been inquiring about the ASPEN (NCT04594369) study with brensocatib (oral DPP-1) for months ahead of the 2Q24 readout. We anticipate this will be a major catalyst based on the large market brensocatib could address in its lead indication, plus potential expansion indications.
  - In our bull case scenario, we believe shares could trade up 55% or more if we see a statistically significant reduction in pulmonary exacerbations exceeding 35% with either dose. This would imply a market cap. of around $7.0B, which we view as reasonable and potentially conservative since the opportunity for brensocatib in NCFB could be >$3.0B in the US alone based on fairly conservative assumptions (~10% peak penetration).
  - In our most likely base case scenario, we believe that the stock could go up around 30% if we see a statistically significant reduction in pulmonary exacerbations in the range of 25% to 35% with either the 10mg or 25mg dose. This would bring shares up near $40 or so, a level not seen since 2021, and imply a market cap. of just around $6.0B.
  - In our least likely bear case scenario, we believe that the stock could go down around 35% if the pulmonary exacerbation reduction is substantially less than 25% for both doses (or a non-statistically significant outcome). This implies a stock price of ~$20/share, which is around where we believe shares are worth based on Arikayce in refractory NTM alone (and negative net cash). Arikayce is selling well in refractory NTM, where it is on track to hit >$300M in sales for 2023 (here) mostly in the US, and has strong expansion potential in front line NTM in the US and RoW following positive ARISE data. This level attributes no value to front line NTM or anything in the pipeline including TPIP, and it also does not reflect excessive concern for the balance sheet. Hence, the stock could trade higher or lower than this level when ASPEN data are reported depending on potential progress for these programs in the interim and how the market weighs these factors. The floor value could rise ahead of ASPEN (1) if INSM gets the green light from the FDA to file for Accelerated Approval for Arikayce in frontline MAC based on the ARISE data, and/or (2) if the Ph.2 PAH-ILD data are positive (expected in 1H24). Alternatively, the floor value could be lower if there is a heightened focus on the balance sheet in the scenario of negative ASPEN data. INSM ended 3Q23 with cash, cash equivalents, and marketable securities of approx. $786M; however, the company's cash burn gets a fair amount of investor attention

(~$132M in 3Q23) and INSM has approx. $1.15B in long-term debt. The company's current guidance is that the cash on hand can support operations through the ASPEN results in 2Q24, leaving a meaningful amount of cash remaining on the balance sheet at that time. INSM has stated that they are not funded through profitability, and they will need to raise at some point; so if ASPEN data are not positive, investors may assume that the company finds themselves in a pinch without as much financing flexibility.

WILLOW Data Have Raised Some Questions for Investors Ahead of ASPEN

- **Why are the Ph.2 WILLOW data controversial?** When INSM reported WILLOW (NCT03218917) data in February 2020 (here), the stock rallied 41% (vs. 2% XBI). However, the results were not completely consistent, which has made some wary of ASPEN. This includes **(1)** a lack of dose response, **(2)** a lack of perfect concordance between NE reduction and clinical effect, and **(3)** seemingly less benefit in patients who are more severe/varied response in subgroups. Some have also pointed out that **(4)** the time to exacerbation curves separate before one would expect maximal and steady-state effect of the drug to be reached, as well as **(5)** potential safety signals as additional points of potential controversy.
- **(1) There was not a dose response on the rate of pulmonary exacerbations.** WILLOW explored two doses of brensocatib, 10 and 25mg, once daily for 24 weeks. A statistically significant reduction in the rate of pulmonary exacerbations was seen with the 10mg dose (36% reduction; p=0.041), but not with the 25mg dose (25% reduction; p=0.167) (**Exhibit 5**). According to management, there were a handful (~2-3) of hyper exacerbating patients (who had as many as 6 exacerbations in as few as 6 months) in the 25mg dose cohort, which skewed the results. The baseline characteristics further highlight this dynamic, which shows that 41% (n=36) of patients in the 25mg arm had ≥3 exacerbations in the previous 12 months, as compared to 28% (n=23) and 29% (n=25) in the 10mg and placebo arms, respectively. Since past pulmonary exacerbations are believed to be a decent predictor of future exacerbations according to KOLs, we believe that INSM's reasoning is plausible for the lack of dose response. An alternative explanation which has been raised by KOLs is that some NE may be necessary for proper function, and 25mg might produce too much NE inhibition for some patients, whereas 10mg might represent a sweet spot for brensocatib. The rate of exacerbations was a secondary endpoint in the Ph.2, while the primary endpoint was time to first exacerbation (**Exhibit 7**); brensocatib significantly prolonged this over the 24-week period vs. placebo (p=0.027 for the 10mg group; p=0.044 for the 25mg group). The FDA has asked INSM to swap the order of these endpoints for the ASPEN study, so the rate of exacerbations is now the primary endpoint and the time to first exacerbation is now a secondary endpoint.
- **(2) There was a lack of perfect concordance between the degree of NE reduction and clinical effect (Exhibit 5).** Neutrophils are the most common type of white blood cell and play a role in pathogen destruction and inflammatory mediation. In chronic inflammatory lung diseases, neutrophils accumulate in the airways and result in excessive active neutrophil serine proteases/NSPs that cause lung destruction and inflammation. Treatment with brensocatib may decrease the damaging effects of inflammatory diseases by inhibiting DPP1 and its activation of NSPs. While no dose response was seen with the pulmonary exacerbation endpoint, brensocatib showed a dose dependent decrease in NSPs

in WILLOW. Brensocatib similarly inhibited NE activity in a dose dependent fashion in all populations tested. At 4 weeks, the NE activity reduction was 66.5%, 30.9%, and 3.40% in the 25mg, 10mg, and placebo groups, respectively. The dose dependent reductions in NSPs and NE activity are encouraging, though we and investors find the lack of perfect concordance between these reductions and clinical effect (i.e., exacerbations) curious. It seems reasonable to assume that the reduction of NSPs/NEs with brensocatib may lead to lower pulmonary exacerbations, as literature suggests that elevated NE is associated with exacerbation and disease severity (*Chalmers et al., 2017*). However, KOLs have mentioned that there has never been a great correlation between NE and clinical outcomes and are not bothered by the lack of perfect concordance. KOLs note that tissue levels of NE likely differ from plasma levels of NE, and different patients could have different critical thresholds of NE levels in various compartments. Most KOLs we have spoken with believe that the preponderance of science suggests that NE is likely to be a worthwhile therapeutic target in NCFB, and is more than just a biomarker in the disease, but the ASPEN trial is needed to prove this hypothesis. KOLs believe that NCFB patients with more NE activity may be most likely to benefit from NE inhibition, and it is good that the ASPEN trial is targeting patients with 2 or more exacerbations in the past 12 months, because NE activity seems to correlate with exacerbations. That being said, these relationships still need to be proven by ASPEN.

- **(3) When looking at the time to first exacerbation data according to subgroup, it seems like there may be less of a benefit for those with more severe disease.** INSM believes that a randomization imbalance which resulted in a handful of hyper exacerbators being enrolled in the 25mg group may have skewed the results. We think this is a plausible explanation, though we also wonder if this outcome is due to something else, such as brensocatib simply not working as well in those with more severe disease, even though these might be thought to be optimal enrichment targets. The subgroup data available are limited; however, a forest plot of subgroups and their performance on the time to first exacerbation endpoint have been disclosed (**Exhibit 6**). Across several of the subgroups that suggest more severe disease, including ≥3 exacerbations in the previous 12 months, long-term use of macrolides, baseline bronchiectasis severity index score, and hospitalization in the previous 24 months, brensocatib seems to perform worse. Brensocatib also seemed to work best in those with baseline NE concentration in sputum below the lower limit of quantification (0.016 µg per milliliter), which could call into question the merit of NE as a pharmacologic target. We note that the observation of less benefit in sicker patients does not seem to hold for one subgroup (predicted FEV at baseline), though on the whole it might seem that the drug may not perform as well in sicker patients. We do not have access to the individual patient data for those more severe, so it is difficult to know if there is any credence to this hypothesis. However, INSM likely has these results and conducted numerous subgroup analyses on those with severe disease. Thus, if brensocatib did not work or work as well in severe patients, the company would have likely excluded them from enrolling in ASPEN. Some have also pointed to the Eastern Europe subgroup data, which appear better than other geographic regions. However, the confidence interval is large and likely represents a small sample size (~8% of sites). In fact, all of the confidence intervals for the subgroup analysis forest plot of WILLOW data overlap with each other, so it is unclear whether any of the subgroup results truly stand out from the overall results.

- **(4) In WILLOW, the time to exacerbation curves begin to separate before one would expect maximal and steady-state concentrations of the drug to be reached.** Brensocatib was explored in a first-in-human study (*Palmér et al., 2018*) to assess safety, tolerability, pharmacokinetics, and pharmacodynamics. Part I explored five different doses, whereas Part II explored 10, 25, and 40mg. Subjects in the 10mg cohort were dosed for 21 days, while those in the 25 and 40mg cohorts were dosed for 28 days. A clear response to treatment was seen starting around day 12. Dosing was too short to see the maximum effect for the 10mg cohort, though an increase in inhibition was seen with increasing dose. The data suggest that almost a month of treatment is required before steady-state inhibition of whole blood NSP activity (~25 days after initiation of dosing for whole blood NE and NSP activity). Given the approx. month required to reach steady state, it was surprising to see the time to exacerbation curves in WILLOW begin to separate from placebo at an earlier time point than expected (**Exhibit 7**). It is not clear to us what drove this outcome, nor have we heard a rationale from KOLs or INSM. The curves do separate much more at later time points, which gives us some comfort around this observation. We also note that this endpoint does have some limitations, as it is unclear that delaying the time to first exacerbation over 24 weeks translates into a clinically meaningful benefit for a patient population that would be on chronic therapy, which further limits the concern, in our view. This was a topic previously discussed during an Antimicrobial Drugs Advisory Committee/AdCom meeting in 2018, as well as at an FDA public workshop for inhaled antibacterial drugs for cystic fibrosis and NCFB. Thus, we acknowledge that the seemingly earlier-than-expected benefit on the time to exacerbation with brensocatib is curious, though there are limitations with this endpoint, which is not the primary in ASPEN, thus we feel comfortable with this dynamic.
- **(5) WILLOW showed modest skin and dental safety signals, which makes some nervous about a longer study (Exhibit 7).** As brensocatib is a DPP1 inhibitor, skin- and dental-related AEs are of special interest. This is a dynamic informed by patients with Papillon-Lefèvre syndrome/PLS, which is a rare autosomal recessive disease characterized by mutations of the DPP1 gene and near-complete loss of DPP1 function and NSP activity. PLS patients typically suffer from palmoplantar hyperkeratosis (excessive epidermal thickening of the palms and soles) and periodontitis (gingival inflammation). Moreover, GSK2793660, an irreversible DPP1 inhibitor previously showed epidermal desquamation on palmar and plantar surfaces and was subsequently terminated (*Miller et al., 2017*). In the Ph.1 first-in-human study, there were a total of six skin findings of special interest, five of which were in those treated with brensocatib, and four were seen in the highest dose group (40mg). Regarding dental signals, a few subjects reported mild gingival bleeding, though these events typically did not occur spontaneously, but due to probing of the gingiva. Exclusion criteria in WILLOW were structured to avoid those with severe periodontal disease and patients underwent dental assessment at baseline and at weeks 8 and 24. In WILLOW, 24% (n=21), 15% (n=12), and 12% (n=10) of patients experienced a skin adverse event in the 25mg, 10mg, and placebo groups, respectively. A dental event was experienced by 10% (n=9), 16% (n=13), and 4% (n=3) of those in the 25mg, 10mg, and placebo groups, respectively. None of these events were considered to be a serious AE, though these signals still make some investors nervous. We also note that the fourth Data Safety and Monitoring Board/DSMB was held in May 2023, where it was recommended that the ASPEN study continue as planned. Given that

brensocatib has demonstrated a manageable safety profile in both the first-in-human and Ph.2 studies, as well as the fact that it is a reversible inhibitor of DPP1 (unlike GSK2793660) and there are strategies in place to minimize enrollment of potentially at risk patients, we remain comfortable with the safety profile.

Graveyard of Failed NCFB Agents Deserves Attention

- **The laundry list of agents that either failed in trials or were dinged by the FDA does not provide comfort, though we think brensocatib is better positioned for success.** There are currently no approved therapies for NCFB, but this is not as a result of a lack of prior attempts, since many have failed in trials, been suspended or been denied approval by the FDA. Some investors have pointed to this dynamic as a negative for INSM and while we acknowledge the failures in the space do not provide comfort, we also believe the company has learned from these examples and think brensocatib is better positioned for success (especially as it is not an inhaled therapy, unlike many of the prior failures). On the other hand, we also note that those failed therapies produced enough evidence in a Ph.2 study to support the movement to a pivotal trial, similar to WILLOW. As discussed below, several of the notable failures include **(1)** Bayer AG's (BAYN, Not Rated) ciprofloxacin dry powder for inhalation/DP, **(2)** Aradigm's (Not Rated) inhaled liposomal ciprofloxacin, **(3)** Gilead's (GILD, MP, Graybosch) aztreonam, and **(4)** Pharmaxis' (PXS, Not Rated) inhaled mannitol.
- **Bayer's ciprofloxacin DPI showed mixed data and was given a CRL.** Ciprofloxacin DPI is an inhaled antibiotic consisting of capsules containing 32.5 mg ciprofloxacin inhalation powder, with drug delivered by a pocket-sized inhaler. Bayer ran two Ph.3 trials of the same design, known as RESPIRE 1 (NCT01764841) and RESPIRE 2 (NCT02106832). Two regimens were examined over a 48-week treatment period; twice-daily ciprofloxacin DPI 32.5mg for 28 days on/off treatment or 14 days on/off treatment. The primary endpoint in RESPIRE 1 was the time to first exacerbation event (*De Soyza et al., 2018*). The 28-day on/off regiment had no significant effect on either time to exacerbation or frequency of exacerbation. However, the 14-day regiment significantly delayed the time to the first exacerbation (p=0.0005). Similarly, the 14-day regiment significantly reduced the frequency of exacerbations (39% reduction; p=0.0061), while this was not significant for the 28-day regiment. The mean number of exacerbations during the study was lower than the number of exacerbations in the prior year. The publication notes that the determination of exacerbations in the prior year likely varied among centers, as at the time there was considerable heterogeneity in how this was defined. Moreover, the definition of exacerbation for eligibility relied on clinical judgment, rather than specific criteria. As for RESPIRE 2, the primary endpoints were the time to first exacerbation and frequency of exacerbations (*Aksamit et al., 2018*). The time to first exacerbation endpoint was not reached with statistical significance for either regiment, while only the 28-day regiment hit the frequency of exacerbation endpoint (45% reduction; p=0.0014). Exacerbation rates were much lower than expected and lower than those observed in RESPIRE 1. Moreover, while the primary diagnosis of COPD was an exclusion criterion, 28% of those enrolled had a history of COPD (vs. 16% in RESPIRE 1). Regarding trial enrollment, RESPIRE 2 enrolled more patients from Asia and Eastern Europe, with variability in clinical practice potentially impacting the determination of exacerbation and treatment prior to study enrollment. An AdCom later voted against approval for both regiments and the drug later received a CRL. The

experience with the RESPIRE studies emphasizes the importance of exacerbation definition, both for inclusion criteria and the endpoint for the study.

- **Aradigm's inhaled liposomal ciprofloxacin also showed mixed data, with the FDA eventually dinging the therapy with a CRL.** ARD-3150 is a once-daily inhaled antibiotic composed of liposome-encapsulated ciprofloxacin and free ciprofloxacin. The therapy was explored in two identical Ph.3 trials; ORBIT-3 (NCT01515007) and ORBIT-4 (NCT02104245). Treatment or placebo was administered once daily for six 56-day treatment cycles for 48 weeks. Treatment over 48 weeks was associated with a reduction in the frequency of exacerbations compared with placebo in ORBIT-4, but not in ORBIT-3. ORBIT-4 showed an approx. 37% reduction (p=0.0006), while the reduction was approx. 15% in ORBIT-3 (p=0.26). A similarly mixed result was seen for the time to first exacerbation endpoint (p=0.032 for ORBIT-4 and p=0.97 for ORBIT-3). The statistical analysis plan called for stratified analyses; however, some strata were found to have no or very few subjects, and both stratified and non-stratified analyses were conducted (primary endpoint of median time to first exacerbation was not significant in either trial when stratified). In the publication of these data (*Haworth et al., 2019*), the authors conclude that the time to first exacerbation endpoint might not be a reliable outcome measure, especially within the setting of chronic disease with the potential for frequent exacerbations (similarly discussed at the AdCom for the therapy). The publication also lists an imbalance in chronic macrolide use between arms (and lack of stratification for baseline macrolides), as well as a lower-than-expected number of exacerbations during the treatment period for placebo patients as study limitations. An AdCom later voted against approval and ARD-3150 later received a CRL. The ARD-3150 story highlights the importance of controlling what you can (e.g., stratification), picking the right endpoint that can show treatment benefit, and enrolling the right patients.
- **Deja vu yet? Gilead's aztreonam also showed mixed data in two pivotal trials and the program was canned.** Aztreonam inhalation solution (also known as Cayston) is an antipseudomonal antibiotic formulated for inhalation; it is approved for the improvement of respiratory symptoms in CF. The therapy was evaluated in two identical Ph.3 studies, AIR-BX1 (NCT01313624) and AIR-BX2 (NCT01314716). Each study included two 4-week courses of double-blind inhalation treatment (aztreonam 75mg or placebo) given three times a day, followed by 4 weeks off treatment. Unlike other studies that focused on the exacerbation rate or delay, the primary endpoint was the change from baseline in Quality of Life-Bronchiectasis Respiratory Symptoms scores (QOL-B-RSS) at 4 weeks (*Barker et al., 2014*). QOL-B-RSS numerically increased in all groups in both studies at weeks 4 and 12, though the differences were not statistically significant at weeks 4 or 12 in AIR-BX1 or week 12 in AIR-BX2; the difference at week 4 was significant but not clinically meaningful. The risk of development of the first exacerbation was not statistically different between treatment groups in both studies. The publication of these data notes that some unsuccessful aerosolized antibiotic trials in NCFB used doses optimized for cystic fibrosis, while airway intolerance may obscure clinical benefits. Stratification of patients, airway clearance techniques for inhaled antibiotics, and overlap with other lung diseases were also listed as possible factors in the study result. Given the mixed results, GILD discontinued further development of the program. This outcome further highlights the importance of study duration, as well as endpoint selection.

- **Pharmaxis' inhaled mannitol missed the exacerbation rate endpoint though hit on the time to first exacerbation.** Mannitol is a naturally occurring sugar alcohol that improves mucus clearance when inhaled, likely by drawing water into the airway lumen by osmotic gradient. 400mg inhaled mannitol or low-dose mannitol control twice daily were evaluated for 52 weeks in a Ph.3 study (NCT00669331). The primary endpoint was the exacerbation rate, while the time to first exacerbation was a secondary endpoint (*Bilton et al., 2014*). The annual rate of exacerbations in the mannitol and control arms were 1.69 and 18.4, respectively; the rate ratio was 0.92 and not statistically significant (p=0.31). Time to first exacerbation was longer in the mannitol arm (165 days vs. 124 days with control), which was significant (p=0.021). This study allowed for the end of an exacerbation to be immediately followed by another one. The impact of varying the definition of the end of an exacerbation on the overall exacerbation rate was demonstrated by a post hoc exploration of separating events by a 2-week period (rate ratio 0.88, p=0.086). This could potentially explain the improvement in time to the first exacerbation despite a lack of effect on the rate. These results underscore the importance of separating exacerbation events in a clinical trial. Fortunately, in the WILLOW study, any exacerbation that occurred less than 4 weeks from the prior exacerbation was not considered a new exacerbation.

Looking at Both Sides of the Bull/Bear Debate for ASPEN

- **After digging deeper into brensocatib, NCFB, ASPEN, and conducting several KOL calls, we have identified a handful of key debates that we believe are worth highlighting ahead of the readout in 2Q24; we ultimately come away with a positive view and see rationale for why brensocatib could be successful.** In addition to the mixed Ph.2 WILLOW data and the multiple prior failures in NCFB, we see several key investor debates ahead of ASPEN, including **(1)** the mechanism of action, **(2)** trial design, **(3)** exacerbation definition, **(4)** baseline characteristics, **(5)** disease heterogeneity, **(6)** placebo response, **(7)** trial sites/size, and **(8)** the blended/blinded event rate. As outlined below, we acknowledge that there are multiple bull/bear arguments to be made for most of these topics, though we ultimately came away with a positive view overall and believe there is a higher likelihood that INSM could prevail in ASPEN.

(1) Mechanism of Action

- **Brensocatib's unique targeted mechanism of action positions it better for success, as compared to the numerous failures in the space, in our view (Exhibit 8).** Brensocatib is an oral, selective, and reversible inhibitor of DPP1. This is a differentiated treatment approach as compared to many of the therapies previously explored in NCFB, many of which were inhaled antibiotics. Brensocatib's direct mechanism of action is to reduce NSPs in circulating neutrophils. Recall, in chronic inflammatory lung diseases, neutrophils accumulate in the airways and result in excessive active NSPs that cause lung destruction and inflammation. The three main NSPs include neutrophil elastase (NE), proteinase 3 (PR3), and cathepsin G (CatG). In WILLOW, brensocatib showed a consistent and dose dependent reduction across all three main NSPs (**Exhibit 5**). This is in direct contrast to other NE specific inhibitors that have failed to achieve their primary endpoint in cystic fibrosis, NCFB, and chronic obstructive pulmonary disease, despite NE being associated with worsening disease (*Polverino et al., 2017*). One possible explanation for this outcome is that the NE specific inhibitors may be challenged in achieving adequate local inhibition near the neutrophils in the lung

and cannot stop the extracellular release of high concentrations of NE before they affect tissue damage. Thus, the failure of specific NE inhibitors, combined with the positive WILLOW data suggest that the inhibition of NE, PR3, and CatG (as well as inhibition prior to extracellular release) may be required for efficacy in NCFB. This remains to be seen in ASPEN, though we view the mechanism of action favorably and see the logic of it working in this disease, as it did in WILLOW.

- **KOLs unanimously view brensocatib's approach favorably.** We spoke with a handful of pulmonologists to get a better understanding of how brensocatib could address NCFB, given what is known about the disease. Encouragingly, all KOLs that we spoke to view the approach favorably, as there is evidence that links NE and the severity of NCFB (as well as increased NE when people exacerbate), and that "*all roads lead back to the neutrophil*", which increases our confidence ahead of ASPEN. NCFB is characterized by the dilation of the bronchial tree, caused by the destruction of structural components of the bronchial wall, resulting from a cycle of infection and inflammation (*Stockley et al., 2013*). We know that neutrophils play a key role in the inflammation in NCFB; however, we have also wondered how a therapy such as brensocatib can benefit NCFB patients who have a disease which is characterized by a structural derangement of hyperdilated bronchi, which appears as a major factor alongside neutrophils. However, while the KOLs noted that while there is certainly some mechanical aspect to exacerbations, and brensocatib can not necessarily be expected to address this structural component of the disease, they do not think that the structural manifestations of the disease are what is driving most of the sequelae. Rather, NCFB has more to do with increased mucous secretion stimulated by NE, which then leads to subsequent infection, inflammation, and a repeat of the vicious cycle. So while targeting NE may not promote reverse remodeling by making bronchial tubes regain their normal morphology, this is not what is driving most of the problems NCFB patients experience, leading up to exacerbations, according to this KOL. KOLs believe that the holy grail would be an intervention that could stop structural damage before it occurs, although they see a role for an agent which is able to calm neutrophils and view this as the best target we currently have.
- **What about the safety signals seen with DPP1 inhibition?** As outlined above, skin- and dental-related adverse events are of special interest for brensocatib, given clinical manifestations seen in patients with PLS (near-complete loss of DPP1 function), as well as prior signals experienced with GSK2793660. We acknowledge that these signals are worth watching for in the ASPEN study; however, we remain comfortable with the overall safety profile and are not all that concerned with the mechanism. Brensocatib has demonstrated a manageable safety profile in the prior studies, the fourth DSMB was held in May 2023 and recommended that ASPEN continue as planned, and there are strategies in place to minimize the enrollment of potentially at-risk patients. Moreover, brensocatib is a reversible inhibitor of DPP1 (refers to the covalent interaction, see literature here), whereas GSK2793660 was an irreversible inhibitor, which may have played a role in the safety signals seen, though this is unknown and purely speculation.

(2) Trial Design:

- **WILLOW and ASPEN are nearly identical in design, while the powering was increased such that a smaller treatment effect could still be statistically significant (Exhibit 9).** The WILLOW study enrolled 256 patients (≥18 years old) and was 80% powered for an approx. 40% reduction in exacerbations.

Meanwhile, ASPEN enrolled almost 1,800 patients (≥12 years old) and has more than 90% power to show a 30% reduction in exacerbations. Management noted that statistical power will be achieved all the way into the low-20s in terms of having a statistically significant outcome. This is within the threshold of what is considered to be clinically meaningful, though management does not anticipate being in that range. We note that if this were the case for WILLOW, the 25mg dose may have likely hit statistical significance (25% reduction; p=0.167). When speaking about the design, management has noted that they "*changed as little as possible from Ph.2 to Ph.3*". Both the 10 and 25mg doses are being evaluated, the inclusion-exclusion criteria are largely the same, the definition of exacerbation remains unchanged, and the primary endpoint was a secondary in WILLOW. ASPEN includes patients who are under the age of 18 (≥12 years old); however, this was driven by a pediatric regulatory requirement and will not be related to the analysis for the main study. Management recently noted that they "*... think the trial's really well-designed to at least what we can anticipate and what we've learned from studying all the other trials and WILLOW on how to manage that... I don't think the trial's going to let down the drug. And we do only need just that one dose, one dose to hit, and we're good.*" (November 2023). Given WILLOW was a well-sized study (>250 patients) that produced positive results, we are encouraged that INSM changed as little as possible between the Ph.2 and pivotal. Moreover, we believe that the increase in power for a smaller treatment effect was a prudent move, especially given the much larger study and risk of a placebo response, as discussed in more detail below.

- **A 12-month study better positions ASPEN for success, in our view.** WILLOW was only 24 weeks in duration, whereas ASPEN is approx. double the length with a 52-week treatment period. We know that the duration of treatment is important, especially as brensocatib takes a bit of time to reach steady state (~1 month), as well as from the experiences with other trials in the space. In WILLOW (**Exhibit 7**) the treatment arms separated from the control arm more overtime, suggesting that a longer duration of treatment could show additional benefits with brensocatib. Moreover, according to several KOLs, a predictor of pulmonary exacerbation is having a history of pulmonary exacerbations, so the longer treatment period should allow more opportunity for these events. The majority of patients in WILLOW (50%+) treated with brensocatib had zero pulmonary exacerbations at month six. Additionally, as noted above, the larger (and longer) trial should help smooth out the data. Seasonality sometimes plays a role in exacerbations, when patients encounter environmental triggers at certain times of the year, so a 12-month study such as ASPEN should be inherently less prone to imbalances than a 6-month trial such as WILLOW. We do not know whether there were any imbalances in seasonally-induced exacerbations in WILLOW, or if they hurt or helped the brensocatib arms, but we believe the 12-month duration of ASPEN is less likely to face potential confounding from seasonality.
- **WILLOW missed the exacerbation endpoint for one dose, so what gives us confidence in a positive outcome in ASPEN?** As outlined above, a statistically significant reduction in the rate of pulmonary exacerbations was seen with the 10mg dose in WILLOW (36% reduction; p=0.041), but not with the 25mg dose (25% reduction; p=0.167). As WILLOW and ASPEN are similarly designed, some have pointed to the lack of significance with the higher dose as a point of concern (i.e., could we see the same outcome in ASPEN?). We do not think there is any merit to this concern, as INSM has previously explained what potentially drove

the statistical miss in WILLOW (hyper exacerbators) and the power has been increased in ASPEN for a smaller treatment effect (to a level where the 25mg arm may have reached statistical significance in the Ph.2). Finally, as management noted above, only one dose needs to hit. Net-net, WILLOW was a successful study, and we are encouraged that ASPEN has been similarly designed.

(3) Exacerbation Definition:

- **Exacerbations will always be inherently subjective to some degree, so it is critical that the definition be clearly established and consistently applied in order to limit variability in the trial, especially given how heterogeneous NCFB patients are (Exhibit 10) and globally ranging ASPEN is.** As we have seen in prior studies (specifically RESPIRE 1), the definition of an exacerbation is a very important consideration for successful trials in NCFB. At the time RESPIRE 1 was conducted (started in 2013), there were varying definitions of exacerbations in clinical practice, which may have influenced patients' eligibility for the trial. Moreover, the exacerbation definition for eligibility relied on clinical judgment, rather than specific criteria, so that the determination of exacerbations in the prior year likely varied among centers and potentially played a role in the mixed study outcome. On the other hand, the endpoint definition was defined using more specific criteria. These factors likely contributed to the lower-than-expected number of on-trial exacerbations in RESPIRE 1 (another dynamic we discuss below) and the authors encourage investigators of future studies to utilize a rigorous definition for exacerbations qualifying as entry criteria. Given NCFB patients are already known to be heterogeneous, combined with potential heterogeneity in the definition of an exacerbation, this is a point of potential concern ahead of ASPEN. This is a dynamic that may be heightened by a larger study across multiple geographies with varying clinical practices.
- **The brensocatib studies utilize more stringent definitions for enrollment and the endpoint.** Patients enrolling in WILLOW were required to have at least 2 documented pulmonary exacerbations in the past 12 months before screening, defined by the need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections. During the study, exacerbations were defined according to modified consensus criteria as the presence of at least three of the following symptoms for at least 48 hours that results in a physician's decision to prescribe an antibiotic agent: increased cough, increased sputum volume or change in sputum consistency, increased sputum purulence, increased breathlessness or decreased exercise tolerance, fatigue or malaise, and hemoptysis. Severe exacerbations were those that led to hospitalization. As for ASPEN, the trial also requires at least 2 documented exacerbations, with the same definition as WILLOW (need for antibiotic prescription). The clinical trial listing for ASPEN does not explicitly define exacerbation for the endpoint, though we assume it is the same as WILLOW. For ASPEN, we are encouraged that the inclusion criteria for an exacerbation is more rigorous, while the endpoint definition utilizes very specific criteria. However, we still believe that the definition of exacerbation could be subject to some variability, especially as these patients are known to be heterogeneous. Additionally, it should also be noted that each physician is treating patients with both placebo and brensocatib, which should minimize between-physician differences in prescribing tendencies, if any.

(4) Baseline Characteristics:

- **Baseline characteristics between WILLOW and ASPEN match up well (Exhibit 11).** One of the unknowns, as one moves from a Ph.2 to a larger Ph.3 trial, is that you could have a different patient profile, especially as ASPEN is being conducted across almost 400 sites in nearly 40 countries. However, earlier in 2023 INSM disclosed baseline characteristics for ASPEN, which show a nice overlap with the prior study. Management noted that they can look at a country level for how many patients were being enrolled, as well as what the characteristics are for that country. This was done on a regular weekly basis to make sure that the behavior ongoing is not unexpected. Thus, management feels "*...extremely confident that the performance of the patients in the study will be not dissimilar to what was seen in the WILLOW study*" (2Q23 earnings). Depending on if you are a bull or a bear, the similar baseline patient characteristics could be viewed positively (i.e., Ph.3 results could end up being more like the 10mg dose arm in Ph.2) or negatively (i.e., Ph.3 results could end up more like 25mg dose arm in Ph.3). We end up on the positive side of this debate and believe that the larger trial should smooth out the data by attenuating extremes and sway results to look more like the Ph.2 10mg cohort when we look at the data in totality. Moreover, given the heterogeneous nature of the disease, as discussed more below, we are encouraged that ASPEN includes a lower percentage of patients with a history of COPD as secondary (16.4% and 14.3% in WILLOW and ASPEN, respectively) or a history of asthma as secondary (25.0% and 17.9% in WILOW and ASPEN, respectively). ASPEN also has an incrementally lower percentage of patients who have ≥3 exacerbations, which could also be considered a positive, especially given the WILLOW data (25mg arm) were skewed due to hyper exacerbators.

(5) Disease Heterogeneity:

- **NCFB is widely considered to be a heterogeneous disease and heterogeneity is a common confounder of clinical trial outcomes (Exhibit 12).** NCFB is characterized by abnormal and permanent dilatation of the bronchi, which are associated with specific clinical manifestations, including cough, sputum production, recurrent respiratory infections, and general malaise (*Amati et al., 2019*). Most cases of the disease are considered to be idiopathic or post-infective; however, it can also be a complication that arises from several other heterogeneous disorders, such as COPD, asthma, inflammatory bowel disease, etc. (*McDonnell et al., 2017*). Moreover, in autoimmune diseases such as rheumatoid arthritis, it is difficult to know if bronchiectasis is part of the disease process, or if it is due to pulmonary infection in an immunocompromised host. We are encouraged that INSM has already demonstrated that they can be adept at navigating development challenges presented by heterogeneous lung conditions, as evidenced by their recent success in the ARISE trial (here) which greatly exceeded expectations in frontline NTM which is also very heterogeneous. In addition, we are encouraged that KOLs do not consider any of these patient groups to be any more challenging than any others. Hence, while INSM has provided limited information on the nature of the patients in WILLOW (nor did the company collect etiology information), we believe disease heterogeneity may not be a major problem for ASPEN. As noted before, the forest plot data suggest that brensocatib may not work as well in those with more severe disease; however, we still do not have great visibility into this dynamic. Patients' response to brensocatib based on underlying disease or severity remains a little bit of an open question as we head into the ASPEN readout, but when we asked management about the disease heterogeneity, they suggested that a response was seen across a

spectrum of patients regardless of their background (COPD, asthma, prior smoker, etc.) so we believe this may not be a problem for ASPEN either.

- **We spoke with KOLs extensively about disease heterogeneity, who assured us that it would not be a problem.** As one reads papers on NCFB and the prior failures in the space, the topic of heterogeneity is front and center. Moreover, as we know from prior experience in other diseases and study readouts, heterogeneity can be one of the more difficult dynamics to overcome in a successful trial, thus we probed several KOLs on the topic. While the physicians agreed that NCFB is a heterogeneous disease, they all also appeared to be generally unconcerned with the dynamic in ASPEN. One physician mentioned that following several of the failures in the space and as our understanding of NCFB improves, there has been a movement to try and include patients who match a phenotype that is likely to respond to what you are testing (movement away from FEV towards exacerbations). Moreover, another KOL noted that while there are many etiologies of NCFB, the pathway of the disease remains similar, with unchecked neutrophilic inflammation and airway damage. Another physician mentioned that many of these etiologies eventually converge, especially as patients get sicker (i.e., more exacerbations). Thus, as long as you rule out other causes of inflammation and exclude patients with COPD, asthma, cystic fibrosis, etc., there is no other way to run these studies (until science advances to a higher level). As outlined above, NCFB can also present in conjunction with autoimmune diseases, though one KOL noted that these patients are not more challenging (or easy) to deal with. Net-net, we acknowledge that disease heterogeneity is an unknown factor for ASPEN, though we have incrementally more comfort with the dynamic after speaking with KOLs, as it is clear that INSM is doing what they can to enroll patients who are likely to benefit from brensocatib.

(6) Placebo Response:

- **Placebo response and/or a lower-than-expected overall rate of exacerbations could influence the outcome in ASPEN (Exhibit 13).** As we have previously seen in several of the failures across the space, the mean number of exacerbations in the clinical trial setting is often lower than the number of exacerbations expected. This is in contrast to KOL comments that past rates of exacerbations are believed to be a decent predictor of future exacerbations. However, participation in clinical studies is known to influence patient behavior, especially as those who opt for a clinical trial may be more motivated, combined with potentially more careful (or frequent) care by physicians in a study setting (which is especially important for NCFB, as care is often provided by those without deep expertise in the disease). In an NCFB clinical trial setting, patients could be more compliant with airway clearance of other activities which are known to have an effect. Moreover, a KOL mentioned to us that we could also see a regression toward the mean for some patients in a study setting. As ASPEN requires at least 2 exacerbations in the past 12 months, a patient who has historically only had one or two exacerbations for a decade, but then altered their behavior and experiences a second or third exacerbation in the past 12 months, could be enrolled. However, it is then likely the exacerbation rate for this patient could regress towards the mean (i.e., 1 exacerbation in this example), especially in a clinical study setting. This is a dynamic that we have also seen in the prior WILLOW study. Patients were required to have at least 2 exacerbations in the past 12 months; however, those randomized to the placebo arm showed 1.37 exacerbations per person per year, which is slightly lower than the 2 per year required for enrollment. With

placebo patients potentially performing better in the study than they traditionally do in the real world, this introduces some risk to ASPEN, as this could make it harder to show a statistically significant difference between placebo and brensocatib.

- **Several factors provide us with some comfort around the placebo response dynamic.** First, one of the KOLs that we spoke to mentioned that INSM helped to create the bronchiectasis patient registry in the US, which is where many of the patients enrolled in ASPEN presumably come from (at least in the US with ~18% of trial sites here). In our view, this adds another layer of checks and balances to ensure that the population enrolled in ASPEN has been well-defined and is likely already receiving top-notch care from physicians who are involved in the patient registry. To us, it seems reasonable to assume that their placebo response in a clinical study could be lower than the average patient, as they are likely already receiving high-quality care from their physician, which may not change much between the real world and the clinical study. However, we acknowledge that this could remain an issue outside of the US, which makes up the bulk of the study sites (>80%) if INSM is not careful about site selection and patient referral patterns. Second, since regression towards the mean would not be expected to favor one arm or the other, the effect should theoretically be a wash and it should not influence the treatment effect, even though it could impact absolute numbers. Third, as discussed more below, we know that the blended/blinded event rate in ASPEN was 1.12 to 1.15 over the last 3 months (as of January 6, 2023), which could suggest that brensocatib is having a drug effect. Moreover, INSM conservatively assumes an exacerbation rate of 1.2 events per year (the same as WILLOW). Lastly, even if there is a placebo effect in ASPEN, we remain optimistic as the study is highly powered (90%) for a smaller treatment effect (vs. WILLOW). The Ph.2 study was not as well powered (80%) and still showed statistically significant results, thus we know brensocatib has a real drug effect.

(7) Trial Size/Sites:

- **ASPEN is much larger than WILLOW and is being conducted at many more trial sites (and in more countries), which could also influence heterogeneity (Exhibit 14).** The Ph.2 WILLOW study was conducted across a total of 106 clinical sites, 36 (34%) of which were in the US, while the remaining 70 (66%) were ex-US. Moreover, WILLOW included sites from 13 countries, including the US. Meanwhile, ASPEN includes 379 sites, 70 (18%) of which are in the US, while the remaining 309 (82%) are ex-US. Moreover, ASPEN includes sites from 36 countries, including the US. This implies that there are 23 new countries included in ASPEN (64% of the overall geographies) as well as 273 new sites (72% of the overall sites). Our analysis based on the trial site zip codes suggests that ASPEN includes incrementally more Eastern European countries (~13%), as well as new countries in Latin America (~15%), though ~18% of the sites remain in the US (down from ~34% in WILLOW). Given that NCFB is already a heterogeneous disease, we think the large expansion from Ph.2 to Ph.3 could introduce some additional heterogeneity, especially with the potential for differing treatment patterns across geographies (including the level of overall care), as well as different smoking patterns, particularly in Eastern Europe. Recall, in the forest plot data discussed above, brensocatib performed much better in Eastern Europe, though the confidence interval is large and likely represents a small sample size (~8% of sites were in Eastern Europe in WILLOW). One of the KOLs that we spoke to also mentioned that there may be more post-infective cases of NCFB in Latin America, with less effective treatment (and higher frequency) of

pneumonia, tuberculosis, etc. Another physician noted that pollution and climate could also play a role across different geographies. Additionally, we do not have data from many of these geographies in WILLOW as they are new for the Ph.3, so it is difficult to know how patients in these countries may behave in a clinical study setting, which is a major unknown heading into the ASPEN readout.

- **Similar to the KOLs view on heterogeneity, they are not overly concerned about geographic differences.** We asked several physicians what they think about the larger size of ASPEN and how it could influence the outcome. One KOL referenced the inclusion criteria of the trial, noting that with the requirement of 2 or more exacerbations to enroll, the patients should generally be similar across geographies (similar to their viewpoint on heterogeneity). Another physician mentioned that it is possible that treatment patterns could be slightly different across geographies, including airway clearance strategies, though they were not concerned as this could be smoothed out by the randomization schema of the study. Moreover, they noted that differences across geographies may be more of a factor for studies in cystic fibrosis and COPD; however, NCFB develops over many years, and it is thought that the end pathway is similar wherever you are. Thus, it should not be affected by seasonal changes month to month or other geographic factors and the KOL does not have concerns that this will be a major issue for ASPEN. While it is possible that new countries and sites in ASPEN could introduce variability or additional heterogeneity, we believe that having more sites, including those in Eastern Europe and Latin America, could help smooth out the data. Additionally, we know from the baseline characteristics and the blended/blinded event rate (more on this below) that the patients in ASPEN look generally comparable to WILLOW, which gives us increased comfort with this dynamic.

(8) Blended/Blinded Event Rate:

- **The blended/blinded event rate in ASPEN is slightly lower than WILLOW, but still within the range of what we have seen previously (Exhibit 15).** In the Ph.2 study, the placebo group demonstrated 1.37 events per patient per year, as compared to 0.88 and 1.03 for the 10 and 25mg groups, respectively. The placebo event rate was higher than the assumed exacerbation rate of 1.2 events per patient per year (the same assumption is made for ASPEN), though lower than the inclusion criteria of at least 2 exacerbations in the past 12 months. As for the Ph.3, the company previously disclosed that the blended and blinded event rate was 1.12 to 1.15 over the last 3 months (as of January 6, 2023); INSM has not provided an updated blended/blinded rate to our knowledge (it was provided at JPM '23, so we could get an updated figure at JPM '24, though this remains to be seen). Depending on whether you are a bull or a bear, the lower blended/blinded event rate could be looked at favorably or unfavorably. On one hand, the lower event rate could suggest that brensocatib is having a drug effect. On the other hand, ASPEN has been executed during the pandemic and post-pandemic period (dosing began in December 2020), so it is feasible that patients' quarantining and social distancing behavior during the trial could be driving a lower overall rate of events, which is something we know has been a headwind for prior studies. However, INSM said that they have been enrolling patients with at least 2 exacerbations in the last 12 months during the pandemic (enrollment occurred between December 2020 and April 2023), so these patients are reliable exacerbators even after taking pandemic precautions into consideration, which likely enriched the patient population, in our view. We also note that the blinded/blinded event rate for ASPEN is still roughly comparable to what was seen in

WILLOW, which further highlights that similar patients were enrolled across both studies. Thus, we remain comfortable with the lower event rate even after accounting for the quarantining precautions.

INVESTMENT THESIS

We believe INSM shares are poised to appreciate as the company commercializes Arikayce in patients with refractory nontuberculous mycobacterial (NTM) lung disease caused by mycobacterium avium complex (MAC). While we believe that Arikayce is the primary driver of INSM shares, brensocatib (non-cystic fibrosis bronchiectasis) and treprostinil palmitil inhalation powder/TPIP (pulmonary arterial hypertension/PAH) could further bolster INSM's valuation. Following these 3 programs, Arikayce aims to expand into non-pulmonary indications that could diversify the company's portfolio.

VALUATION

We estimate a risk-adjusted per share price target for INSM of $50 in 12 months. We value INSM based on discounted cash flow analysis which uses a 10% discount rate and a 2% terminal growth rate.

RISKS TO VALUATION

Risks include the potential for disappointing clinical data, regulatory setbacks, failure to obtain intellectual property protection abroad, and commercial shortfalls. Since INSM is presently unprofitable and only has one commercial product, any of the possible aforementioned setbacks may impact the stock significantly.

Exhibit 1. We Estimate Up/Down of +55%/-35% on the ASPEN Readout in 2Q24

	Bull	Base	Bear
Frequency of Pulmonary Exacerbation (either dose)	Statistically Significant	Statistically Significant	Not Statistically Significant
Magnitude of Pulmonary Exacerbation Reduction (either dose)	>35%	25-35% Reduction	<25% Reduction
Safety	Generally Well Tolerated	Generally Well Tolerated	Not Well Tolerated
Stock Up/Down	Up 55%+	Up 30%	Down 35%
Scenario Probability	30%	50%	20%

Pivotal Phase 3 ASPEN data for brensocatib in 2Q24 has the potential to be one of biggest catalysts in our coverage universe this year. We see an up/down of +55%/-35% on the readout.

- In our **Bull Case**, we think shares could trade up 55% or more if we see a statistically significant pulmonary exacerbation reduction exceeding 35% (with either dose). This would imply a market cap. of around $7.0B, which we view as a reasonable valuation, especially as the opportunity in non-cystic fibrosis bronchiectasis could be >$3.0B in the US alone.
- In our **Base Case**, which we believe is the most likely, we think the stock could go up around 30% if we see a statistically significant pulmonary exacerbation reduction in the 25% to 35% range (with either dose). This would bring shares up to the low $40s, a level not seen in several years (early 2021) and imply a market cap. of just around ~$6.0B.
- In our **Bear Case**, which we view as least likely, we believe the stock could go down around 35% if we see a pulmonary exacerbation reduction that is less than 25% with both doses. This would imply a stock price of around $20/share, which is what we believe shares are worth on the basis of Arikayce (refectory MAC) alone and neg. net cash (see **Exhibit 3**).

What does the exacerbation delta mean? As we previously outlined (Deep Dive on INS1007; Bronchiectasis - Ain't Nobody Got Time For That), a 20% delta could translate to a number need to treat/NNT ≤ 3, which means for every 3 patients treated over a year, adding brensocatib could prevent 1 additional exacerbation. This is better than AZN's (OP, Berens) Daliresp in COPD, which showed an NNT of 5. Thus, the 25-35% reduction in our base case could translate to an even better NNT (< 3).

Source: Leerink Partners Research

Exhibit 2. Key Takeaways From Our ASPEN Preview and Deep Dive

Key Takeaways

Non-cystic fibrosis bronchiectasis is a large indication with no approved treatments. INSM estimates that there are ~1.7M-6M diagnosed patients worldwide (~340K-520K in the US, ~350K-500K in the EU5, and ~1M-5M in Asia-Pacific).

- Positive data in non-cystic fibrosis bronchiectasis could potentially unlock several other even larger markets, including chronic rhinosinusitis without nasal polyposis/CRSsNP, where management estimates there are ~26M patients in the US alone. Other potential areas of expansion include rheumatoid arthritis, lupus nephritis, and hidradenitis suppurativa.

We have been getting numerous inbounds on ASPEN, months ahead of when data are expected. We think the up/down on the results could be +55%/-35%, making it one of the biggest catalysts in our coverage universe in 2024.

- We like the risk/reward for ASPEN given the greater probability for a win and the magnitude of the potential opportunity in NCFB (plus potential expansion indications which could drive additional upside).
- In our Bull Case, we think shares could trade up 55% or more if we see a statistically significant pulmonary exacerbation reduction exceeding 35% (with either dose). This would imply a market cap. of around $7.0B, which we view as a reasonable valuation, especially as the opportunity in non-cystic fibrosis bronchiectasis could be >$3.0B in the US alone.

Despite some questionable features of the WILLOW data, prior failures in the space, and some minor other areas of uncertainty, we come away with a positive outlook and see good potential for brensocatib to succeed in ASPEN.

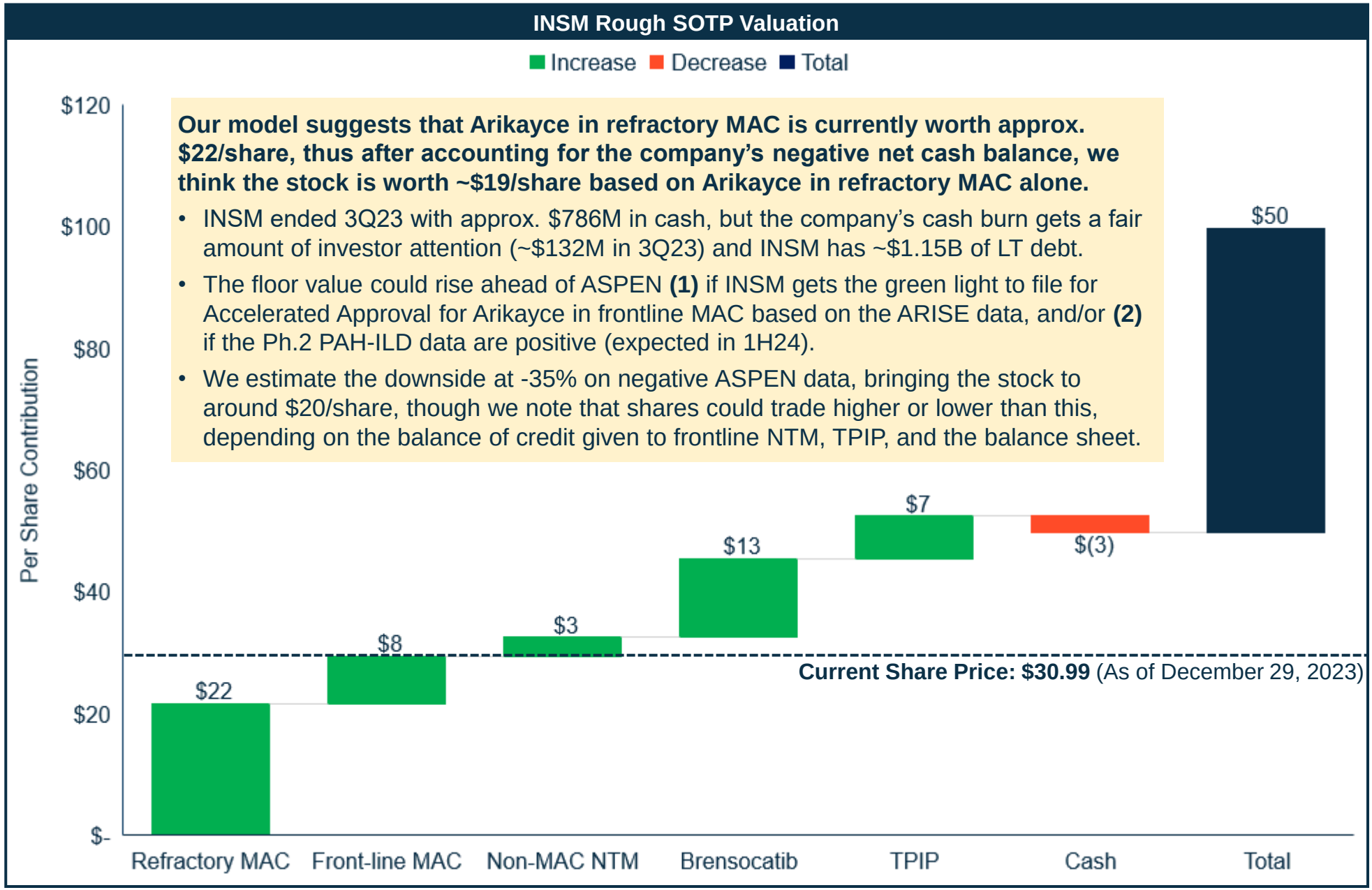
- We acknowledge that the WILLOW data raised some questions given the **(1)** lack of dose response and **(2)** concordance between neutrophil elastase/NE reduction and clinical effect. However, we see plausible rationale for why we saw inconsistencies in WILLOW and believe the data are positive on the whole and de-risk the brensocatib program.
- The company applied learnings from WILLOW, as well as the several historical failures in the non-cystic fibrosis bronchiectasis space to design ASPEN for success. In our deep dive and conversations with MEDACorp KOLs, it is apparent to us that INSM is controlling for the most obvious and logical variables that could trip up ASPEN.

After digging deeper into brensocatib, NCFB, ASPEN, and conducting several KOL calls, we identified a handful of key debates that we believe are worth highlighting ahead of the ASPEN readout in 2Q24.

- These include **(1)** the mechanism of action, **(2)** trial design, **(3)** exacerbation definition, **(4)** baseline characteristics, **(5)** disease heterogeneity, **(6)** placebo response, **(7)** trial sites/size, and **(8)** the blended/blinded event rate. As outlined within, we acknowledge that there are multiple bull/bear arguments to be made for most of these topics, though we ultimately came away with a positive view overall and believe there is a higher likelihood that INSM could prevail with ASPEN.

Source: Leerink Partners Research

Exhibit 3. INSM is Worth ~$19 on Arikayce in Refractory MAC Plus Neg. Net Cash



Source: Leerink Partners Research

Exhibit 4. Looking at Either Side of the Bull/Bear Debate on Key ASPEN Topics

Overview of Key Debates and Summary of our Thoughts	
1. Mechanism of Action	Bull View: Unique MoA positions brensocatib for success, which is differentiated vs. failed inhaled therapies. KOLs like the mechanism, which targets all three NSPs (NE, PR3, and CatG).
	Bear View: Targeting neutrophils will not repair the damaged lung structure in NCFB, and previously DPP1 inhibition has shown safety signals including skin and dental findings (i.e., GSK2793660).
2. Trial Design	Bull View: WILLOW & ASPEN are similar in design, while the longer duration (approx. 2x of WILLOW) and increased power (90%) for a smaller treatment effect (30%) are positives for ASPEN.
	Bear View: WILLOW missed on the exacerbation endpoint & similarly designed ASPEN could too.
3. Exacerbation Definition	Bull View: To enroll in ASPEN, the study leverages inclusion criteria for an exacerbation that are more rigorous (e.g., need for antibiotics), while the study endpoint definition uses specific criteria.
	Bear View: The definition of exacerbation could still experience variability, adding to heterogeneity.
4. Baseline Characteristics	Bull View: ASPEN baseline characteristics are very similar to WILLOW, which was a positive study.
	Bear View: Baseline characteristics of patients in ASPEN are similar to WILLOW, thus ASPEN results could look more like the 25mg cohort in the Ph.2, which missed statistical significance.
5. Disease Heterogeneity	Bull View: Pathway of the disease is similar regardless of etiology, which is thought to converge when patients get sicker. INSM is doing what they can to enroll the right patients that will benefit.
	Bear View: NCFB is a very heterogenous disease with many different etiologies. Thus, it remains to be seen how patients respond to brensocatib treatment based on underlying disease or severity.
6. Placebo Response	Bull View: This dynamic would impact both arms and ASPEN is highly powered for a smaller effect.
	Bear View: Those enrolled in clinical studies could experience lower-than-expected exacerbations.
7. Trial Sites/Size	Bull View: NCFB's end pathway is similar regardless of location and baseline study data are similar.
	Bear View: The increase in sites/geographies in ASPEN could introduce additional heterogeneity
8. Blended/Blinded Event Rate	Bull View: The lower blended/blinded event rate suggests that brensocatib is having a drug effect.
	Bear View: The lower blended/blinded event rate suggests lower-than-expected exacerbations.

Source: Leerink Partners Research

Exhibit 5. No Exacerbation Dose Response & Disconcordant NE vs. Clinical Data

#1 WILLOW Controversy: Lack of Dose Response

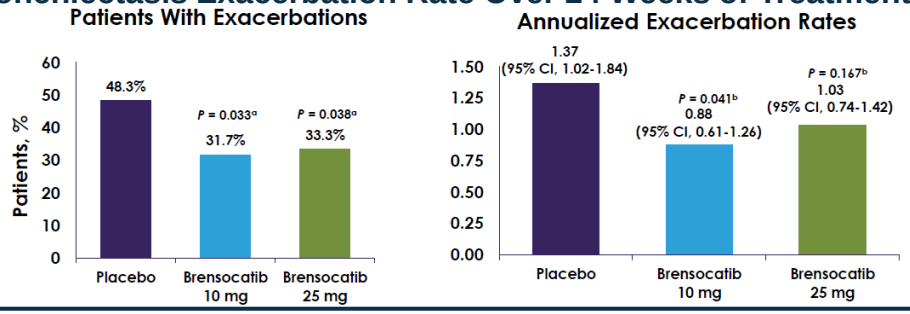
A statistically significant reduction in the rate of pulmonary exacerbations (secondary endpoint) was seen at the 10mg dose (36% reduction; p=0.041), but not at the 25mg dose (25% reduction; p=0.167).

There were a handful of hyper exacerbating patients in the 25mg dose cohort, which skewed the results. Baseline characteristics illustrate this dynamic, by showing that 41% (n=36) of patients in the 25mg arm had ≥3 exacerbations in the previous 12 months, as compared to 28% (n=23) and 29% (n=25) in the 10mg and placebo arms, respectively.

Rate of Pulmonary Exacerbations – Secondary Endpoint

Frequency of Pulmonary Exacerbations	Brensocatib 10mg (n=82)	Brensocatib 25mg (n=87)
Reduction vs. Placebo	36%	25%
P-Value	0.041	0.167

Bronchiectasis Exacerbation Rate Over 24 Weeks of Treatment

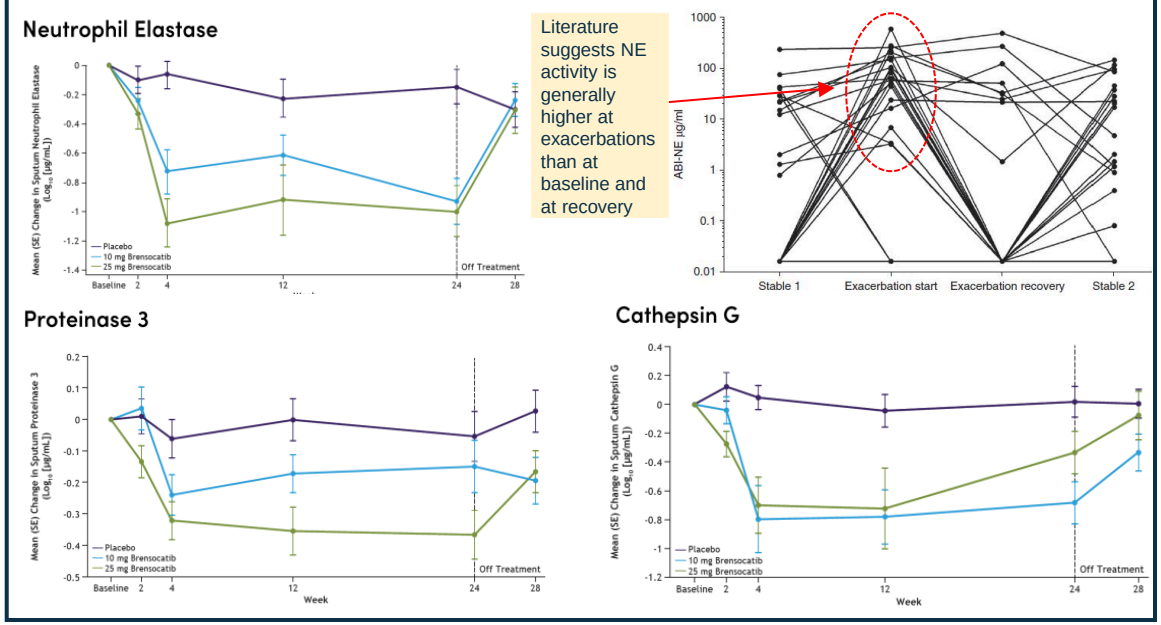


#2 WILLOW Controversy: Lack of Concordance Between NE and Clinical Effect

While no dose response was seen for exacerbations, brensocatib did show a dose dependent reduction in NSPs in WILLOW. At 4 weeks, the NE activity reduction was 66.5%, 30.9%, and 3.40% in the 25mg, 10mg, and placebo groups, respectively.

We find the lack of concordance between these reductions and clinical effect curious, especially as literature suggests that elevated NE is generally associated with exacerbation and disease severity. However, KOLs have mentioned that there has never been a perfect correlation.

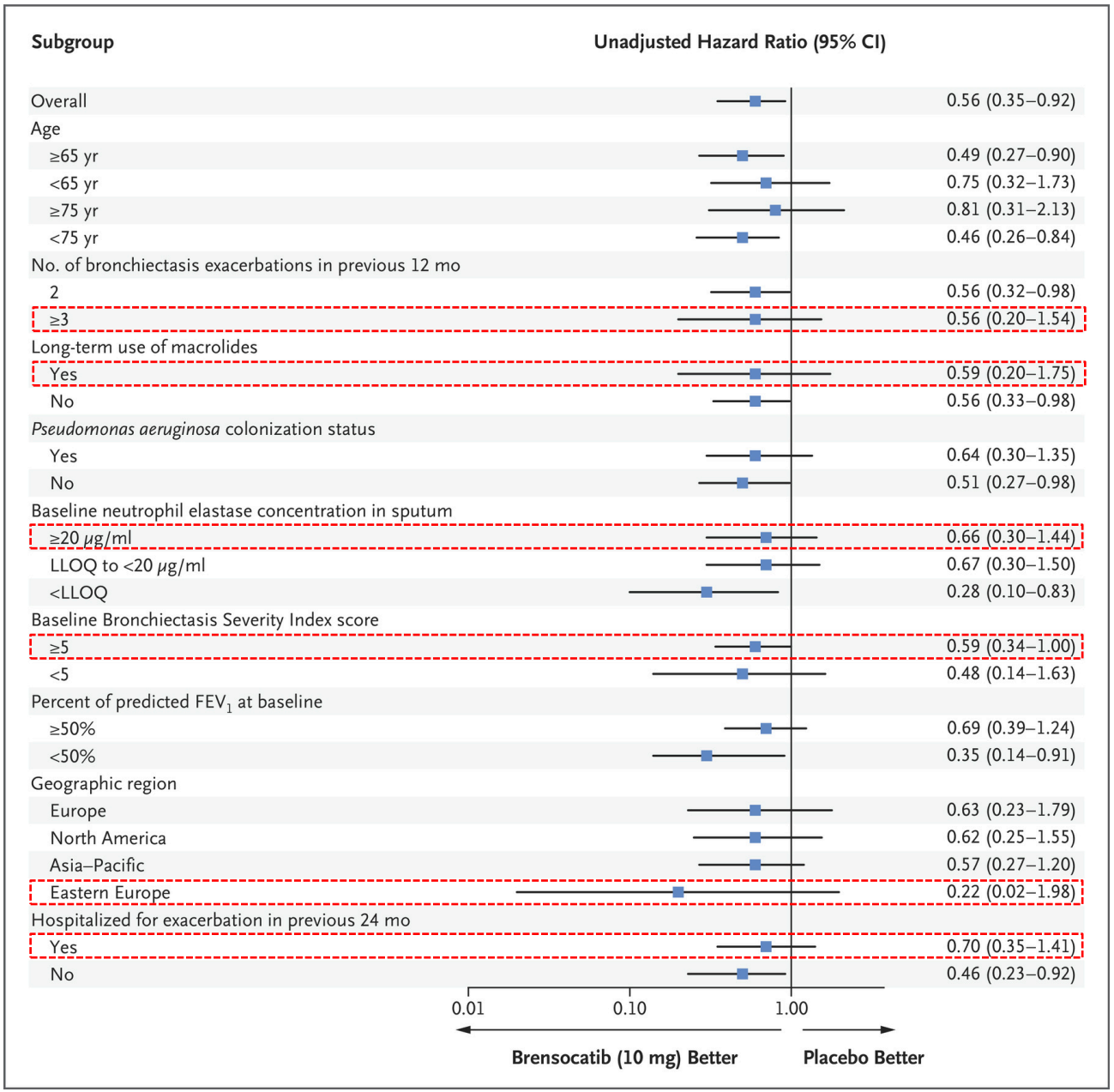
What Did WILLOW Show for NSP Reduction & What Can We Learn From Literature?



Source: Leerink Partners Research, ATS 2020 Presentation, INSM Corporate Presentation, *Chalmers et al., 2017*

ª Cochran-Mantel-Haenszel test, *P* values vs placebo; ᵇ Negative binomial model, *P* values for incidence rate ratio vs placebo.

Exhibit 6. Subgroups in WILLOW Highlight Response Ranges Across Patients



#3 WILLOW Controversy: Less Benefit in Severe Patients

- When looking at the time to first exacerbation data according to subgroups, it seems like there may be less of a benefit for those with more severe disease.
- Across subgroups suggestive of more severe disease, including ≥3 exacerbations in the previous 12 months, long-term use of macrolides, baseline BSI score, and hospitalization in the previous 24 months, brensocatib seems to perform slightly worse.
- This dynamic does not seem to hold for one subgroup (predicted FEV at baseline), though overall it still seems that the drug may not perform as well in sicker patients.
- Moreover, data collected in Eastern Europe stands out to us. While the overall results favor brensocatib, data presented at ERS International 2020 suggest this was not the case for the 25mg dose. We take a closer look at the study sites and geography in **Exhibit 14** to see how this may influence ASPEN.

Source: Leerink Partners Research, *Chalmers et al., 2020*

Exhibit 7. Early Separation for Time to Exacerbation & Safety Spark Some Debate

#4 WILLOW Controversy: Time to Exacerbation Curves Separate Before One Would Expect

A first-in-human study suggests that almost a month of treatment is required before steady-state inhibition of whole blood NSP activity (~25 days after initiation of dosing for whole blood NE and NSP activity).

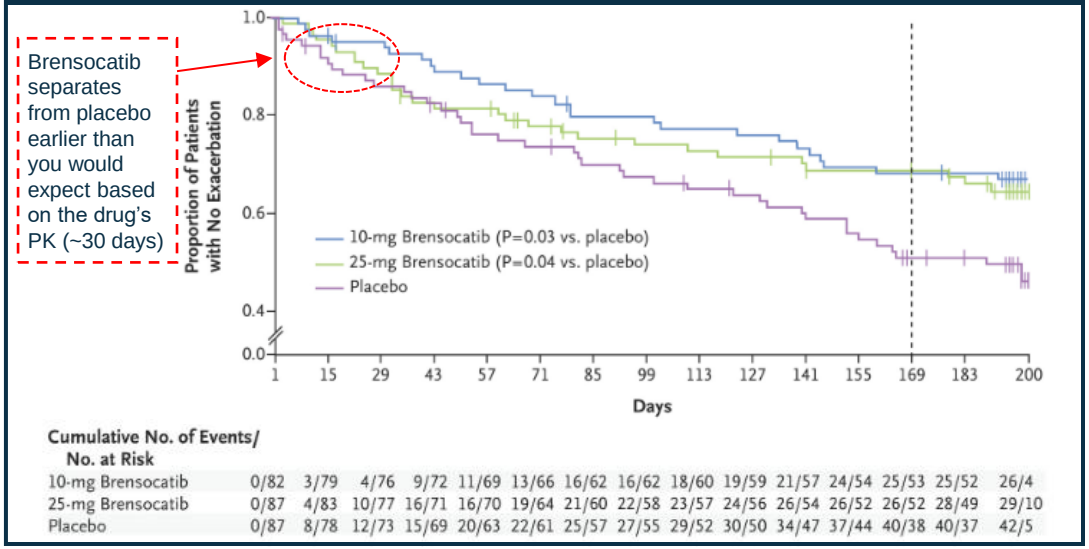
Given the approx. month required to reach steady state for brensocatib, it was surprising to see the time to exacerbation curves in WILLOW begin to separate from placebo at an earlier timepoint than expected. However, the curves separate much more at later time points and there are limitations with this endpoint.

#5 WILLOW Controversy: Skin & Dental Safety Signals with DPP1 Inhibition

Brensocatib is a DPP1 inhibitor, thus skin and dental-related AEs are of special interest. This is a dynamic informed by patients with PLS, a disease characterized by near-complete loss of DPP1 function and NSP activity. PLS patients typically suffer from palmoplantar hyperkeratosis and periodontitis.

Brensocatib has shown a handful of these signals in the Ph.1 and Ph.2 trials thus far. Exclusion criteria were structured to avoid those who may be at risk (periodontal disease). Moreover, the fourth DSMB was held in May 2023, where it was recommended that the ASPEN study continue as planned.

Time To Exacerbation Curves – WILLOW Primary Endpoint



WILLOW Safety

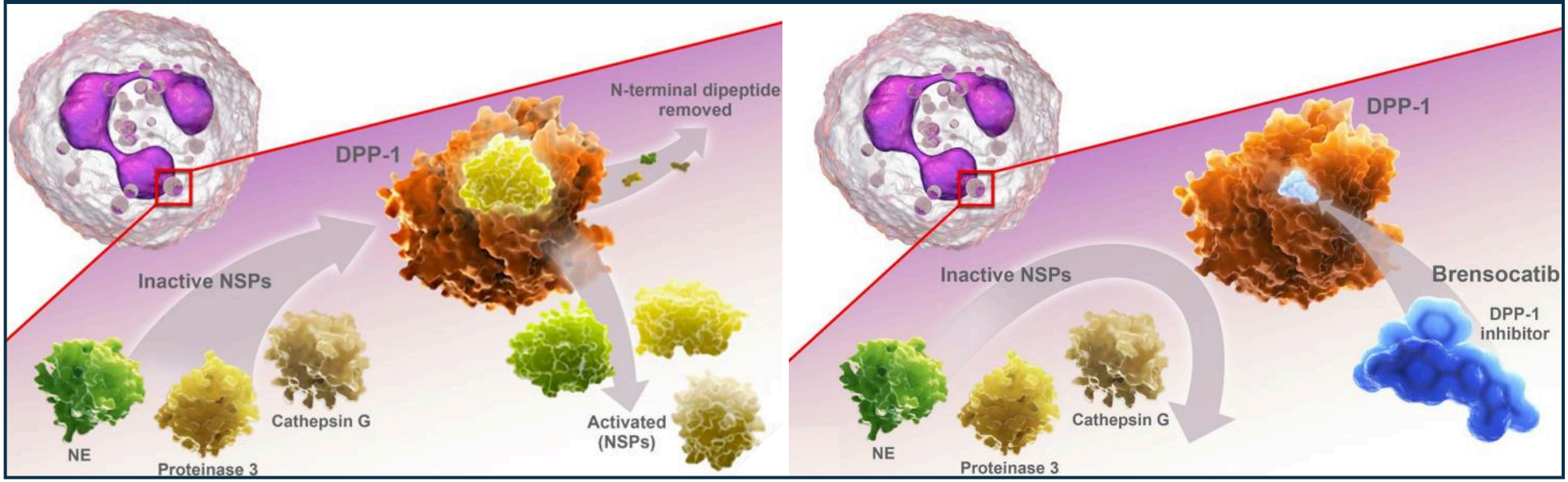
	Placebo	10mg	25mg
Rates of AEs Leading to Discontinuation	10.6%	7.4%	6.7%
Rates of Adverse Events of Special Interest (AESIs)			
Periodontal Disease	2.4%	7.4%	10.1%
Hyperkeratosis	0%	3.7%	1.1%
Infections Considered AESIs	18.8%	16.0%	16.9%

Previously, GSK2793660, an oral **irreversible** DPP1 inhibitor showed epidermal desquamation on palmar and plantar surfaces in a Ph.1 study in healthy volunteers and was subsequently terminated (*Miller et al., 2017*). 7/10 patients receiving GSK2793660 showed these signals (which lasted for several weeks) beginning 7-10 days after dosing commencement.

Source: Leerink Partners Research, *Chalmers et al., 2020*, *Palmér et al., 2018*, *Miller et al., 2017*

Exhibit 8. Brensocatib's MoA Makes Sense to Us & KOLs, But Some Qs Remain

Brensocatib's Mechanism of Action Targets DPP1



Despite many failures in the NCFB space (many of which were inhaled antibiotics), we think brensocatib's unique mechanism of action better positions it for success in the ASPEN study.

- Brensocatib's direct mechanism of action is to reduce NSPs in circulating neutrophils. In chronic inflammatory lung diseases, neutrophils accumulate in the airways and result in excessive active NSPs that cause lung destruction and inflammation. The three main NSPs include neutrophil elastase (NE), proteinase 3 (PR3), and cathepsin G (CatG).
- In WILLOW, brensocatib showed a consistent and dose dependent reduction across all three main NSPs. This is in contrast with other NE specific inhibitors that have failed to achieve their primary endpoint in cystic fibrosis, NCFB, and chronic obstructive pulmonary disease, despite NE being associated with worsening disease (*Polverino et al., 2017*).
- KOLs with whom we have spoken unanimously view brensocatib's approach favorably, based on evidence linking NE to the severity of NCFB (as well as increased NE when people exacerbate), such that "*all roads lead back to the neutrophil.*"

- One debate has been on the safety signals with DPP1 inhibition (i.e., skin- and dental-related), as clinical manifestations have been seen in patients with PLS (near-complete loss of DPP1 function), as well as prior signals experienced with GSK2793660. **Brensocatib has shown a manageable safety profile so far and several DSMBs have been held.**

Source: Leerink Partners Research, INSM Corporate Presentation, *Polverino et al., 2017*

Exhibit 9. Trial Design is Similar; Will Significant Outcome w/ 10mg be Repeated?

	Ph.2 WILLOW	Ph.3 ASPEN
Sample Size	256	>1,700
N in the Placebo Arm	87	≥540
N in the 10mg Dose Cohort	82	≥540
N in the 25mg Dose Cohort	87	≥540
Number of Sites	116	~380
Number of Countries	14	~36
Age Inclusion Criteria	18- to 85-year-olds	18- to 85-year-olds*
Exacerbation Inclusion Criteria	≥2 in previous 12 months	≥2 in previous 12 months
Exacerbation Definition for Inclusion	Need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 months before screening	Need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 months before screening
Primary Endpoint	Time to First Exacerbation	Rate of Pulmonary Exacerbation
Secondary Endpoint	Rate of Pulmonary Exacerbation	Time to First Exacerbation
Duration of Therapy	24 Weeks	52 Weeks
Power	80% for a 40% reduction	90% for a 30% reduction
Mean Exacerbation Rate	1.37 (actual) 1.2 (planned)	1.12 – 1.15 (blended and blinded) over the last 3 months as of 01/06/2023

INSM changed as little as possible between Ph.2 and Ph.3. Since WILLOW was a well-sized study (>250 patients) that produced positive results, we are encouraged by this dynamic. Moreover, **ASPEN has more stat. power (90%) for a smaller effect and is longer in duration**.

As the trials are similarly designed, some have pointed to the lack of significance for the higher dose as a point of concern (i.e., could we see the same outcome in ASPEN?). **We are not as concerned, since we believe INSM's explanation of baseline imbalances has merit.**

Source: Leerink Partners Research, ATS 2020 Presentation, INSM Corporate Presentation

*Study will include children as young as 12 years old per FDA pediatric requirement but will not be part of the main analysis. Only patients ≥18-year-olds will be enrolled and analyzed as part of the main study.

Exhibit 10. Rigorous Definitions are Used, But Variability Could Still be a Factor

As we have seen in prior studies (specifically RESPIRE), the definition of an exacerbation is a very important consideration for successful trials in NCFB. There can be varying definitions of exacerbations in clinical practice, which can have an impact on who is included in a trial and then on the exacerbation rate seen in the actual study.

WILLOW and ASPEN both utilize the same robust definition for pulmonary exacerbations for trial inclusion:

- **Pulmonary Exacerbation Inclusion Criteria for WILLOW:** ≥2 documented exacerbations defined by need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 months before screening.
- **Pulmonary Exacerbation Inclusion Criteria for ASPEN: :** ≥2 documented exacerbations defined by need for antibiotic prescription by a physician for the signs and symptoms of respiratory infections in the past 12 months before screening.

Similarly, both studies define a pulmonary exacerbation (for the endpoint) with stringent criteria:

- **Primary Endpoint Definition of Pulmonary Exacerbation in WILLOW:** Exacerbations were defined according to modified consensus criteria as the presence of at least three of the following symptoms for at least 48 hours that resulted in a physician's decision to prescribe an antibiotic agent: increased cough, increased sputum volume or change in sputum consistency, increased sputum purulence, increased breathlessness or decreased exercise tolerance, fatigue or malaise, and hemoptysis. Severe exacerbations were those that led to hospitalization (*Chalmers et al., 2020*).
- **Primary Endpoint Definition of Pulmonary Exacerbation in ASPEN:** The clinical trial listing does not explicitly define exacerbation for the endpoint in ASPEN, but we assume it is the same as WILLOW (above).

- Failures have highlighted that there are varying definitions of an exacerbation across geographies and clinical practices, which has likely influenced patients' eligibility for clinical trials. Some definitions also relied on clinical judgement, rather than specific criteria, thus the determination of exacerbations for inclusion may vary among study centers.
- As NCFB patients are already known to be heterogenous (as discussed more later), combined with potential heterogeneity in the definition of an exacerbation, this dynamic has become a point of potential concern for ASPEN.

For ASPEN, we are encouraged that the inclusion criteria for an exacerbation is more rigorous, while the endpoint definition likely utilizes very specific criteria. Additionally, each physician is treating patients with both placebo and brensocatib, which should minimize between-physician differences in prescribing tendencies, if any.

Source: Leerink Partners Research, Clinicaltrials.gov, *Chalmers et al., 2020*

Exhibit 11. Baseline Characteristics Are Similar Between ASPEN and WILLOW

Characteristics	Ph.2 WILLOW	Ph.3 ASPEN*
Number of Patients	256	1,682**
Mean Age (Years)	64.1	61.3
≥75 Years (N, %)	48, 18%	262, 15.6%
Female (N, %)	174, 67.9%	1,089, 64.7%
Number of Patients with History of COPD as Secondary*** (N, %)	42, 16.4%	241, 14.3%
Number of Patients with History of Asthma as Secondary*** (N, %)	64, 25%	302, 17.9%
Pseudomonas Aeruginosa Positive (N,%)	89, 34.8%	589, 35.0%
Chronic Macrolide Use (N, %)	40, 15.6%	285, 16.9%
≥3 Exacerbations in Prior 12 Months (N, %)	84, 32.8%	492, 29.3%
2 Exacerbations in Prior 12 Months (N, %)	172, 67.2%	1,190, 70.7%

One of the unknowns, when moving from a Ph.2 to a larger Ph.3 trial, is that there could be a different patient profile. However, earlier in 2023 INSM disclosed baseline characteristics for ASPEN, which show a nice overlap with the prior WILLOW study. **Management feels *"...extremely confident that the performance of the patients in the study will be not dissimilar to what was seen in the WILLOW study*" (2Q23 Earnings).**

The similar baseline patient characteristics could be viewed negatively (i.e., Ph.3 results could end up more like 25mg dose arm in Ph.2). A statistically significant reduction in the rate of pulmonary exacerbations was not seen with the 25mg dose (25% reduction; p=0.167) in WILLOW. **We are not as concerned since we believe INSM's explanation about baseline imbalances in WILLOW is plausible and potentially controllable in ASPEN.**

Source: Leerink Partners Research, INSM Corporate Presentation, 2Q23 Earnings Transcript

*Represents Preliminary Figures
**Evaluable Adult Patients
***As Reported by Medical History

Exhibit 12. NCFB Has Many Etiologies & is Heterogenous, But KOLs Not Worried

Breakdown of Etiologies of Bronchiectasis (Based on Recent Systematic Review)		
Risk Factors	**Total Number of Patients**	**Percentage of Total**
Idiopathic Bronchiectasis	3,857	44.8%
Postinfective Bronchiectasis	2,574	29.9%
Immunodeficiency	429	5.0%
Chronic Obstructive Pulmonary Disease	333	3.9%
Connective Tissue Disease	328	3.8%
Allergic Bronchopulmonary Aspergillosis	223	2.6%
Ciliary Dysfunction	218	2.5%
Asthma	120	1.4%
Inflammatory bowel disease	66	0.8%
Obstructive	67	0.8%
Aspiration/Gastro-Oesophageal Reflux	64	0.7%
Congenital Malformation	33	0.4%
α1-Antitrypsin Deficiency	36	0.4%
Diffuse Panbronchiolitis	27	0.3%
Young's Syndrome	26	0.3%
Pink's Disease	20	0.2%
Yellow Nail Syndrome	11	0.1%
Others	224	2.6%

When asked about heterogeneity, management pointed to the response seen across a spectrum of patients regardless of their background. Moreover, in our conversations with KOLs, they agreed that NCFB is heterogeneous; however, appeared generally unconcerned with this dynamic, noting that trials try to enroll those who match a phenotype that is likely to respond and **while there are many etiologies, the pathway of the disease remains similar (many etiologies also converge with severity).**

NCFB is a heterogenous disease with many different underlying etiologies. INSM has not provided a wealth of information on this topic in WILLOW (nor did the company collect etiology information). Thus, patients' response to brensocatib based on underlying disease or severity remains a key question as we head into the ASPEN readout. **We acknowledge that disease heterogeneity is an unknown factor, though it seems that INSM is doing what they can to enroll patients who are likely to benefit from brensocatib treatment.**

Source: Leerink Partners Research, *Chalmers et al., 2018*

Exhibit 13. Placebo Response Could be a Factor, But ASPEN is Well Powered

As we have previously seen in several of the failures across the space, the mean number of exacerbations in the clinical trial setting is often lower than the number of exacerbations expected, which introduces some risk to ASPEN.

- KOLs have mentioned that past exacerbations are believed to be a predictor of future exacerbations; however, this can be influenced by participation in trials. Those who opt for a clinical trial may be more motivated, combined with potentially more careful (or frequent) care by physicians in a study setting (which is especially important for NCFB, as care is often provided by those without deep expertise in the disease). This may make it harder it more show a statistically significant difference between placebo and brensocatib.
- Another KOL also mentioned that you could also see a regression toward the mean for some patients in a study setting. A patient may experience ~1 exacerbation each year for a decade or more, but then temporarily alters their behavior, triggering another attack in the same 12 months, thus making them eligible for enrollment in ASPEN. However, it is then likely the exacerbation rate for this patient could regress towards the mean (i.e., 1 exacerbation in this example), especially in a clinical study setting.
- This dynamic was seen in WILLOW. Patients were required to have ≥2 exacerbations in the past 12 months; however, those randomized to placebo showed 1.37 exacerbations per person/year, which is slightly lower than the 2 per year required for enrollment.

Despite the potential risk for placebo response, there are several dynamics that provide us with comfort:	
1.	INSM helped to create the bronchiectasis patient registry in the US, which is where many of the patients enrolled in ASPEN presumably come from (~18% of trial sites). This adds another layer of checks and balances to ensure that the population enrolled in ASPEN has been well-defined and likely already receiving top notch care from physicians who are involved in the patient registry (which hypothetically could lower their placebo response as they already receiving top care prior to study entry).
2.	As the regression towards the mean dynamic does not favor one arm or the other, this should theoretically be a wash and should not influence the treatment effect in ASPEN. However, it could influence the absolute numbers for exacerbations.
3.	The blended/blinded event rate in ASPEN was 1.12 to 1.15 over the last 3 months (as of January 6, 2023), which could suggest that brensocatib is having a drug effect. Moreover, INSM conservatively assumes an exacerbation rate of 1.2 events per year.
4.	Even if there is a placebo effect in ASPEN, we remain optimistic as the study is highly powered (90%) for a smaller treatment effect versus WILLOW (40% exacerbation reduction vs. 30% exacerbation reduction). The Ph.2 study was not as well powered (80%) and still showed statistically significant results (with the 10mg dose), thus we know brensocatib has a real drug effect.

Given placebo response and/or a lower-than-expected exacerbation rate has been an issue in prior studies, we believe this dynamic introduces some risk to ASPEN as well. Patients typically perform better in clinical trials and the blended/blinded event rate for ASPEN is lower-than-expected, based on the exacerbations required for study entry, which could make it harder to show a statistically significant difference. **However, as outlined above, there are several factors that provide us with comfort regarding this dynamic in ASPEN.**

Source: Leerink Partners Research

Exhibit 14. Larger Study Footprint and More Sites Could Introduce Variability

Region		Total Ph.2 Sites	Total Ph.3 Sites	Ph.2 Sites Only	Ph.3 Sites Only	Ph.2 and Ph.3 Sites Overlapping	Ph.2 Sites Overlapping with Ph.3 Sites	Ph.3 Sites Overlapping with Ph.2 Sites
Trial Sites	WW	106	379	50	323	56	53%	15%
	US	36 (34%)	70 (18%)	14	48	22	61%	31%
	Ex-US	70 (66%)	309 (82%)	36	275	34	49%	11%

Region		Ph.2	Ph.3	Ph.3 Overlapping with Ph.2
Countries	Total Number of Countries WW	13	36	33%
	Total Number of Countries Ex-US	12	35	31%
Trial Sites	Total Number of Sites WW	106	379	15%
	Total Number of Sites US	36	70	31%
	Total Number of Sites Ex-US	70	309	11%
Eastern Europe	% of EE Countries Rep. WW	15%	17%	--
	% of EE Sites Rep. WW	8%	13%	--
	EE Countries	2	6	33%
	EE Sites	8	48	4%

The Ph.3 ASPEN study is much larger than the Ph.2 WILLOW trial and is being conducted at many more trial sites (and in more countries), which could also influence heterogeneity.

- WILLOW was conducted across a total of 106 clinical sites, 36 (34%) of which were in the US, while the remaining 70 (66%) were ex-US. ASPEN includes 379 sites, 70 (18%) of which are in the US, while the remaining 309 (82%) are ex-US. WILLOW included 13 countries, while ASPEN spans 36 countries. **This implies that there are 23 new countries included in ASPEN (64% of the overall geographies) as well as 273 new sites (72% of the overall sites).**
- Our analysis based on the trial site zip codes suggests that ASPEN includes incrementally more Eastern European countries (~13%), as well as new countries in Latin America (~15%), though ~18% of the sites remain in the US (down from ~34% in the Ph.2 WILLOW trial).

Given that NCFB is already a heterogeneous disease, the expansion from Ph.2 to Ph.3 could introduce some additional heterogeneity, especially with the potential for differing treatment patterns across geographies (including the level of overall care), as well as different smoking patterns, particularly in Eastern Europe. Moreover, pollution and climate could also play a role across different geographies. **However, similar to KOLs view on heterogeneity, those that we spoke to are not concerned with geographic differences. NCFB develops over years, and it is thought that the end pathway is similar wherever you are. Moreover, we know from baseline characteristics that patients are roughly similar between studies, so we have increased comfort with this dynamic.**

Source: Leerink Partners Research, *Chalmers et al., 2020*, Clinicaltrials.gov

Cross comparison by zip code was conducted from sites that were pulled from clinicaltrials.gov. For site listings with zip codes recorded more than once, we assumed the second site was a unique site and recorded it as a separate site. Eastern European countries: Bulgaria, Hungary, Poland, Serbia, Slovakia, and Ukraine.

Exhibit 15. Blended/Blinded Event Rate in ASPEN is Slightly Lower than WILLOW

The blended/blinded event rate for pulmonary exacerbations is slightly lower in ASPEN as compared to the prior WILLOW study. Depending on if you are a bull or a bear, this could be viewed favorably or unfavorably for the ASPEN readout.

- In the Ph.2 study, the placebo group demonstrated 1.37 events per patient per year, as compared to 0.88 and 1.03 for the 10mg and 25mg groups, respectively. This event rate was higher than the assumed exacerbation rate of 1.2 events per patient per year (which is the same assumption that ASPEN makes), though lower than the inclusion criteria of at least 2 exacerbations in the past 12 months.
- As for ASPEN, the company previously disclosed that the blended and blinded event rate was 1.12 to 1.15 over the last 3 months (as of January 6, 2023). INSM has not provided an updated blended/blinded rate to our knowledge (it was provided at the 2023 JPM Healthcare Conference, so we could get an updated figure at JPM '24 in early January 2024, though this remains to be seen).

"That range was 1.12 to 1.15 events per patient per year over the course of the last three months…We assume in the placebo arm an event rate of 1.2 events per patient per year. What we saw in WILLOW was 1.37. What we require for patients coming into the study is two or more exacerbations within the last 12 months. So, what you would expect to see if the drug is operating, and those predictions are accurate is a level that is in the range that we are seeing right now…We are now in excess of 63% of all the patient data we're going to collect out of ASPEN in terms of patient years. So, we know that these ranges aren't going to move significantly from here. It is very encouraging to see 1.12 to 1.15 is at level, it's what we saw in WILLOW."

– Will Lewis (CEO) January 2023

On one hand, the lower event rate could be viewed favorably, as it suggests brensocatib is having a drug effect…

The lower blended/blinded event rate suggests that brensocatib could be having a drug effect in ASPEN. Moreover, as the rate is within the range of what we saw in the prior WILLOW study (1.37 events per patient per year), it **suggests that the patients in ASPEN are consistent in profile and behavior** (which we also know given the overlap in baseline characteristics).

On the other hand, the lower event rate could be viewed unfavorably, as patients may be having a lower-than-expected event rate…

As ASPEN has been executed during and after the pandemic, it is feasible that patients' quarantining, and social distancing behavior could be driving a lower overall rate of events. **However, patients enrolled still required ≥2 exacerbations, so these are patients with reliable exacerbations even after taking pandemic precautions into consideration, which may have enhanced the population.**

Source: Leerink Partners Research, Transcript January 2023

INSM P&L ($MM)	2018	2019	2020	2021	2022	1Q23	2Q23	3Q23	4Q23E	2023E	1Q24E	2Q24E	3Q24E	4Q24E	2024E	2025E
Arikayce (Refractory MAC)	9.8	136.5	164.4	188.5	245.4	65.2	77.2	79.1	80.1	301.6	79.7	86.2	89.5	93.5	349.0	452.5
Arikayce (Front-Line MAC)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	15.0
Arikayce (Non-MAC NTM)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Brensocatib (Non-CF Bronchiectasis)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	54.3
TPIP (PAH)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total Revenue	**9.8**	**136.5**	**164.4**	**188.5**	**245.4**	**65.2**	**77.2**	**79.1**	**80.1**	**301.6**	**79.7**	**86.2**	**89.5**	**93.5**	**349.0**	**521.8**
COGS	(2.4)	(24.2)	(39.9)	(44.2)	(55.1)	(13.8)	(16.6)	(16.7)	(16.8)	(63.9)	(16.7)	(18.1)	(18.8)	(19.6)	(73.3)	(109.6)
R&D	(145.3)	(131.7)	(181.2)	(272.7)	(397.5)	(127.9)	(197.0)	(109.1)	(124.1)	(558.1)	(119.6)	(120.7)	(120.9)	(116.9)	(478.1)	(454.0)
SG&A	(168.2)	(210.8)	(203.6)	(234.3)	(265.8)	(79.9)	(84.4)	(90.6)	(85.7)	(340.6)	(86.9)	(87.1)	(87.7)	(87.9)	(349.6)	(352.2)
Amortization of Intangible Assets	(1.2)	(5.0)	(5.0)	(5.1)	(5.1)	(1.3)	(1.3)	(1.3)	-	(3.8)	-	-	-	-	-	-
Change in Fair Value of Deferred and Contingent Consideration Liabilities				(7.3)	20.8	9.5	(13.5)	(9.0)	-	(13.0)	-	-	-	-	-	-
Operating Expenses	(317.2)	(371.7)	(429.6)	(563.6)	(702.7)	(213.4)	(312.8)	(226.7)	(226.6)	(979.4)	(223.2)	(225.9)	(227.4)	(224.4)	(901.0)	(915.8)
Operating Income	**(307.3)**	**(235.2)**	**(265.2)**	**(375.1)**	**(457.3)**	**(148.2)**	**(235.5)**	**(147.7)**	**(146.5)**	**(677.9)**	**(143.5)**	**(139.7)**	**(137.9)**	**(130.9)**	**(552.0)**	**(394.0)**
Interest Income	10.3	9.9	1.7	0.2	11.1	10.5	11.2	10.6	3.3	35.5	2.6	1.9	1.3	0.7	6.5	0.7
Interest Expense	(25.5)	(27.7)	(29.6)	(40.5)	(26.4)	(20.0)	(20.6)	(20.3)	(8.9)	(69.8)	(8.9)	(9.1)	(9.3)	(9.4)	(36.7)	(38.5)
Other Income (Expense)	(1.6)	(0.5)	0.4	(21.0)	(7.5)	(1.6)	0.7	(1.0)	-	(2.0)	-	-	-	-	-	-
Pretax Income (Loss)	(324.1)	(253.6)	(292.7)	(436.4)	(480.2)	(159.3)	(244.3)	(158.4)	(152.1)	(714.1)	(149.8)	(146.9)	(145.9)	(139.6)	(582.2)	(431.8)
Tax Expense (Benefit)	(0.2)	(0.8)	(1.4)	2.2	(1.4)	(0.5)	(0.5)	(0.5)	-	(1.6)	-	-	-	-	-	-
Net Income (Loss)	**(324.3)**	**(254.3)**	**(294.1)**	**(434.2)**	**(481.5)**	**(159.8)**	**(244.8)**	**(158.9)**	**(152.1)**	**(715.6)**	**(149.8)**	**(146.9)**	**(145.9)**	**(139.6)**	**(582.2)**	**(431.8)**
Diluted EPS	**(4.22)**	**$ (3.01)**	**(3.01)**	**$ (3.88)**	**$ (3.91)**	**$ (1.17)**	**$ (1.78)**	**$ (1.11)**	**$ (1.06)**	**$ (5.11)**	**$ (1.05)**	**$ (1.03)**	**$ (1.02)**	**$ (0.97)**	**$ (4.06)**	**$ (2.85)**
Basic Shares Outstanding	76.9	84.5	97.6	112.0	123.0	136.4	137.6	142.9	143.1	140.0	143.2	143.3	143.5	143.6	143.4	151.6
Diluted Shares Outstanding	76.9	84.5	97.6	112.0	123.0	136.4	137.6	142.9	143.1	140.0	143.2	143.3	143.5	143.6	143.4	156.4

Source: Company Reports, Leerink

INSM Balance Sheet & Cash Flow ($MM)	2018	2019	2020	2021	2022	1Q23	2Q23	3Q23	4Q23E	2023E	1Q24E	2Q24E	3Q24E	4Q24E	2024E	2025E
Net Cash	**45.1**	**37.4**	**82.8**	**(83.2)**	**(1.7)**	**(151.3)**	**(232.2)**	**(364.0)**	**(499.4)**	**(499.4)**	**(637.8)**	**(763.9)**	**(888.9)**	**(1,008.0)**	**(1,008.0)**	**(784.1)**
Cash & Cash Equivalents	**495.1**	**487.4**	**532.8**	**716.8**	**1,148.3**	**998.7**	**917.8**	**786.0**	**650.6**	**650.6**	**512.2**	**386.1**	**261.1**	**142.0**	**142.0**	**140.9**
Total Debt	**450.0**	**450.0**	**450.0**	**800.0**	**1,150.0**	**1,150.0**	**1,150.0**	**1,150.0**	**1,150.0**	**1,150.0**	**1,150.0**	**1,150.0**	**1,150.0**	**1,150.0**	**1,150.0**	**925.0**
Long-Term Debt	450.0	450.0	450.0	800.0	1,150.0	1,150.0	1,150.0	1,150.0	1,150.0	1,150.0	1,150.0	1,150.0	1,150.0	1,150.0	1,150.0	925.0
Change in Cash	**114.0**	**(7.6)**	**35.7**	**185.4**	**358.3**	**(105.1)**	**(352.6)**	**(127.9)**	**(135.4)**	**(721.0)**	**(138.4)**	**(126.1)**	**(125.0)**	**(119.1)**	**(508.6)**	**(1.1)**
Operating Activities	**(258.0)**	**(250.6)**	**(228.5)**	**(330.3)**	**(400.4)**	**(146.3)**	**(122.8)**	**(136.3)**	**(133.4)**	**(538.8)**	**(136.4)**	**(124.1)**	**(123.0)**	**(117.1)**	**(500.6)**	**(343.1)**
Net Income	(324.3)	(254.3)	(294.1)	(434.2)	(481.5)	(159.8)	(244.8)	(158.9)	(152.1)	(715.6)	(149.8)	(146.9)	(145.9)	(139.6)	(582.2)	(431.8)
SOE	26.2	27.0	36.2	46.0	57.7	16.4	18.4	20.0	16.8	71.6	16.4	20.8	20.9	20.5	78.6	80.6
Other	40.1	(23.3)	29.4	57.9	23.4	(3.0)	103.7	2.6	2.0	105.3	(3.0)	2.0	2.0	2.0	3.0	8.0
Investing Activities	**(14.8)**	**(42.3)**	**(6.8)**	**(64.3)**	**(34.6)**	**41.6**	**(274.2)**	**7.1**	**(2.0)**	**(227.4)**	**(2.0)**	**(2.0)**	**(2.0)**	**(2.0)**	**(8.0)**	**(8.0)**
Financing Activities	**386.7**	**285.3**	**271.0**	**612.5**	**793.3**	**(0.4)**	**44.3**	**1.2**	**-**	**45.2**	**-**	**-**	**-**	**-**	**-**	**350.0**
Debt Issue (Payment)	377.9	-	-	350.0	350.0	-	-	-	-	-	-	-	-	-	-	-
Equity Issue (Buyback)	-	261.1	245.9	269.9	292.2	-	-	-	-	-	-	-	-	-	-	350.0
Other	8.8	24.2	25.1	(7.3)	151.1	(0.4)	44.3	1.2	-	45.2	-	-	-	-	-	-

Source: Company Reports, Leerink

INSM DCF Valuation ($MM)	2020	2021	2022	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	TV
Operating Cash Flow	(228)	(330)	(400)	(539)	(501)	(343)	(149)	90	314	506	717	938	1,077	1,182	
CFI+Net Borrowing	(7)	(64)	(35)	(227)	(8)	(8)	(8)	(8)	(5)	(5)	(5)	(5)	(5)	(5)	
FCFE	(235)	(395)	(435)	(766)	(509)	(351)	(157)	82	309	501	712	933	1,072	1,177	
NPV	-	-	-	(766)	(497)	(312)	(127)	60	206	304	393	467	488	487	6,213
Discount periods	-	-	-	-	0.25	1.25	2.25	3.25	4.25	5.25	6.25	7.25	8.25	9.25	

Diluted Shares Outstanding 3Q23	142.9
Net Cash 3Q23	(364.0)
Probability Weighted Value/Share	**50**
Implied Market Cap	7,127

Assumptions	
WACC	10%
Terminal Growth Rate	2%

Source: Leerink, Company Filings

Leerink Partners Catalyst Tracker

Stock (Ticker Symbol)	Lateral Impact (Other companies/stocks)	Drug (Brand or chemical name) / Instrument / Area	Indication / Product Class	Type of Event	Event or Trial Details	Expected Timing	Specific Event Date if known or specified	Impact: H(igh) > 9% M(edium) 3 - 9% L(ow) < 2%	Estimated Stock Up/Down % on Best/Worst Outcomes	Leerink Partners View of Expected Outcome
INSM		TPIP	PH-ILD	Phase 2 Data Announcement	Ph.2 Topline Data	1H24		H		
INSM		Brensocatib	Non-Cystic Fibrosis Bronchietasis	Phase 3 Results Announcement	Ph.3 ASPEN Data	2Q24		H		
INSM		Arikayce	MAC (Front-Line)	Other Event	Registrational ENCORE Study Enrollment Completion	2024		L		
INSM		Arikayce	MAC (Front-Line)	Phase 3 Results Announcement	Registrational ENCORE Study Data	2025		L		

Source: Leerink Partners LLC Equity Research and Company Filings

Disclosures Appendix

Completion: January 1, 2024 20:51 P.M. EDT.
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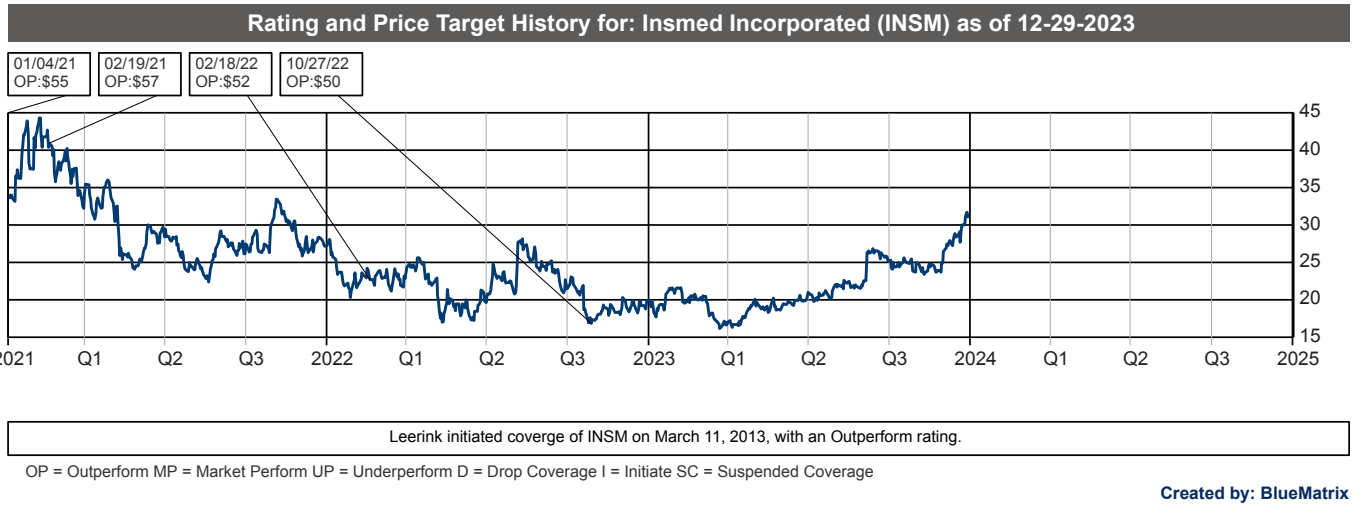
Analyst Certification

I, Joseph P. Schwartz, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

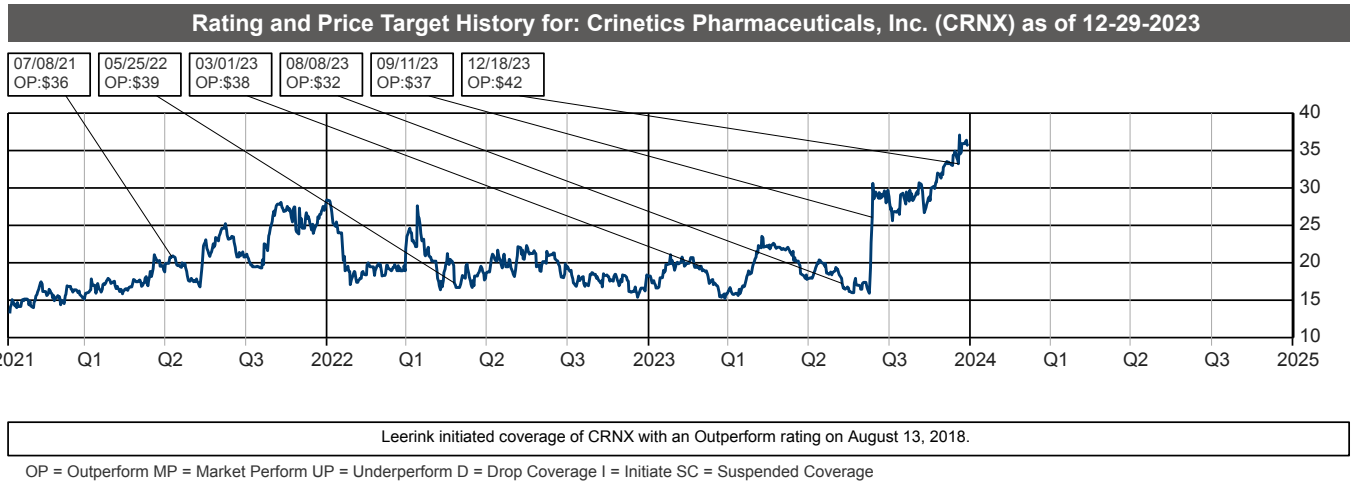


Valuation

We estimate a risk-adjusted per share price target for INSM of $50 in 12 months. We value INSM based on discounted cash flow analysis which uses a 10% discount rate and a 2% terminal growth rate.

Risks to Valuation

Risks include the potential for disappointing clinical data, regulatory setbacks, failure to obtain intellectual property protection abroad, and commercial shortfalls. Since INSM is presently unprofitable and only has one commercial product, any of the possible aforementioned setbacks may impact the stock significantly.

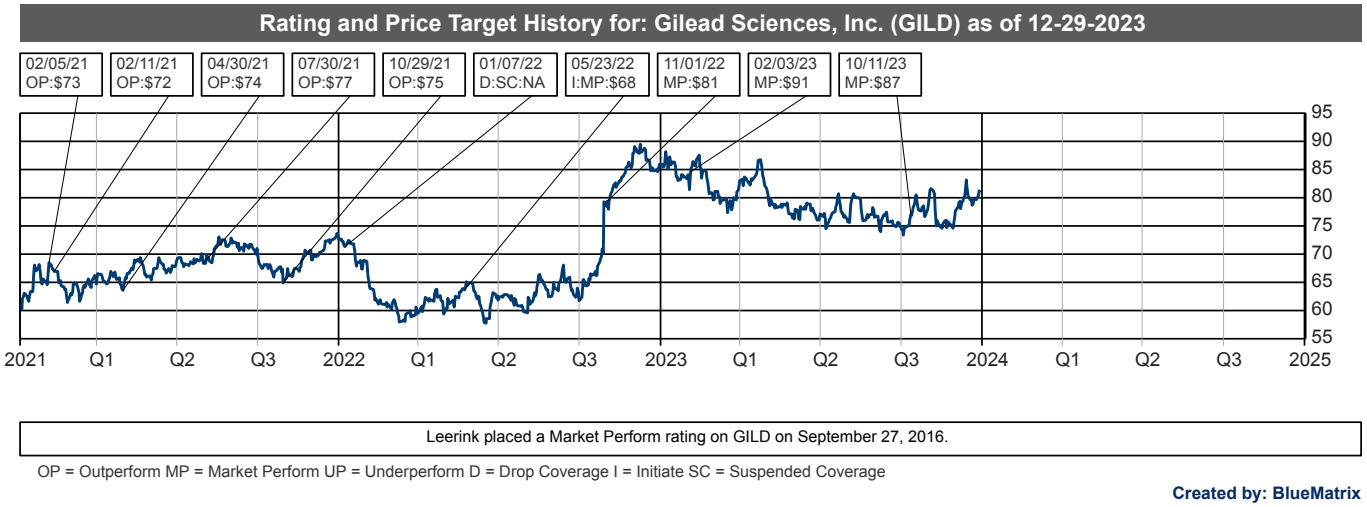


Valuation

We derive our $42 price target using a discounted cash flow (DCF) analysis assuming a 14% discount rate and 4% terminal growth rate. Our model includes paltusotine (acromegaly and NETs), and CRN4894 (congenital adrenal hyperplasia [CAH] and Cushing's disease). We currently estimate gross US/EU peak sales of ~$350M (2035E), ~$630M (2035E), ~$530M (2035E), ~$250M (2035E) for paltusotine (acromegaly), paltusotine (carcinoid syndrome), CRN4894 (CAH), CRN4894 (Cushing's disease), respectively. CRNX fully owns rights to all programs. We account for clinical and regulatory risks in our probability of success (PoS) estimates: 95% US/EU for paltusotine (acromegaly) in switch patients, 85% US/EU for paltusotine (acromegaly) in treatment naive patients, 75% US/EU for paltusotine (carcinoid syndrome), 65% US/EU for CRN4894 (CAH), and 65% US/EU for CRN4894 (Cushing's disease). These valuation parameters reflect encouraging clinical and/or preclinical data offset by uncertain safety/efficacy profiles at their relatively early stages of development.

Risks to Valuation

Crinetics is developing oral, non-peptide drug candidates targeting G protein coupled receptors (GPCRs). As with any novel therapies, the platform comes with safety and efficacy risk. Although preclinical and clinical data seem convincing, the programs (and company) are in the early stages of development and clinical/regulatory development could disappoint. Unpredicted issues may arise, including safety, efficacy, manufacturing, regulatory requirements, market receptiveness, or other unanticipated complications that could impact the stock negatively.

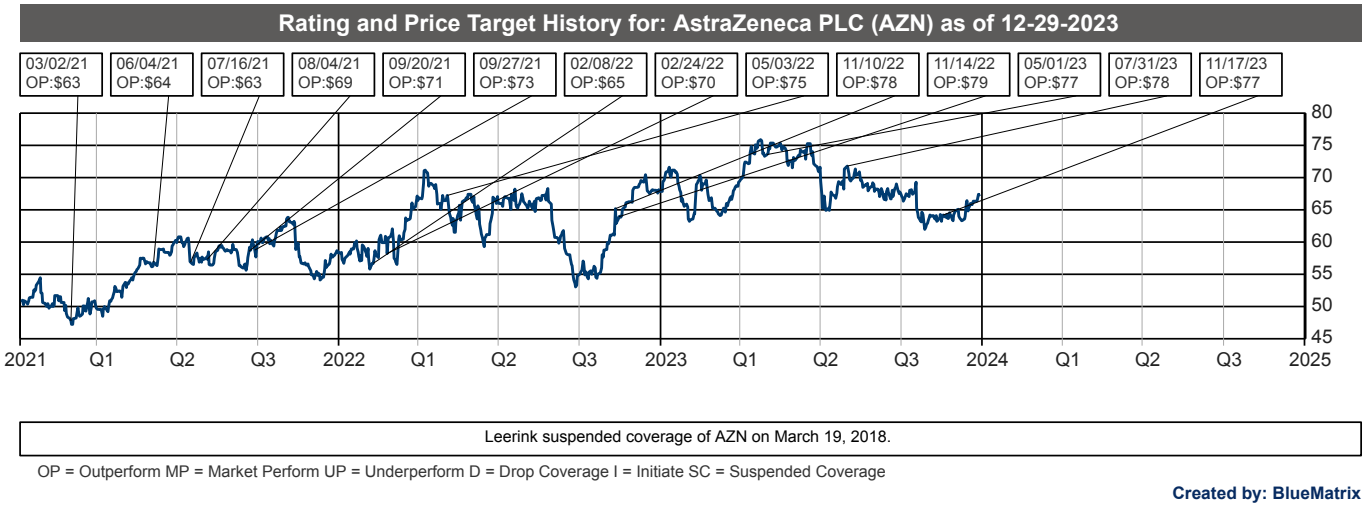


Valuation

Our $87 PT is based on a DCF analysis for Gilead through 2039, using a 6.1% WACC discount rate, 0% terminal growth rate (after 2039), and accounting for net cash. Our projected oncology revenues are generated from a range of outcomes for the company's marketed products (Trodelvy, Yescarta, Tecartus) and select pipeline programs (zimberelimab, domvanlimab, etrumadenant, magrolimab, CART-ddBCMA, KITE-222, and KITE-363), which are derived from a Monte Carlo simulation of the entire IO industry pipeline (Leerink Partners IONIAN model). Outside of oncology, we project risk-adjusted revenues for core virology franchises (HIV, HIV, HCV, HBV/HDV), and COVID-19 (both Veklury and oral remdesivir prodrug, obeldesivir). We do not yet ascribe any value to the company's immunology and other non-virology / oncology pipeline prospects.

Risks to Valuation

To the upside, HIV franchise performance could accelerate more than anticipated with competitive pressures, Gilead could deliver surprisingly compelling oncology pipeline and M&A news flow, and the company could become a target for strategic action given its low valuation. There are numerous oncology and immunology programs in early-phases that could have surprising good early data. To the downside, the HIV franchise could struggle to grow due to competitive and pricing pressures, long-acting HIV and new treatment combination R&D efforts could fail to pan out, oncology pipeline news flow could disappoint, and the company could engage in value-destructive acquisition activity.



Valuation

We value AstraZeneca (AZN) at $77 per ADS based on the results of our discounted cash flow (DCF) analysis, which contemplates our free cash flow forecasts through 2030, assuming a 1.5% terminal growth rate and a weighted average cost of capital (WACC) of 7.5%.

Risks to Valuation

- Clinical trial risk: AstraZeneca has numerous late-stage clinical assets, including Enhertu (trastuzumab deruxtecan) and roxadustat, as well as several approved products with meaningful label expansion opportunities dependent on successful clinical trials, including Imfinzi, Lynparza, and Calquence. Clinical trial failure for late-stage clinical assets represents a risk to our current price target.
- Regulatory risk: Even with positive clinical trial results, marketing authorization requires approval from regulators in various jurisdictions. Regulatory delays or rejections of applications for key pipeline products would represent a risk to our current valuation.
- Competitive risk: AstraZeneca markets products in competitive therapeutic areas, including oncology, renal/cardiovascular, and respiratory. This competition could lead to AZN product sales that are materially below our estimates, representing a risk to our current price target.
- Pricing and reimbursement: Legislation affecting drug pricing, including proposed legislation in the U.S. that could link drug prices to international benchmarks, is a risk for all commercial pharmaceutical companies, including AstraZeneca.

Distribution of Ratings/Investment Banking Services (IB) as of 09/30/23				
			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OP]	211	65.1	64	30.3
HOLD [MP]	101	31.2	7	6.9
SELL [UP]	12	3.7	0	0

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months.

The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

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Leerink Partners expects to receive compensation for investment banking services from Insmed Incorporated and Crinetics Pharmaceuticals, Inc. in the next 3 months.

Leerink Partners makes a market in Insmed Incorporated, AstraZeneca PLC, Crinetics Pharmaceuticals, Inc. and Gilead Sciences, Inc.

Leerink Partners has acted as the manager for a public offering of Crinetics Pharmaceuticals, Inc. in the past 12 months.

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