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Insmed Incorporated

Clearing the air: Deep dive on brenso's mechanism bolsters confidence in ASPEN

Reiterate Rating: BUY | PO: 37.00 USD | Price: 27.44 USD

KOLs optimistic mechanism, ASPEN can net a win

After a strong 2023, Insmed (INSM) shares have underwhelmed YTD (-11%). Beyond broad sector concerns (SPX +5% vs NBI 0%) and a modest (in our view, conservative) Arikayce FY24 guide (see our guidance takes), we suspect the weakness stems from skepticism over novel DPP-1 inhibitor brensocatib (brenso) ahead of its readout in NCFB, ASPEN ("late" 2Q24e). Following conversations with investors, we'd argue there are fundamental questions over: 1) the MoA, given admitted questions over the phase 2 results in an indication that has seen limited historical success; and 2) the ability of brenso to capture meaningful share of management's estimated $5B TAM. In this note, we address the first, reviewing the underlying science and brenso's development strategy with our pulmonology KOLs. Overall, our experts were optimistic for a positive readout, bolstered by the company's thoughtful phase 3 design that should avoid previous pitfalls. With increasing confidence, we continue to see compelling risk/reward for the shares and would be buyers on the recent pullback. Reiterate Buy, $37 PO.

Clinical/ biochemical activity already setting brenso apart

Likely one of the bigger investor concerns, in our view, stems from prior failures from other DPP-1/NSP inhibitors. Indeed, GSK's GSK2793660, AstraZeneca's AZD9668, and Bayer's 85-8501 (all covered by our EU team) all failed to progress beyond a phase 2, each marked by a lack of meaningful NSP inhibition. In stark contrast, brensocatib significantly reduced NSP levels at two doses in a phase 2 accompanied by evidence of clinical benefits. A precise explanation for these differences is unclear, with much about the overall pathway admittedly unclear. Still given clear distinctions in binding, tissue penetration/ distribution, and PK/PD, our KOLs weren't all that concerned, pointing to host of biomarkers offering further support of activity. And with encouraging clinical signs from the trial, notably a blended, blinded event rate mid-study less than placebo, our experts were confident brenso was indeed doing "something."

Experts similarly flag ASPEN design as set up for success

Our KOLs also conceded few NCFB studies have succeeded, a dynamic increasingly attributed to challenges with trial designing and execution—much of this likely due to variability defining and adjudicating exacerbations. Here again, our experts flagged Insmed's efforts as another differentiator given, in their view, ASPEN's well-thought-out design. Beyond building WILLOW's success, incorporating lessons learned, examples include 1) meaningfully expanding powering; 2) stratifying for potentially confounding frequent exacerbators (with COVID potentially acting as a tailwind); and 3) pursuing two separate doses, with a hit on either supportive of a filing.

Estimates (Dec) (US$)	2021A	2022A	2023E	2024E	2025E
EPS	(3.88)	(3.91)	(5.20)	(4.70)	(3.48)
EPS Change (YoY)	-28.9%	-0.8%	-33.0%	9.6%	26.0%
Consensus EPS (Bloomberg)			(5.20)	(4.58)	(3.68)
DPS	0	0	0	0	0
Valuation (Dec)					
Free Cash Flow Yield*	-9.4%	-10.5%	-16.5%	-17.5%	-16.2%

* For full definitions of *iQmethod*℠ measures, see page 20.

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Refer to important disclosures on page 21 to 23. Analyst Certification on page 18. Price Objective Basis/Risk on page 18. **12659857**

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Stock Data

Price	27.44 USD
Price Objective	37.00 USD
Date Established	5-Sep-2023
Investment Opinion	C-1-9
52-Week Range	16.04 USD - 32.00 USD
Mrkt Val (mn) / Shares Out (mn)	3,926 USD / 143.1
Free Float	98.6%
Average Daily Value (mn)	46.50 USD
BofA Ticker / Exchange	INSM / NAS
Bloomberg / Reuters	INSM US / INSM.OQ
ROE (2023E)	NA
Net Dbt to Eqty (Dec-2022A)	58.2%
ESGMeter™	Medium

ESGMeter is not indicative of a company's future stock price performance and is not an investment recommendation or rating. ESGMeter is independent of BofA Global Research's equity investment rating, volatility risk rating, income rating, and price objective for that company. For full details, refer to "BofA ESGMeter Methodology".

Abbreviations (full list page 16):
DPP-1: dipeptidyl peptidase-1
KOLs: key opinion leaders
MoA: mechanism of action
NCFB: Non–cystic fibrosis bronchiectasis
NSPs: neutrophil serine proteases
PE: pulmonary exacerbations
TAM: total addressable market

iQprofile℠ Insmed Incorporated

iQmethod℠ **– Bus Performance***

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Return on Capital Employed	-37.8%	-32.0%	-54.6%	-89.4%	-86.6%
Return on Equity	-126.7%	-193.2%	NM	NM	NM
Operating Margin	-199.0%	-186.4%	-230.3%	-196.8%	-87.9%
Free Cash Flow	(371)	(410)	(646)	(686)	(635)

iQmethod℠ **– Quality of Earnings***

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Cash Realization Ratio	NM	NM	NM	NM	NM
Asset Replacement Ratio	0.8x	1.9x	1.0x	1.0x	1.1x
Tax Rate	0.4%	NM	NM	NM	NM
Net Debt-to-Equity Ratio	-36.6%	58.2%	NM	NM	NM
Interest Cover	-6.1x	-20.0x	-29.5x	-21.3x	-15.7x

Income Statement Data (Dec)

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Sales	188	245	305	377	684
% Change	14.6%	30.2%	24.4%	23.6%	81.4%
Gross Profit	144	190	242	294	520
% Change	15.9%	31.8%	27.1%	21.7%	76.8%
EBITDA	(361)	(447)	(687)	(726)	(585)
% Change	-43.7%	-23.9%	-53.7%	-5.7%	19.5%
Net Interest & Other Income	(61)	(23)	(24)	(35)	(38)
Net Income (Adjusted)	**(435)**	**(482)**	**(728)**	**(777)**	**(640)**
% Change	**-47.8%**	**-10.8%**	**-51.2%**	**-6.8%**	**17.6%**

Free Cash Flow Data (Dec)

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Net Income from Cont Operations (GAAP)	(435)	(482)	(728)	(777)	(640)
Depreciation & Amortization	14	10	16	16	17
Change in Working Capital	(59)	7	(38)	(40)	(134)
Deferred Taxation Charge	NA	NA	NA	NA	NA
Other Adjustments, Net	116	64	115	126	134
Capital Expenditure	(7)	(10)	(10)	(11)	(13)
Free Cash Flow	**-371**	**-410**	**-646**	**-686**	**-635**
% Change	**-64.3%**	**-10.7%**	**-57.4%**	**-6.3%**	**7.4%**
Share / Issue Repurchase	292	312	20	472	493
Cost of Dividends Paid	0	0	0	0	0
Change in Debt	337	0	0	0	0

Balance Sheet Data (Dec)

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Cash & Equivalents	717	1,074	404	159	15
Trade Receivables	24	30	34	38	62
Other Current Assets	96	170	246	256	337
Property, Plant & Equipment	53	56	57	58	60
Other Non-Current Assets	354	327	292	323	358
Total Assets	**1,244**	**1,656**	**1,032**	**834**	**832**
Short-Term Debt	0	0	0	0	0
Other Current Liabilities	135	190	182	189	226
Long-Term Debt	567	1,125	1,133	1,143	1,157
Other Non-Current Liabilities	131	253	270	288	306
Total Liabilities	**833**	**1,568**	**1,585**	**1,620**	**1,689**
Total Equity	**410**	**88**	**(553)**	**(786)**	**(857)**
Total Equity & Liabilities	**1,244**	**1,656**	**1,032**	**834**	**832**

* For full definitions of *iQ*method℠ measures, see page 20.

Company Sector

Biotechnology

Company Description

Insmed Incorporated is a commercial stage biopharmaceutical company focused on rare diseases. The company is addressing areas of high unmet need, fueled by its four pillars: Arikayce, Brensocatib, TPIP, and translational medicine. With Arikayce already on the market, we see commercial synergies and established physician relationships putting Insmed in a good position for commercialization of the clinical stage pipeline.

Investment Rationale

In our view, Arikayce sales should support near-term revenues, bolstered by potential for growth in Brensocatib and TPIP, where we see good clinical efficacy and tolerability. We recognize a number of commercial challenges, but ultimately view a favorable risk/ reward profile given KOL feedback, promising clinical/preclinical data, and under penetration in these markets with high unmet need, supportive of our Buy rating.

Stock Data

Average Daily Volume	1,733,415

Quarterly Earnings Estimates

	2022	2023
Q1	-0.80A	-1.17A
Q2	-0.80A	-1.78A
Q3	-1.09A	-1.11A
Q4	-1.21A	-1.16E

Assessing brenso's clinical potential: does the science support the promise?

Skepticism for brenso's clinical/ commercial profile weighs, offers buying opportunity

Insmed's late-stage asset brensocatib, a DPP-1 inhibitor in development for NCFB, CRSsNP, and HS, is easily its biggest potential value driver, with the team projecting peak potential >$5B, above Arikayce (>$1B) and TPIP (>$2B). Given estimated addressable global populations of ~1M for NCFB, ~400k for CRSsNP, and ~250k for HS and the overall lack of approved/ easily administered treatments, Insmed's forecast seem reasonable. That said, we see meaningful skepticism across the Street for clinical/ regulatory success (2030e adj: BofA $1.84B vs consensus $1.78B) and the overall opportunity (2030e unadj: BofA $3.0B vs cons $2.5B)—with our more bullish outlook supportive of our view recent share pullback constitutes a buying opportunity.

To explore the first question over the science/ MoA in depth ahead of the phase 3 (ASPEN) readout, expected 2Q24, we reached out to our pulmonologist KOLs to discuss 1) the underlying rationale and mechanistic support for targeting DPP-1; 2) brensocatib's phase 1 and 2 efficacy outcomes; 3) the safety data to date, with potential risks associated with longer treatment durations; and 4) ASPEN's design with a focus on handicapping the three potential statistical outcomes with impact to the company's regulatory pathway (i.e., $p \leq 0.01$; $0.01 < p \leq 0.05$; and a miss).

Key questions: Historical precedent adds uncertainty to the readout, though trial design and underlying activity supports KOL confidence

Highlighted below are the major risks/ uncertainties flagged by our experts as well as their responses—which is discussed in greater depth in the report below (Exhibit 1). Given feedback, we wouldn't be surprised if investors collectively see a miss or middling efficacy as more likely than our more optimistic outlook. But while we acknowledge the concerns associated with ASPEN, we continue to see reasons to be encouraged:

Exhibit 1: Our KOLs were largely unconcerned with several common, major concerns voiced by our investors

While these by no means guarantee ASPEN's success, we think there is greater support for brenso's underlying MoA than what is currently reflected in INSM shares

Reasons to be concerned	KOL responses
1) MoA: Role of NSPs in NCFB still unclear, with similar approaches failing to show a benefit	• Though pathophysiology of NCFB unclear, growing evidence NSP mediate tissue damage/ progression • Failure of GSK's DPP-1 and Astra's and Bayer's NE inhibitors AstraZeneca's AZD9668 and Bayer's BAY 85-8501 likely due to insufficient DPP-1/ NE inhibition
2) Dose-Dependent Response: While brenso's efficacy was solid in WILLOW, there was a lack of a dose-dependent response in PEs	• Potentially due to a greater portion of hyper-exacerbators in the 25mg group • 25mg may causes too much immunosuppression, resulting in greater PEs—which should become clear over longer duration of ASPEN
3) Prior NCFB Trial Failures: few trials in the space have succeeded	• Many of these studies focused on antibiotics/ anti-inflammatories, where there's modest benefit • Endpoint selection and trial design are likely key • ASPEN design likely addresses many of these pitfalls, leveraging lessons learned from WILLOW
4) Activity Beyond PEs: Despite success on PE, QoL trends look less favorable	• PROs admittedly variable; QoL-B has a nuanced history in NCFB and does not always track PEs • Positive trends in FEV1 in WILLOW provide some support for a QoL benefit in ASPEN • Longer duration of follow-up may be able to demonstrate clear trends
5) Blended-Blinded Rate: While the blended-blinded rate looks positive, is it supportive	• Blended, blinded PE event rate for ASPEN 1.12-1.15 is lower than the assumed ASPEN (1.20) and demonstrated WILLOW (1.37) placebo rates • Event rate generally consistent with WILLOW, a positive sign albeit early

Source: BofA Global Research

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- **MoA: the role of NSPs in bronchiectasis is not well characterized, with several other similar approaches unable to demonstrate much benefit.** Despite solid brenso phase 1 and 2 data, some investors have pointed to a lack of evidence establishing a clear link between DPP-1/ NSPs and NCFB/ PEs given the failure of other candidates targeting this pathway, e.g., GSK's DPP-1 inhibitor GSK2793660 and NE inhibitors AstraZeneca's AZD9668 and Bayer's BAY 85-8501 (all three companies covered by our EU team).

  Admittedly the pathophysiology of NCFB isn't entirely clear. That said, there is growing evidence (Chalmers, et al., 2017), and acceptance within the clinical

community, NSPs are a key mediator of tissue damage and clinical progression—with increasing evidence interrupting this process can provide benefit (Chalmers JD, 2023). At the same time, there is solid rationale as to why the other assets failed—including critically, an inability to lower DPP-1 and/or NE activity/ levels to a meaningful degree (Gramegna A, 2017; Palmér R, 2018; Stockley, et al., 2013).

We recognize these, in and of themselves, are by no means a guarantee of ASPEN's success. Still, we think there is greater support for brenso's underlying MoA than what is currently reflected in INSM shares.

- **While WILLOW was overall solid, there wasn't a dose-dependent response in PEs, with the correlation in NE activity also weak.** Another major concern, in our view, stems from the lack of a dose-dependent response in WILLOW. While both active arms met the primary, those receiving 10mg saw a 36% PE decline (p=0.04) vs only 25% in the 25mg cohort (p=0.17). These also did not track NE activity levels, with greater declines in the 25mg arm vs the 10mg (see Exhibit 11).

  For its part, Insmed believes the presence of a few hyper-exacerbators in the 25mg cohort may have skewed the data, though our KOLs conceded this was hard to confirm. Indeed, while acknowledging this a possible cause, they also felt it could just have been statistical noise. Alternatively, one theorized it may be the result of too much immunosuppression, leading to an increase in bacterial infections, which in turn could have triggered more exacerbations.

  Ultimately, though, none felt it was a major red flag, given 1) their confidence in the MoA, and 2) the rest of the favorable efficacy/ molecular trends, with ASPEN's design—exploring 2 doses, larger population, longer treatment duration—providing confidence it would be able to address the other underlying potential issues.

- **Previous NCFB studies have had a poor track record, underscoring the challenges of designing a trial capable of identifying effective agents.** A recent literature review found that of 23 bronchiectasis trials, only 12 met their primaries (Crichton M, 2019). We certainly recognize the historical overhang; that said there are several caveats. For one, many of these studies focused on drug classes that provide modest benefits, i.e., antibiotics and anti-inflammatories. In addition, the review authors point to endpoint selection and/or design as being significant contributors given a range of definitions exacerbation and overall inclusion criteria.

  In contrast, we think—supported by our KOLs—ASPEN's design addressed many of these pitfalls, leveraging lessons learned from WILLOW in terms of inclusion criteria, endpoint definition, duration, and powering assumptions.

- **Beyond respiratory endpoints, QoL endpoints missed.** Despite demonstrating robust activity on the pulmonary endpoints, WILLOW failed to produce clinically meaningful improvements on any of the quality-of-life metrics: QoL-B respiratory symptoms scores or exploratory endpoints (i.e., the LCQ and SGRQ). Indeed, on the QoL-B, the treatment group trended marginally worse vs placebo in the 10mg cohort (-2.0 points difference; 95% CI -3.9 to 0.02) although this was in-line in the 25mg cohort (0.2 points; 95% CI -1.8 to 2.2) (Chalmers DJ, 2020).

  The QoL-B, a self-administered questionnaire designed to test the overall quality of life for bronchiectasis patients, is a validated tool used broadly in various respiratory indications. However, PROs are admittedly variable, with prior trials in NCFB failing to show concurrent QoL-B benefits in-line with PE reductions. That said, with the literature suggesting a relationship between pulmonary function (i.e., FEV1) and QoL-B respiratory symptoms, we think WILLOW's positive FEV1 trends auger well for ASPEN to capture a PRO benefit (Ghosh P, 2021). Ultimately, management felt the longer duration of follow-up in ASPEN may provide greater acuity in QoL improvements, rationale our KOLs agreed with (Crichton M, 2019).

- **Does the 1.12-1.15 blended-blinded rate suggest a statistically significant result?** In Jan 2023, the company announced the blended, blinded PE event rate for ASPEN was 1.12-1.15, lower than both the 1.20 and 1.37 placebo rates assumed for ASPEN and observed in WILLOW, respectively. While declining to providing further color, in early 2024 Insmed reported this value remains in the same "neighborhood", and, while admittedly difficult to draw clear conclusions, the team suggests it's consistent with that seen in WILLOW. Acknowledging PE rates can be variable, assuming a 1) placebo rate in-line, with 2) greater powering, we think the early update is, while immature, still encouraging.

DPP-1 inhibitor analysis: a deep dive

Brenso was developed to inhibit processing enzyme DPP-1 given role of downstream NSPs in pulmonary and I&I disorders/diseases

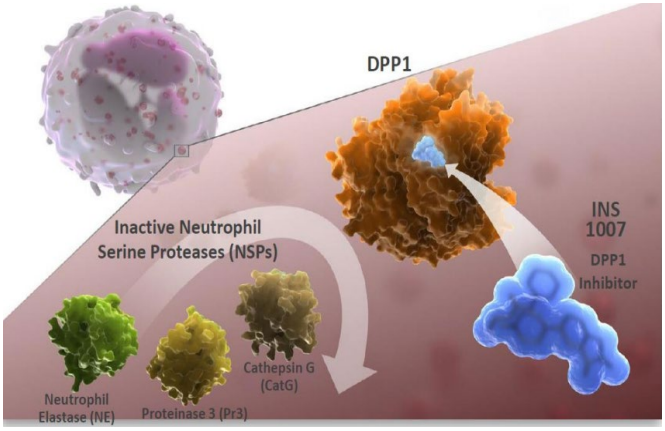
Initially developed by AstraZeneca as AZD7986, brensocatib is a second-generation DPP-1 inhibitor. DPP-1 (also known as cathepsin C, CTSC) is an enzyme that activates neutrophil serine proteases (NSPs)—proteins enabling killing of bacterial pathogens—during the maturation of these white blood cells in the bone marrow.

Uncontrolled, or hyper-active NSPs, have long been associated with negative health effects, particularly in the lungs where prolonged activity has been linked to excessive mucous secretion, tissue degradation, and extended inflammation (Exhibit 3). In contrast, low levels of NSPs do not seem to be linked to similar detrimental impacts, given individuals lacking DPP-1 (e.g., those with Papillon-Lefèvre syndrome, PLS, a rare autosomal recessive disorder) don't appear to suffer from infections at disproportionate rates. For these reasons, it's been hypothesized targeting DPP-1/ NSP maturation could be an effective therapeutic approach to addressing neutrophil-driven lung diseases, including bronchiectasis, cystic fibrosis, and COPD (Chalmers DJ, 2020) (Palmér R, 2018).

Brensocatib is a small molecule designed to bind to DPP-1 reversibly and competitively, but with high-potency. In pre-clinical studies, it prevented activation of all three NSPs—neutrophil elastase (NE), proteinase 3 (Pr3), and cathepsin G (CatG; Exhibit 2)—in a dose dependent manner. Moreover, in animal models, treatment effects linked to administration and discontinuation—as observed in circulating neutrophils—were delayed, effects consistent with its proposed activity, i.e., occurring during maturation of these cells in the bone marrow. (Palmér R, 2018).

In addition, targeting DPP-1 may have mechanistic advantages over directly inhibiting NSPs, an approach also being explored (e.g., Astra's AZD9668 and Bayer's BAY 85-8501; see below). In theory, moving upstream may ensure reduced NSP levels are maintained even if a few doses of the are missed. Indeed, neutrophil maturation occurs in ~15 day cycles, and it doesn't appear brief interruptions of brenso have a large impact on NSP levels, a positive given adherence can be a variable for oral therapies (Palmér R, 2018).

Exhibit 2: Brensocatib is a reversible DPP-1 inhibitor
Inhibition of DPP-1 should result in reduced activity of NSPs—NE, Pr3, CatG



Source: Company presentations

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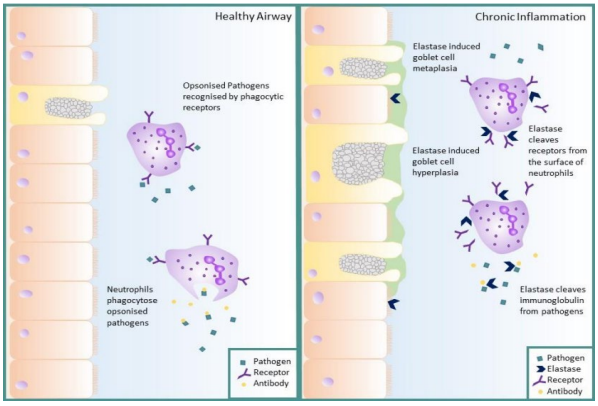
Exhibit 3: Hyperactivity of NSPs results in chronic inflammation
NE hyperactivity prompts an increase in goblet (i.e. mucin secreting) cell production



Source: Company presentations

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Brenso phase 1 activity encouraging—although NE may not be an ideal marker, potentially contributing to some initial questions over the MoA

AstraZeneca conducted a phase 1 of AZD7986/ brensocatib to evaluate its safety/ tolerability and PK/PD via a two-part design in 81 healthy volunteers. In the first part, five single doses were tested in 9 subjects (including 3 placebo): 5, 15, 35, 50, and 65 mg; in the second part 10, 25, or 40 mg were administered once daily in 9, 11, and 16 participants, respectively (3, 3, and 6 of whom were given placebo, respectively)—for 21, 28, and 28 days (Palmér R, 2018).

To assess brenso's activity, study investigators focused on NE. While a comprehensive review is beyond the scope of this note, NE has long been associated with several pulmonary diseases given the damage it can cause to normal tissues—including notably cystic fibrosis, COPD, asthma, and bronchiectasis (Gramegna A, 2017). Admittedly, its role outside of bronchiectasis is better characterized, including both CF as well as COPD, where, for example, early data suggests a ~50% reduction in NE levels may be enough to be therapeutically relevant (Palmér R, 2018). At the same time, systemic reviews suggest a strong correlation between sputum NE levels and 1) risk of exacerbation; 2) time to next exacerbation; and 3) mortality in bronchiectasis (Gramegna A, 2017).

Our KOLs similarly acknowledged while NE likely plays a major role in exacerbations, it's still unclear what the precise extent is, with bronchiectasis pathogenesis not completely understood. But although the other NSPs, CatG and Pr3, may contribute to the disease, they still felt there is clear evidence NE is a factor—and monitoring its activity is a reasonable approach to assessing drug activity.

Among key findings, administration of brenso led to a dose-dependent inhibition of NE activity starting ~12 days after initiation and reaching mean steady-state levels of -30, -49, and -59% for the 10, 25, and 40mg daily doses, respectively. Upon discontinuation, NE levels returned at a rate consistent with the onset of treatment, dynamics akin to the pre-clinical data. Importantly, and consistent at least with observations of PLS patients, there was seemingly no impact on the level of circulating neutrophils (Palmér R, 2018).

Similarly, brenso generally tolerable, though skin issues likely to remain a focus

In terms of safety, overall AZD7986/ brensocatib was considered well-tolerated, with no SAEs reported, the remaining AEs adjudicated as mild or moderate. In addition, there was one discontinuation (25mg) due to a skin AE (lichenoid drug eruption). Although the participant had previously been diagnosed with lichen planus, investigators could not exclude the possibility brensocatib may have contributed.

In addition, investigators also focused on skin and dental side effects. Both are common in PLS, which is characterized by higher incidences of periodontitis (gum infection) and palmoplantar hyperkeratosis (thickening of the skin on the palms/ soles).

Among patients in the phase 1, there did not seem to be a specific impact on gingiva. However, 6 patients did experience skin-related issues, including mild skin exfoliation, mild hyperkeratosis, mild hypertrophy, and dry skin. Five of these were in the treatment group, 4 of whom received the highest dose. That said, of these, 3 experienced these AEs before there were major reductions in blood NE levels; in addition, most symptoms resolved spontaneously (Palmér R, 2018).

Favorable trends aside, skepticism over MoA likely remains given setbacks from other programs

While our KOLs agreed there was mechanistic support for targeting DPP-1 to treat neutrophil-driven lung diseases, we wouldn't be surprised if some of the investor skepticism for brensocatib stems from issues GSK encountered with its DPP-1 inhibitor program, GSK2793660.

Indeed, the phase 1 of GSK2793660 was suspended after 7/10 participants receiving repeat dosing experienced epidermal desquamation (abnormal skin peeling)—a known complication of PLS. Although these symptoms largely resolved by the end of follow-up, more critically, the inhibition of NSP activity was relatively modest, easily raising questions over both the efficacy and safety of the MoA (Miller BE, 2017).

Our KOLs were less concerned. Beyond additional de-risking of brensocatib in the phase 2 WILLOW (discussed in detail below), they noted several key potential distinctions between Insmed's drug and GSK's. For one, while GSK2793660 clearly inhibited DPP-1 in the blood stream, it may not have been able to sufficiently penetrate cells/ tissues—including the bone marrow, where DPP-1 is critical for neutrophil maturation, with its ~1.5 hours half-life shorter than breno's 20-34 hours (Palmér R, 2018).

As far as the differing side-effect profiles are concerned, the brensocatib phase 1 investigators suggested there may be distinct DPP-1 pathways—one related to NSP activation and the other related to epidermal surfaces—especially given brenso's skin-related effects events did not seem to correlate with NE activity. They also noted PLS heterozygotes (i.e., genetic carriers) do not have often skin symptoms of homozygotes, despite having reduced (13-47%) DPP-1 activity—implying reductions of >80% may be required (GSK2793660 reduced DPP-1 by 93%; not measured in the brenso phase 1).

Ultimately, it remains unclear as to why brensocatib reduced NSP levels at greater levels than '660, but the culmination of PK/PD, binding properties, and activation of differing pathways could easily account for this variability (Palmér R, 2018), (Miller BE, 2017).

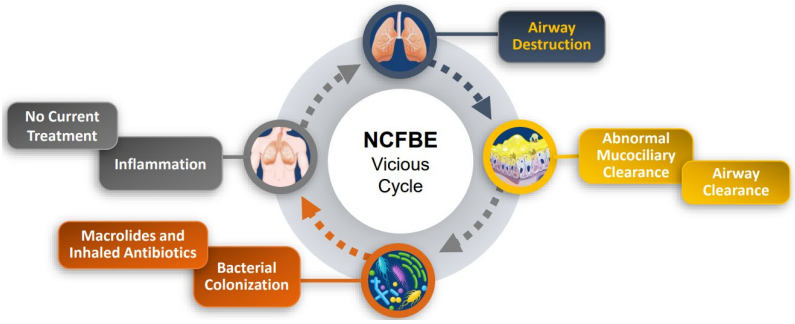
In addition, we note the seeming failure of two direct NE inhibitors, Astra's AZD9668 (Stockley, et al., 2013) and Bayer's BAY 85-8501 (Gramegna A, 2017)—although there did not seem to be significant changes in NE activity in either case, unlike brenso, adding support the molecules are mechanistically distinct.

Phase 2 development advances brenso for treatment of NCFB (WILLOW)

On the basis of the phase 1, Insmed—which licensed AZD7986 in Oct 2016—initiated WILLOW, a phase 2, specifically in non-cystic fibrosis bronchiectasis in 2017. NCFB is an inflammatory pulmonary condition in which airways become chronically dilated following an insult to airway epithelium (see our Insmed initiation). This in turn, prompts mucosal production and immune cell infiltration, making the lungs more susceptible to bacterial infection (King, 2018) (O'Donnell, 2022). A cycle of infection and inflammation ensues, resulting in the typical symptoms: cough, sputum production, chest pain, fatigue, and pulmonary infections (Macfarlane L, 2021) (Exhibit 4).

These acute flares of respiratory symptoms are known as pulmonary exacerbations (PEs) and are a major cause of morbidity as well as mortality. Indeed, PEs typically worsen pulmonary fibrosis, putting patients at greater risk for subsequent exacerbations, and accelerating lung function declines (Worth H, 2023). A retrospective analysis presented at the 2023 ATS Conference based on data from the US bronchiectasis and NTM Research Registry (BRR) lends further support for this model. Patients with prior exacerbations had a significantly greater frequency of PEs over the following 1-2 years (+11%, P < 0.01) and 3-4 years (+22%, P<0.0001)—with a >2x greater likelihood of having an event at years 3-4 if they had ≥1 PE at baseline (Aksamit TR, 2023).

Exhibit 4: Non-cystic fibrosis bronchiectasis results from an insult to airway epithelium
A cycle of infection and inflammation persists, with no approved therapies to address the underlying disease



Source: Company presentations

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NCFB patients may be divided into mild, moderate, and severe based on lung function. While exacerbations contribute to lung function declines, the severity of disease does not always go hand-in-hand with exacerbation frequency. Indeed, some patients may present as hyper-exacerbators, despite having relatively preserved lung function.

Select KOL feedback

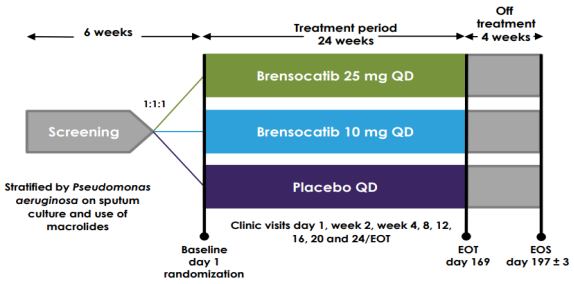
I think brensocatib is a fantastic drug so far...

In the case of bronchiectasis you have this exuberant inflammation that is further causing more lung damage and bringing about this vicious cycle dominated by neutrophil serine proteases... so a therapy that essentially reduces this neutrophilic inflammation makes a lot of sense here...

I would say the excitement is very high ... you finally have a drug that's dealing with the actual vicious cycle, rather than the aftermath... literally just having them cough and do a chest beat...

In WILLOW, 256 NCFB patients were randomized into three arms, receiving placebo or 10 or 25mg daily for 24 weeks. Despite positive phase 1 safety data from 40mg cohort, management opted against this dose, admitting the toxicology profiles had not be completed prior to WILLOW's initiation (Exhibit 5, Exhibit 6). WILLOW's primary endpoint was time to first exacerbation over 24 weeks, with key secondary efficacy endpoints including rate of exacerbations, ppFEV1, and NE sputum concentration.

Exhibit 5: WILLOW (phase 2) trial design
Examines the effects of 10mg and 25mg on time to first PE over 24 weeks



Source: Company presentations

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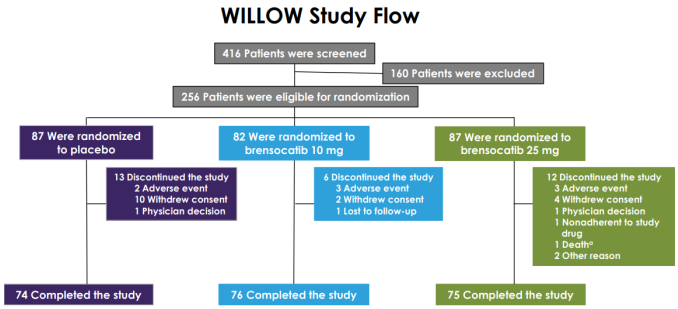
Exhibit 6: Low drop-out rates in WILLOW given relatively benign safety
A total of 6/169 (~4%) discontinued study due to adverse events vs 2/87 (2%) in the placebo group



Source: Company presentations

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Select KOL feedback

... the WILLOW trial, this was a very well-done study, they identified a clear patient population, they did a randomized trial with two dosing strategies... and they clearly defined what an exacerbation was... an exacerbation is kind of a murky thing, it's similar to exacerbations in COPD and asthma, which are always a little bit difficult to define, but you have to do it obviously when you have a clinical trial...

Safety profile remains solid with limited evidence of increased PLS-symptoms

Similar to the phase 1, brensocatib's safety profile was favorable in WILLOW, with the drug deemed well tolerated by the investigators—nor did our experts flag any major issues. A total of 63% in the 10mg and 54% in the 25mg cohorts had an AE (excluding bronchiectasis exacerbations) vs 38% placebo, with the majority categorized as mild or moderate (88% 10mg and 75% 25mg; Exhibit 7). There was one patient death in the 25mg treatment group, although it was not considered treatment related. In addition, a greater portion of placebo patients discontinued therapy vs either of the two active arms due to an AE (Chalmers DJ, 2020).

Exhibit 7: No major adverse events stand out between placebo vs two treatment groups
Cough was the most common adverse event followed by headache and sputum increase

Event	Placebo (n=85)	10mg (n=81)	p-value for 10mg vs Placebo	25mg (n=89)	p-value for 25mg vs Placebo
Any adverse event-no. (%)	67 (79)	75 (93)	0.01	74 (83)	0.47
Any adverse event, excluding bronchiectasis exacerbations-no. (%)	32 (38)	51 (63)	0.001	48 (54)	0.03
Maximum severity of events-no. (%)					
Grade 1: mild	21 (25)	27 (33)	0.22	30 (34)	0.19
Grade 2: moderate	33 (39)	44 (54)	0.04	37 (42)	0.71
Grade 3: severe	13 (15)	3 (4)	0.01	6 (7)	0.07
Grade 4: life-threatening	0	1 (1)	0.30	0	NE
Grade 5: death	0	0	NE	1 (1)	0.33
Most common adverse events-no. (%)					
Cough	10 (12)	15 (19)	0.22	12 (13)	0.73
Headache	3 (4)	8 (10)	0.10	12 (13)	0.02
Sputum increased	6 (7)	9 (11)	0.36	9 (10)	0.47
Dyspnea	2 (2)	3 (4)	0.61	9 (10)	0.04
Infective exacerbation of bronchiectasis	9 (11)	5 (6)	0.31	4 (4)	0.13
Diarrhea	9 (11)	5 (6)	0.31	3 (3)	0.06
Adverse event resulting in discontinuation of placebo or brensocatib-no. (%)	9 (11)	6 (7)	0.48	6 (7)	0.37

Source: Chalmers et al.

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Once again, there was acute focus on skin, dental, and infection-related AEs. As discussed above, the first two are known symptoms related to PLS. At the same time, infection remains of interest given brensocatib's underlying mechanism, i.e., "defanging" neutrophils, which are among the first line of defense against pathogens. Admittedly, data suggest DPP-1 is unlikely to have an impact on the maturation, release, and/or overall function of neutrophils. Still, it remains top of mind for many clinicians.

Overall, the incidence of these AEs were modestly higher in both treatment cohorts vs the placebo in WILLOW—with the highest proportion of skin-related AEs in the 25mg cohort and dental AEs in the 10mg cohort, although placebo arm had the greatest incidence of infection (Exhibit 8). Our KOLs did not find these rates worrisome, though they noted there would likely continue to be significant interest in these outcomes in the phase 3 ASPEN (see below) given the longer treatment duration (52 vs 24 weeks), reflecting a closer representation of what chronic treatment should look like.

Exhibit 8: Adverse evets of special interest in WILLOW
The treatment groups had a slightly higher incidence of skin/ dental AEs than placebo

Event	Placebo (n=85)	10mg (n=81)	25mg (n=89)
AEs of special interest-no. (%)	23 (27)	27 (33)	35 (40)
Skin	10 (12)	12 (15)	21 (24)
Dental	3 (4)	13 (16)	9 (10)
Infection	15 (18)	11 (14)	15 (17)
Most common serious adverse events-no. (%)			
Infective exacerbation of bronchiectasis	9 (11)	5 (6)	4 (4)
Pneumonia	3 (4)	0 (0)	4 (4)

Source: Chalmers et al.

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Select KOL feedback

Thinking about the MoA, the analogy I often use is it's like if you have a fire in your house and you want firefighters to come put out the fire, that's an important function to prevent your house from burning down… however if when they put out the fire they spray too much water and cause additional damage elsewhere, that's not as positive… you don't want a tiny candle burning to result in them spraying your entire house down…

In this trial, not a single patient stopped therapy because of symptoms akin to those seen in PLS, but again this was a 24 week trial… you wonder what happens at 52 weeks… is it just that you need a longer period of time for those infection issues to manifest?

I would expect it's possible for infections elsewhere to occur… but if these are the only things that are happening you can monitor and stop that before it truly progresses…

… also, the safety signs that you would look for, hyperkeratosis, gum disease… at least at 24 weeks, didn't bear out…

But, what will change if it's going on for 52 weeks, I don't know… that's where some of my concerns on the safety profile come into play because you now have more patients over a longer period of time, particularly things that you never want to see, like bleeding into the brain… but there's no mechanistic rationale as to why that would happen…

Efficacy trends very favorable, with declines in PEs and NSPs—although 10mg outperformance likely causing some pause

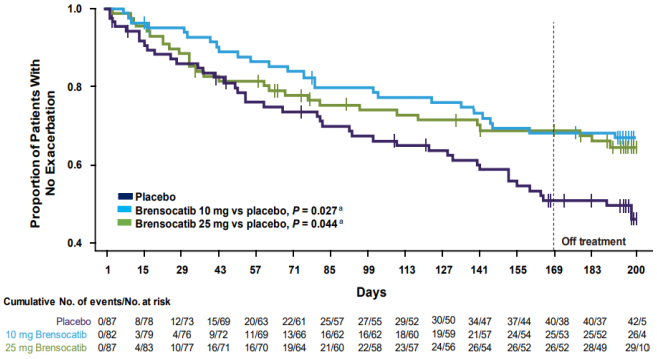
In terms of efficacy, the WILLOW data were encouraging with both doses of brensocatib meeting the primary endpoint—time to first PE—with a p=0.03 in the 10mg and p=0.04 in the 25mg dosing cohorts. The DPP-1 inhibitor also reduced overall PEs by 36% in the 10mg cohort and 25% in the 25 mg cohort, although curiously only the former met statistical significance (p=0.04) vs the latter (p=0.17).

Select KOL feedback

I found the WILLOW data very compelling, there was almost a 40% reduction in exacerbations, and they couldn't even do the proper statistics for the median time to first exacerbation because it pushed the 10mg and 25mg groups too far out… severe exacerbations were also greatly reduced… but again, the numbers were small, relatively

The other thing that's happening is you're not necessarily just dealing with acute exacerbations, reducing PEs may be a signal that you're also addressing the chronic inflammation… and therefore preserving lung integrity, lung function, all that stuff… and so in bronchiectasis decreasing exacerbations may mean that you are doing both…

Exhibit 9: Reduction in time to first exacerbation
Brensocatib significantly prolonged the time to first PE in both dose cohorts



Source: Company presentations

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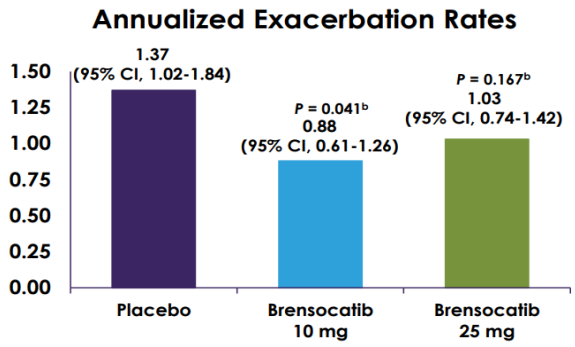
Exhibit 10: Frequency of exacerbations per patient per year
Brensocatib significantly reduced PE rates in the 10 mg group, with positive trends in the 25 mg cohort



Source: Company presentations

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While it's unclear why PE responses were not dose-dependent—admittedly one of the biggest investor inbounds—management noted the 25mg cohort had more hyper-exacerbators (up to 6 PEs), which may have contributed to the attenuation in the 25mg arm based on post-hoc analyses. While our KOLs indeed acknowledged this possibility, they still felt more data was needed. That said, they didn't think this outcome invalidated brenso, with the 10mg dose clinically meaningful, in their view.

These favorable efficacy trends broadly tracked NSP reductions. While Insmed has not yet disclosed the magnitude of the effect at week 24, NE activity was significantly lower in both the treatment groups vs the placebo in WILLOW, both arms reaching stat sig: 10mg cohort/ P=0.034 and 25mg cohort/ P=0.021 (Exhibit 11) (Chalmers DJ, 2020).

As noted above, there is some debate in the field over the exact role NE plays in bronchiectasis, which unlike other neutrophil-driven lung diseases like COPD and CF, is less well characterized. Notably, in WILLOW, NE reductions did not correlate perfectly with PE improvements: while there were greater declines in NSP activity in the 25mg arm vs the 10mg arm (Exhibit 11), participants treated with the latter dose had greater PE improvements (Chalmers DJ, 2020). All that said, our experts didn't see cause for concern, admitting hyper-exacerbators may indeed have confounded the results.

Select KOL feedback

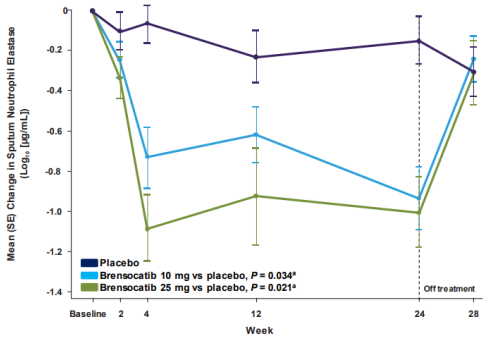
Neutrophil elastase concentration in the sputum was reduced… so the drug is doing what it's supposed to do, but there's also concern that NE isn't a mediator for reduction in exacerbations… it also brings into question whether this mechanism is at play… or if it's potentially something else… you know, it's not just NE, there's CatG and others that are involved… that's one challenge with upstream inhibition… you don't really know what's driving the activity

The one slight concern is that whole issue of the 25mg dose having less of an effect on exacerbation reduction than the 10mg dose… One hypothesis may be its just pure chance… but, it could also be that if you immunosuppress too much, at least this pathway, it may lead to exuberant bacterial infections… worse exacerbations and more exacerbations… there's like a U-shaped curve…

I think this is just a combination of statistical noise plus some imbalances, particularly ≥ 3 exacerbation group in the 25mg… it may be that these hyper-exacerbators have a different phenotype or are a different type of patient, with different characteristics…

Those kinds of issues get washed away when you have a larger trial, where you are more likely to have more equal distribution of those issues…

Exhibit 11: Brensocatib reduced neutrophil elastase concentrations in WILLOW
While [NE] was lower for both treatment groups, the higher 25mg dose reached greater statistical significance



Source: Company presentations

BofA GLOBAL RESEARCH

No stone unturned, no detail overlooked: ASPEN designed to definitively answer the question over brenso's clinical value

Based on WILLOW's positive results, Insmed initiated a double-blind, placebo controlled pivotal phase 3 of brensocatib for NCFB, ASPEN in Dec 2020. The trial design is similar to the phase 2, a positive—in our view—given the strength of the results. Still, there are a few notable differences including the 1) primary endpoint, with rate of PEs selected over time to first exacerbation prior; 2) some of the stratification criteria; 3) treatment length, extended to 52 weeks from 24; and 4) overall powering.

Regarding the latter, Insmed took a very conservative approach. While the placebo exacerbations incidence rate was 1.37 per person-year in WILLOW, the team still assumed the rate would be 1.20. In addition, enrollment was substantially increased (N=1,682 vs 256), leaving ASPEN 90% powered to detect a 30% reduction in PEs vs 80% power to detect a 40% delta in WILLOW.

According to our experts, baseline characteristics between the two trials look similar (Exhibit 12), offering another measure of support considering the historically poor success rates of bronchiectasis RCTs (see below). In addition, ASPEN's results will be stratified by 1) *P. aeruginosa* and 2) hyper-exacerbators, which should help answer some questions over the lack of a dose-dependent response in the 25mg group (see above).

Exhibit 12: Baseline characteristics for WILLOW and ASPEN
Key differences, albeit unlikely to have a meaningful impact on the outcome, include the lower frequency of secondary COPD and asthma

Characteristics	ASPEN*	WILLOW
Number of patients	1,682**	256
Mean age (years)	61.3	64.1
≥75 years (n, %)	262,15.6%	48, 18%
Female (n, %)	1,089, 64.7%	174, 67.9%
Number of patients with history of COPD as secondary*** (n, %)	241, 14.3%	42, 16.4%
Number of patients with history of asthma as secondary*** (n, %)	302, 17.9%	64, 25.0%
Pseudomonas aeruginosa positive (n, %)	589, 35.0%	89, 34.8%
Chronic macrolide use (n, %)	285, 16.9%	40, 15.6%
≥3 exacerbations in prior 12 months (n, %)	492, 29.3%	84, 32.8%
2 exacerbations in prior 12 months (n, %)	1,190, 70.7%	172, 67.2%

Source: Company presentations; * preliminary figures; **evaluable adult subjects; *** As reported by medical history

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Select KOL feedback

On the first point, we know whether the baseline characteristics in WILLOW resulted in any imbalances… the groups look pretty balanced to me… it was mainly the increase in exacerbations in the 25mg group that stood out to me, that was an outlier and yet that group still nonetheless showed a benefit, albeit not largely stat sig on the primary…

Other things to think about on the baseline characteristics is confounding with other disease states, particularly COPD and asthma… because exacerbations these patients are having could really be related to COPD and asthma vs bronchiectasis… in WILLOW, the trial rates were in the 20% range, that makes sense, if it was like 50% I would have to question whether it's actually doing anything for bronchiectasis… looking at the baseline characteristics for ASPEN, there's a slightly lower incidence of COPD and asthma in ASPEN… this only increases the probability of a positive trial…

…and, overall, the baseline characteristics are pretty in line with what I am seeing in the clinic…

Based on its powering assumptions, Insmed believes a 20% or greater reduction in PE would meet the p ≤ 0.01 threshold, with a 15-20% improvement reaching p ≤ 0.05. In addition to an encouraging early blended-blinded rate (1.12-1.15; see above) Insmed has highlighted, 1) the dropout rate in ASPEN has been in-line or better than that observed in WILLOW; and 2) the independent Data Safety Monitoring Committee has met 5 times to review safety updates and unanimously voted to recommend continuing the study.

Ultimately, in our conversations with management, the team stressed there is no "plan B", that is, ASPEN was specifically designed to identify whether brensocatib offers a clinical benefit for NCFB. And if the study fails, it means the answer is negative—no prespecified or post-hoc subgroup analyses are planned, with a negative outcome triggering the end of development.

Here though, we'd argue Insmed has a favorable regulatory path—likely facilitated by the lack of effective options for NCFB and ASPEN's design. FDA approval requires hitting statistical significance on only one dose (10 or 25mg). Notably though, as the company is only running a single phase 3 (instead of 2 separate studies), the p value must be ≤ 0.01. That said, the agency indicated a willingness to be flexible as long as one of the doses in ASPEN is still ≤ 0.05, agreeing, in this case, to consider the WILLOW data as part of an NDA. At the same time, brensocatib has been granted Breakthrough Therapy Designation by FDA and PRIME designation by EMA.

KOLs: ASPEN well designed to avoid previous pitfalls—with additional tailwinds from COVID-19

Overall, our KOLs were favorable on ASPEN's design. Looking at the primary endpoint, most saw potential for greater resolution vs WILLOW on the primary given the longer

treatment duration and larger population possibly offsetting, at least partially, the typical attenuation in efficacy that occurs when progressing from a phase 2 to a phase 3.

Despite their favorable outlook on ASPEN, along with the positive WILLOW data, our KOLs admitted there were some uncertainties regarding the trial and specifically the endpoint—likely a major driver of investor concern.

Previous NCFB studies have a poor track record—which may come down to trial design, including selection criteria and endpoint definition

On one hand, bronchiectasis trials have largely failed. In a literature review, across 31 primary endpoints evaluated in 23 RCTs, only 14 reached stat sig (i.e., 48%)—with only 12 of these studies meeting their primaries. To be fair, many of these trials focused on drug classes that have had little success, i.e., antibiotics and anti-inflammatories. Still, the list of studies did include NE inhibitor AZD9668 (discussed above) and CXCR2 receptor inhibitor AZD5069 (discontinued for COPD in 2020).

But beyond MoA, trial design likely had a significant impact, particularly with regards to endpoint selection and/or design according to the authors of the review. Among studies using exacerbation-based endpoints, definitions varied considerably, with several categorized as "subjective." These differences included number of symptoms, time-period, self-identified vs physician diagnosed, and even surrogate markers (e.g., antibiotic use). For example, among 19 studies included in the review with exacerbation end-points, 11 required a history of PE for entry, with only two necessitating this be longer than 12 mos. Inclusion criteria was similarly heterogeneous (Crichton M, 2019).

Our KOLs weren't as concerned for ASPEN, nothing 1) its focus on establishing a defined patient population, stratified for confounding factors, 2) the efforts to specify and standardize the definition of an exacerbation, and 3) its expanded treatment length/ trial population, both of which should limit variability/ confounding effects.

With exacerbations likely to increase post C-19 related lock-downs, the overall resolution may increase

Our experts also thought COVID-19 could be a tailwind for the study. Much of the enrollment occurred in 2021, when lockdowns were still ongoing/ common. According to the literature, in general bronchiectasis patients had fewer exacerbations during this phase of the pandemic—likely due to the decrease in exposure to potential triggers, although other studies suggest there was a renewed adherence to treatment regimens given concerns about the virus (Borecki S, 2023). Indeed, in Zambon's (private, not covered) phase 3 PROMIS-II for nebulized CMS powder in NCFB, the PE rate in the placebo group was reduced ~50% during the pandemic, a factor contributing to the trial's failure. In contrast, however, patients in ASPEN may experience the reverse, that is, having more exacerbations upon exiting lock-downs—potentially increasing the overall resolution of the trial.

Select KOL feedback

So what could go wrong… you have to ask the question what is the likelihood that the findings from WILLOW were simply just by chance… were there certain imbalances in the patient characteristics such that ones in ASPEN could result in a negative trial… or, are there things in ASPEN that have now changed…

Starting with the latter, the primary endpoint is exacerbation rate and not time to first exacerbation, the primary in WILLOW, which isn't concerning… the concern here would be if you have a drug that works, but is only mildly effective… you would need a larger, longer trial to demonstrate efficacy because you would have greater power…

In this case, you have doubled the time period and you have also increased the patients by a lot… so if you already have pretty strong data in the phase two this will only increase the probability of that holding true…

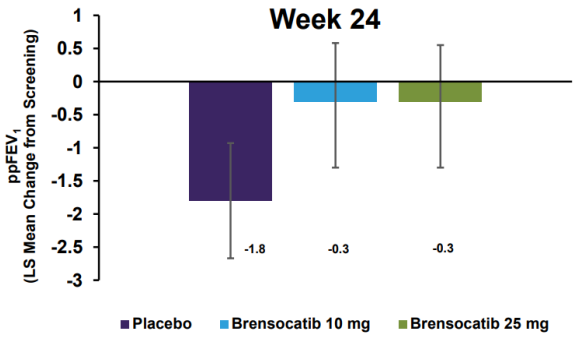
So I am not really concerned about the 1.37 placebo rate in WILLOW as long as the event rate in ASPEN is not significantly lower… if it's like 25% lower than in WILLOW, then it just become a question of power…

Optimism PROs may hit, which while likely to impact commercial opportunity, not critical for approval

Beyond PE, our KOLs flagged the 1) QoL-B, a PRO that measures how patients feel and function, and 2) ppFEV1, a functional measure (percent predicted forced expiratory volume in 1 second) as key secondaries to focus on given potentially positive commercial implications. According to our experts, success on both could easily make a clearer case for use in (especially) more mild/ moderate cases, where patients may have fewer exacerbations (discussed above).

Admittedly, in WILLOW, the QoL-B did not reach the minimally important difference (Chalmers DJ, 2020). That said our experts thought it easily possible 24 weeks of therapy was not sufficiently long enough to capture a benefit, especially as the onset of treatment responses required ~12 days given brenso's MoA (see above). Similarly, ppFEV1 was also not statistically significant in WILLOW, though declines were markedly lower in those treated with brensocatib, -1.8 ± 0.9 in placebo vs -0.3 ± 0.9 in the 10mg arm and -0.3±0.8 in the 25mg (Exhibit 13), (Chalmers DJ, 2020). As with the PROs, there was optimism greater exposure/ greater population would reveal a clear separation.

Exhibit 13: Reduction in post-bronchodilator ppFEV1 at week 24
Treatment with brensocatib appears to offer a benefit to pulmonary function, though more data is needed to determine the magnitude



Source: Company presentations

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Select KOL feedback

The question is, how do exacerbations play a role in this… and there are two concepts at play… the first is that when you have an exacerbation your lung function declines… your lung function is measured by FEV1, everyone's FEV1 over time declines after it peaks in your mid-20s… but when you have progressive lung disease your rate of decline accelerates…

And when you have an exacerbation, it's basically an added hit on your lung function and so every time it happens your lung function is worse… so preventing exacerbations from happening will help mitigate that decline in lung function that happens…

Abbreviations

AEs: adverse events
ANC: asymptotic normalization coefficients
ATS: American Thoracic Society
BRR: Bronchiectasis Research Registry
CatG: cathepsin G
CMS: colistimethate sodium
COPD: chronic obstructive pulmonary disease
CRSsNP: chronic rhinosinusitis without nasal polyps
CTSC: cathepsin C
DPP-1: dipeptidyl peptidase-1
EMA: European Medicines Agency
FDA: Food and Drug Administration
FEV1: forced expiratory volume
HS: hidradenitis suppurativa
LCQ: Leicester Cough Questionnaire
MoA: mechanism of action
NCFB: non-cystic fibrosis bronchiectasis
NDA: new drug application
NE: neutrophil elastase
NSPs: neutrophil serine proteases
PE: pulmonary exacerbation
PLS: Papillon-Lefèvre syndrome
ppFEV1: percent predicted forced expiratory volume in one second
Pr3: proteinase 3
PRO: patient-reported outcomes
QoL: quality of life
QoL-B: Quality of Life-Bronchiectasis (a PRO)
RCTs: randomized controlled trials
SAEs: serious adverse events
SGRQ: St. George's Respiratory Questionnaire
TPIP: treprostinil palmitil inhalation powder
TAM: total addressable market

Bibliography

Aksamit TR, L. N. (2023). Association of Baseline and Subsequent Bronchiectasis Exacerbations in Patients From the US Bronchiectasis and NTM Research Registry (BRR). *ATS Poster Sessopm*.

Borecki S, V. I. (2023). Treatment adherence and anxiety levels of bronchiectasis patients in the COVID-19 pandemic . *Medicine*, 102:19.

Chalmers DJ, H. C. (2020). Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. *The New England Journal of Medicine*, 2127-2137.

Chalmers JD, K. R. (2023). Dipeptidyl peptidase 1 inhibition as a potential therapeutic approach in neutrophil-mediated inflammatory disease. *Front Immunol*, Dec 14:14:1239151.

Chalmers, J., Moffitt, K., Suarez-Cuartin, G., Sibila, O., Finch, S., Furrie, E., . . . Fardon, T. (2017). Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis. *Am J Respir Crit Care Med.*, May 15;195(10):1384-1393.

Crichton M, A. S. (2019). A systematic review of pharmacotherapeutic clinical trial end-points for bronchiectasis in adults. *European Respiratory Review* , 1-14.

Ghosh P, G. I. (2021). Translation and validation of the Quality-of-Life Bronchiectasis questionnaire in Swedish, and correlation with clinical outcomes. *European Respiratory Journal* , 58: Suppl. 65.

Gramegna A, A. F. (2017). Neutrophil elastase in bronchiectasis. *Respir Res*, Dec 19;18(1):211. doi: 10.1186/s12931-017-0691-x.

Hnin K, N. C. (2015). Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. *Cochrane Library*, (8):CD001392.

J, C. (2017). Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis. *Am J Respir Crit Care Med*, May 15;195(10):1384-1393.

King, P. (2018). The Role of the Immune Response in the Pathogenesis of Bronchiectasis. *BIoMed Research International*.

Macfarlane L, K. K. (2021). Diagnosis and management of non-cystic fibrosis bronchiectasis. *Clin Med (London)*, 571-577.

Metersky ML, L. M. (2023). Outcomes of Patients With Bronchiectasis by Disease Severity: Subgroup Analysis From theBrensocatib WILLOW Study. *ATS Poster Session*.

Miller BE, M. R. (2017). Epithelial desquamation observed in a phase I study of an oral cathepsin C inhibitor (GSK2793660). *British Journal of Clinical Pharmacology*, 2813-2820.

O'Donnell, A. (2022). Bronchiectasis — A Clinical Review. *New England Journal of Medicine*, 533-545.

Palmér R, M. J. (2018). Dipeptidyl Peptidase 1 Inhibitor AZD7986 Induces a Sustained, Exposure-Dependent Reduction in Neutrophil Elastase Activity in Healthy Subjects. *American Society for Clinical Pharmacology & Therapeutics*, 1155-1164.

Somayaji R, G. C. (2019). Duration of antibiotic therapy in non-cystic fibrosis bronchiectasis. *Curr Pulmol Rep*, 1-9.

Stockley, R., De Soyza, A., Guna, K., Perrett, J., Forsman-Semb, K., Entwistl, N., & Snell, N. (2013). Phase II study of a neutrophil elastase inhibitor (AZD9668) in patients with bronchiectasis. *Respir Med*, Apr;107(4):524-33.

Worth H, B. R. (2023). In 'real world' patients with COPD, exacerbation history, and not blood eosinophils, is the most reliable predictor of future exacerbations. *Respiratory Research*, 24; 2.

Price objective basis & risk

Insmed Incorporated (INSM)

Our 12-month PO is based on our NPV analysis of revenue forecasts assumptions. We model sales of Arikayce for refractory NTM-PD and frontline expansion (modified by a LOS of 80%). We assume a collective value for the pipeline: Brensocatib in NCFB (LOS: 65%), with potential expansion into CF (LOS: 20%), CRSsNP, and HS (LOS: 15%) and TPIP for PAH and PH-ILD (LOS: 50%). Given a WACC of 15%, in line with peers of similar size and risk, and a terminal growth rate of -10%, -40%, we estimate a value of $12/sh for Arikayce, $18/sh for Brensocatib, $8/sh for TPIP, $0.62/sh for the early pipeline, and $-2/sh for net cash, resulting in $37/sh.

Upside risks: 1) Arikayce full approval, 2) validation of Brensocatib in phase 3, with strong clinical efficacy and no safety concerns, 3) robust efficacy/ safety profile for TPIP in PAH and PH-ILD, 4) growth of translational medicine pipeline, including on-track IND-approvals, and 5) indications of strong commercial support from payers/ community-based providers.

Downside risks: 1) failure to achieve full approval/ commercial expansion of Arikayce in the EU and Japan, 2) failure to meet safety/ efficacy profile in Brensocatib (phase 3), especially due to meaningful infection risk, 3) marginal tolerability improvements, diminished efficacy, and/ or lack of differentiation of TPIP, 4) competition from disease modifying PAH agents, 5) failure of translational medicine pillar, 6) regulatory delays, and 7) commercial pushback from payers/providers.

Analyst Certification

I, Jason Zemansky, hereby certify that the views expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or view expressed in this research report.

US - Biopharmaceuticals Coverage Cluster

Investment rating	Company	BofA Ticker	Bloomberg symbol	Analyst
BUY				
	89bio, Inc	ETNB	ETNB US	Geoff Meacham
	Acumen Pharma	ABOS	ABOS US	Geoff Meacham
	Agios Pharmaceuticals	AGIO	AGIO US	Greg Harrison, CFA
	Amylyx Pharmaceuticals	AMLX	AMLX US	Geoff Meacham
	BioMarin	BMRN	BMRN US	Geoff Meacham
	BioXcel Therapeutics	BTAI	BTAI US	Greg Harrison, CFA
	BridgeBio Pharma	BBIO	BBIO US	Greg Harrison, CFA
	Caribou	CRBU	CRBU US	Geoff Meacham
	CRISPR Therapeutics	CRSP	CRSP US	Geoff Meacham
	Eli Lilly and Company	LLY	LLY US	Geoff Meacham
	HUTCHMED	HCM	HCM US	Alec W. Stranahan
	Immatics	IMTX	IMTX US	Alec W. Stranahan
	Insmed Incorporated	INSM	INSM US	Jason Zemansky
	Intellia Therapeutics	NTLA	NTLA US	Greg Harrison, CFA
	Janux Therapeutics	JANX	JANX US	Geoff Meacham
	Keros	KROS	KROS US	Greg Harrison, CFA
	Kiniksa Pharmaceuticals, Ltd.	KNSA	KNSA US	Geoff Meacham
	Krystal Biotech	KRYS	KRYS US	Alec W. Stranahan
	Kura Oncology	KURA	KURA US	Jason Zemansky
	Liquidia Corporation	LQDA	LQDA US	Greg Harrison, CFA
	Lyell Immunopharma	LYEL	LYEL US	Geoff Meacham
	MeiraGTx	MGTX	MGTX US	Alec W. Stranahan
	Merck & Co.	MRK	MRK US	Geoff Meacham
	Mineralys Therapeutics	MLYS	MLYS US	Greg Harrison, CFA
	Neumora Therapeutics	NMRA	NMRA US	Geoff Meacham

US - Biopharmaceuticals Coverage Cluster

Investment rating	Company	BofA Ticker	Bloomberg symbol	Analyst
	Rani Therapeutics	RANI	RANI US	Geoff Meacham
	Regenxbio, Inc.	RGNX	RGNX US	Alec W. Stranahan
	Revolution Medicines	RVMD	RVMD US	Alec W. Stranahan
	Rocket Pharmaceuticals, Inc.	RCKT	RCKT US	Greg Harrison, CFA
	Royalty Pharma	RPRX	RPRX US	Geoff Meacham
	Sana Biotechnology	SANA	SANA US	Geoff Meacham
	SpringWorks	SWTX	SWTX US	Alec W. Stranahan
	Syndax Pharmaceuticals	SNDX	SNDX US	Jason Zemansky
	Travere Therapeutics Inc	TVTX	TVTX US	Greg Harrison, CFA
	Turnstone Biologics	TSBX	TSBX US	Geoff Meacham
	Vertex Pharmaceuticals Inc.	VRTX	VRTX US	Geoff Meacham
	Werewolf Therapeutics	HOWL	HOWL US	Jason Zemansky
	Xencor	XNCR	XNCR US	Alec W. Stranahan
NEUTRAL				
	AbbVie	ABBV	ABBV US	Geoff Meacham
	Alector, Inc	ALEC	ALEC US	Greg Harrison, CFA
	Amgen Inc.	AMGN	AMGN US	Geoff Meacham
	Arcus Biosciences	RCUS	RCUS US	Jason Zemansky
	Beam Therapeutics	BEAM	BEAM US	Greg Harrison, CFA
	Biogen Inc.	BIIB	BIIB US	Geoff Meacham
	Bristol-Myers Squibb	BMY	BMY US	Geoff Meacham
	Cytokinetics, Incorporated	CYTK	CYTK US	Jason Zemansky
	Editas Medicine	EDIT	EDIT US	Greg Harrison, CFA
	Erasca	ERAS	ERAS US	Alec W. Stranahan
	Esperion	ESPR	ESPR US	Jason Zemansky
	Exscientia	EXAI	EXAI US	Alec W. Stranahan
	IGM Biosciences	IGMS	IGMS US	Greg Harrison, CFA
	Johnson & Johnson	JNJ	JNJ US	Geoff Meacham
	Kymera Therapeutics	KYMR	KYMR US	Geoff Meacham
	Moderna	MRNA	MRNA US	Geoff Meacham
	Pfizer	PFE	PFE US	Geoff Meacham
	Recursion Pharmaceuticals, Inc.	RXRX	RXRX US	Alec W. Stranahan
	Tyra Biosciences	TYRA	TYRA US	Greg Harrison, CFA
	Vir	VIR	VIR US	Geoff Meacham
	Y-mAbs Therapeutics, Inc	YMAB	YMAB US	Alec W. Stranahan
UNDERPERFORM				
	AlloVir, Inc.	ALVR	ALVR US	Jason Zemansky
	CureVac	CVAC	CVAC US	Geoff Meacham
	Day One Biopharmaceuticals	DAWN	DAWN US	Alec W. Stranahan
	Novavax	NVAX	NVAX US	Alec W. Stranahan
	Regeneron Pharmaceuticals Inc.	REGN	REGN US	Geoff Meacham
	Reneo Pharmaceuticals	RPHM	RPHM US	Jason Zemansky
	TG Therapeutics	TGTX	TGTX US	Alec W. Stranahan
	United Therapeutics Corporation	UTHR	UTHR US	Greg Harrison, CFA
RSTR				
	Gilead Sciences Inc.	GILD	GILD US	Geoff Meacham

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Business Performance	Numerator	Denominator
Return On Capital Employed	NOPAT = (EBIT + Interest Income) × (1 − Tax Rate) + Goodwill Amortization	Total Assets − Current Liabilities + ST Debt + Accumulated Goodwill Amortization
Return On Equity	Net Income	Shareholders' Equity
Operating Margin	Operating Profit	Sales
Earnings Growth	Expected 5 Year CAGR From Latest Actual	N/A
Free Cash Flow	Cash Flow From Operations − Total Capex	N/A

Quality of Earnings	Numerator	Denominator
Cash Realization Ratio	Cash Flow From Operations	Net Income
Asset Replacement Ratio	Capex	Depreciation
Tax Rate	Tax Charge	Pre-Tax Income
Net Debt-To-Equity Ratio	Net Debt = Total Debt − Cash & Equivalents	Total Equity
Interest Cover	EBIT	Interest Expense

Valuation Toolkit	Numerator	Denominator
Price / Earnings Ratio	Current Share Price	Diluted Earnings Per Share (Basis As Specified)
Price / Book Value	Current Share Price	Shareholders' Equity / Current Basic Shares
Dividend Yield	Annualised Declared Cash Dividend	Current Share Price
Free Cash Flow Yield	Cash Flow From Operations − Total Capex	Market Cap = Current Share Price × Current Basic Shares
Enterprise Value / Sales	EV = Current Share Price × Current Shares + Minority Equity + Net Debt + Other LT Liabilities	Sales
EV / EBITDA	Enterprise Value	Basic EBIT + Depreciation + Amortization

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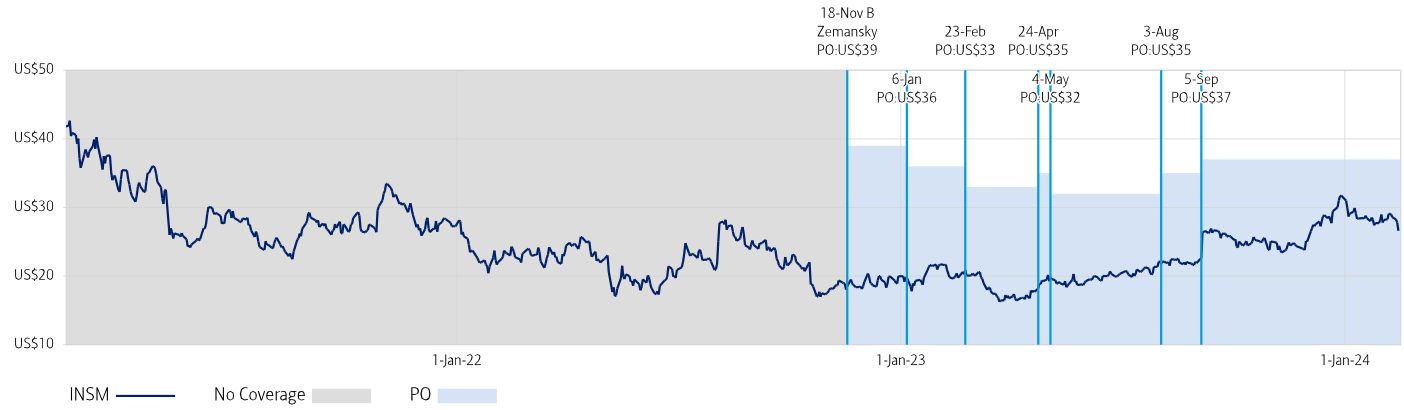
Insmed (INSM) Price Chart



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Equity Investment Rating Distribution: Health Care Group (as of 31 Dec 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	234	60.94%	Buy	115	49.15%
Hold	80	20.83%	Hold	36	45.00%
Sell	70	18.23%	Sell	29	41.43%

Equity Investment Rating Distribution: Global Group (as of 31 Dec 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	1895	53.62%	Buy	1083	57.15%
Hold	832	23.54%	Hold	454	54.57%
Sell	807	22.84%	Sell	383	47.46%

[R1] Issuers that were investment banking clients of BofA Securities or one of its affiliates within the past 12 months. For purposes of this Investment Rating Distribution, the coverage universe includes only stocks. A stock rated Neutral is included as a Hold, and a stock rated Underperform is included as a Sell.

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Investment rating	Total return expectation (within 12-month period of date of initial rating)	Ratings dispersion guidelines for coverage cluster[R2]
Buy	≥ 10%	≤ 70%
Neutral	≥ 0%	≤ 30%
Underperform	N/A	≥ 20%

[R2] Ratings dispersions may vary from time to time where BofA Global Research believes it better reflects the investment prospects of stocks in a Coverage Cluster.

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