BofA SECURITIES

Insmed Incorporated

Clearing the air II: Clinical success creates path to ~$5B peak sales; PO to $40

Reiterate Rating: BUY | PO: 40.00 USD | Price: 27.15 USD

Debate over commercial opportunity overdone; $5B in reach

Insmed (INSM) shares continue to face pressure (YTD INSM -12% vs NBI +2%), largely we think, due to skepticism over DPP-1 inhibitor brensocatib ahead of the pivotal ASEPN readout in NCFB. As we previously argued, we suspect this stems from fundamental concerns over 1) the novel mechanism (see our MoA deep dive) and 2) the total market opportunity—the latter of which we review in this note. To get a clearer picture of the commercial landscape and dynamics likely to drive prescriber uptake/ payor discussions, we spoke with our pulmonologist KOLs again, analyzing the commercial potential of brensocatib across four scenarios reflecting different potential ASPEN outcomes (a miss and PE reductions of 15-20%; 20-35%; and 35%+). Ultimately, we think concerns are overdone, with ample room to achieve peak sales nearing Insmed's >$5B peak guidance for NCFB and CRSsNP, even under our more conservative assumptions. Supported by strong prescriber sentiment, we are increasing our LoS for the trial to 70% from 65% prior, underscoring our conviction in a positive outcome and meaningful upside (2030e BofA unadj $2.8B vs $2.5B cons). Reiterate Buy and raise our PO to $40 from $37 prior.

Low barriers to entry, with upside even on a modest win

Given the lack of effective agents in the space (current SoC includes airway clearance methodologies marked by modest efficacy), our KOLs saw limited barriers to entry. Indeed, even in the case of a modest 15% PE reduction—the floor, according to our KOLs, necessary to be clinically relevant—we see potential upside of ~$2.8B by 2035. In contrast, should ASPEN's results look similar to the phase 2 WILLOW data (i.e., PE reductions ranging from the mid-20s to <35%, the most likely outcome in our view), we forecast a peak potential of ~$4.2B with further upside/ downside based on the exact outcome. Alternatively, should brenso drive reductions >35%—admittedly unlikely, we think—peak sales could reach $5.2B by 2035 with room for additional upside from incremental increases in market penetration and pricing premium within the bounds of our experts' guidance. Ultimately though, with downside protection from an ASPEN miss from Arikayce 1L and TPIP, we continue to like the risk/ reward profile for shares.

Win likely to improve outlook for I&I indications

Beyond NCFB, we think a positive outcome for ASPEN has clear readthroughs to indications beyond NCFB and in I&I—notably CRSsNP (phase 2b enrolling; top-line expected 2025e) and HS (phase 2 planned to initiate 2H24 pending positive data from ASPEN), with neutrophils thought to have an outsized role in pathology. We currently model each with a LoS of 15% and wouldn't be surprised if much of the Street similarly forecasts modest contributions, if any.

Estimates (Dec) (US$)	2022A	2023A	2024E	2025E	2026E
EPS	(3.91)	(5.34)	(4.93)	(4.04)	(1.90)
EPS Change (YoY)	-0.8%	-36.6%	7.7%	18.1%	53.0%
Consensus EPS (Bloomberg)			(4.52)	(3.56)	(1.78)
DPS	0	0	0	0	0
Valuation (Dec)					
Free Cash Flow Yield*	-10.2%	-13.6%	-14.7%	-13.2%	-7.0%

* For full definitions of *iQmethod℠* measures, see page 15.

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Refer to important disclosures on page 16 to 18. Analyst Certification on page 13. Price Objective Basis/Risk on page 13. 12663014

Timestamp: 23 February 2024 05:00AM EST

23 February 2024

Equity

Key Changes

(US$)	Previous	Current
Price Obj.	37.00	40.00
2025E Rev (m)	684.5	584.8
2026E Rev (m)	1,379.0	1,162.3
2025E EPS	-3.78	-4.04
2026E EPS	-1.10	-1.90

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Stock Data

Price	27.15 USD
Price Objective	40.00 USD
Date Established	22-Feb-2024
Investment Opinion	C-1-9
52-Week Range	16.04 USD - 32.00 USD
Mrkt Val (mn) / Shares Out (mn)	4,032 USD / 148.5
Free Float	98.6%
Average Daily Value (mn)	45.77 USD
BofA Ticker / Exchange	INSM / NAS
Bloomberg / Reuters	INSM US / INSM.OQ
ROE (2024E)	NA
Net Dbt to Eqty (Dec-2023A)	NA
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:

CRSsNP: chronic rhinosinusitis without nasal polyps
HS: hidradenitis suppurativa
I&I: inflammation and immunology
LoS: likelihood of success

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iQprofile℠ Insmed Incorporated

iQmethod℠ **– Bus Performance***

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Return on Capital Employed	-32.0%	-49.7%	-67.5%	-82.2%	-52.1%
Return on Equity	-193.2%	NM	NM	NM	NM
Operating Margin	-186.4%	-232.5%	-199.2%	-116.6%	-25.0%
Free Cash Flow	(410)	(550)	(593)	(531)	(281)

iQmethod℠ **– Quality of Earnings***

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Cash Realization Ratio	NM	NM	NM	NM	NM
Asset Replacement Ratio	1.9x	2.4x	1.0x	1.1x	1.1x
Tax Rate	NM	NM	NM	NM	NM
Net Debt-to-Equity Ratio	58.2%	NM	NM	NM	NM
Interest Cover	-20.0x	-19.0x	-17.0x	-14.0x	-5.4x

Income Statement Data (Dec)

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Sales	245	305	377	585	1,162
% Change	30.2%	24.4%	23.6%	55.0%	98.8%
Gross Profit	190	240	294	444	895
% Change	31.8%	26.0%	22.8%	51.0%	101.4%
EBITDA	(447)	(699)	(735)	(665)	(273)
% Change	-23.9%	-56.4%	-5.2%	9.6%	59.0%
Net Interest & Other Income	(23)	(37)	(44)	(49)	(53)
Net Income (Adjusted)	**(482)**	**(750)**	**(796)**	**(730)**	**(344)**
% Change	**-10.8%**	**-55.7%**	**-6.2%**	**8.2%**	**52.9%**

Free Cash Flow Data (Dec)

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Net Income from Cont Operations (GAAP)	(482)	(750)	(796)	(730)	(344)
Depreciation & Amortization	10	11	16	17	18
Change in Working Capital	7	(39)	(67)	(90)	(249)
Deferred Taxation Charge	NA	NA	NA	NA	NA
Other Adjustments, Net	64	242	265	286	308
Capital Expenditure	(10)	(13)	(11)	(13)	(14)
Free Cash Flow	**-410**	**-550**	**-593**	**-531**	**-281**
% Change	**-10.7%**	**-33.9%**	**-7.9%**	**10.5%**	**46.9%**
Share / Issue Repurchase	312	171	469	295	21
Cost of Dividends Paid	0	0	0	0	0
Change in Debt	0	(1)	0	0	0

Balance Sheet Data (Dec)

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Cash & Equivalents	1,074	482	508	271	10
Trade Receivables	30	41	38	53	84
Other Current Assets	170	406	256	305	443
Property, Plant & Equipment	56	65	67	69	73
Other Non-Current Assets	327	335	333	350	453
Total Assets	**1,656**	**1,330**	**1,201**	**1,048**	**1,063**
Short-Term Debt	0	0	0	0	0
Other Current Liabilities	190	226	301	454	654
Long-Term Debt	1,125	1,155	1,166	1,180	1,197
Other Non-Current Liabilities	253	281	310	339	369
Total Liabilities	**1,568**	**1,662**	**1,777**	**1,973**	**2,220**
Total Equity	**88**	**(332)**	**(576)**	**(925)**	**(1,157)**
Total Equity & Liabilities	**1,656**	**1,330**	**1,201**	**1,048**	**1,063**

* For full definitions of *iQmethod*℠ measures, see page 15.

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	1,685,749

Quarterly Earnings Estimates

	2023	2024
Q1	-1.17A	-1.31E
Q2	-1.78A	-1.12E
Q3	-1.11A	-1.01E
Q4	-1.28A	-1.49E

Background: High unmet need in NCFB supports commercial upside

While clinical success is the first hurdle, commercial outlook bigger question

Insmed's brensocatib, a DPP-1 inhibitor currently in a pivotal study for NCFB (ASPEN), remains a key source of debate, arguably contributing to recent share underperformance (INSM -12% vs NBI +2%). Following discussions with investors, we think there are two fundamental questions weighing on the drug's outlook. The first concerns the MoA, with previous attempts to inhibit DPP-1 and downstream NE largely failing, with other studies in NCFB similarly coming up short. At the same time, we suspect much of the skepticism reflects uncertainty over the opportunity, with many questioning whether brenso can capture meaningful share of what management estimates to be a >$5B TAM (which includes earlier-stage indication CRSsNP but not HS).

In our previous deep dive, we reviewed the first question, exploring the underlying science along with brenso's development strategy with our pulmonology KOLs. Ultimately, despite the concerns, we saw multiple reasons to be optimistic given brenso's clinical evidence to date as well as Insmed's thoughtful approach to ASPEN (see our brensocatib science review).

In this note, we focus on the second question to get a better sense of 1) what the NCFB patient population looks like, including frequency and ease of diagnosis; 2) unmet need, including likely prescriber interest and willingness to treat, especially by community-based pulmonologists; 3) payer response, specifically regarding access; and 4) the competitive landscape, along with potential benefits of a first-mover advantage.

Following discussions with our KOLs, we think a peak sales opportunity in NCFB of >$4B is well within reach—with opportunities for further upside depending on how close the reduction in PEs comes to the upper bounds established in WILLOW (i.e., the 36% in the 10mg cohort). Indeed, our KOLs were altogether optimistic on the outcome, suggesting 1) the potential for substantive pricing premiums based on the activity, given historical precedent, and 2) swift and robust uptake. Thus, while we recognize potential hurdles in entering an undeveloped market—potential payor pushback/prescriber education posing challenges—we still see solid upside for brenso even under conservative assumptions.

Based on their feedback, we have constructed four different scenarios based on ASPEN's potential readouts: 1) a miss; 2) reduction in PEs of 15-low 20s%; 3) low 20s-35%; and 4) 35%+. For each outcome, we forecast bresno's upside factoring in likely 1) pricing, 2) compliance rates, and 3) market penetration to quantify peak sales expectations. Ultimately, given our outcomes, we see potential paths to Insmed's forecast of >$5B TAM.

Diagnosis straightforward, unlikely to be a commercial bottleneck—although brenso approval unlikely to meaningfully expand overall market

According to our KOLs, diagnosis of bronchiectasis is overall straightforward and would be unlikely, by itself, to limit the opportunity. Indeed, following sputum collection and standard pulmonary function tests—both of which are routine and serve largely to exclude other potential issues—a positive diagnosis is made primarily on the basis of a chest radiograph or CT scan to confirm abnormal bronchial dilation (Smith, 2017).

Admittedly symptoms can be relatively nondescript, which can delay this process. However, our experts emphasized this could easily be driven by the absence of disease modifying treatments (antibiotics and anti-inflammatories are used to mitigate symptoms)—leaving prescribers to delay moving to a scan before ruling out other, more addressable conditions.

Select KOL feedback

it's such an easy diagnosis… it's just a question of whether someone orders a CAT scan when they have a coughing patient…

but, NCFB is often misdiagnosed and diagnosed late, symptoms are non-descript… the main one is really just cough, sometimes shortness of breath, often people are diagnosed with asthma/ COPD, given inhalers or bronchodilators that don't really help… it's not until someone does a CAT scan of the lungs that you identify actual bronchiectasis…

…so it can take years to be diagnosed, and by that point a significant amount of progressive lung disease and damage may have already occurred…

As part of its overview of the opportunity in NCFB, Insmed estimated a total addressable global population of ~1M. Our KOLs didn't disagree with this outlook. Still, given the overall ease of diagnosis, most didn't feel approval of an agent like brensocatib would measurably increase the overall addressable market. However, they did concede greater patient awareness/ interest and prescriber follow-up could well facilitate earlier diagnosis.

Thus, while some studies have estimated a ~8% annual growth rate in diagnosed patients 2001-2013—largely a product of improving diagnostics, we assume an overall total 5% growth in NCFB's prevalence from 2025 (brenso's potential launch) to 2030 (Weycker D, 2017).

Select KOL feedback

usually certain conditions are not diagnosed or checked for because there is no treatment that affects it or helps it, so people are like why do I care? … but in this case, there are some treatment options, the airway clearance methods

so I don't think this is going to be the case like Tyvaso for PH-ILD… I don't necessarily think the approval of the drug will lead to a massive uncovering of patients with the disease… still, if the drug does come out it may lead to greater awareness, greater education, earlier CAT scans…

Unmet need high, with current options focused on managing symptoms—with most KOLs predicting strong interest among prescribers in an approved agent

As mentioned above, there are no disease-modifying therapies available for NCFB. Rather, current treatment is two-pronged, designed to manage symptoms and reduce future exacerbations primarily by limiting/ prevent infections. These are accomplished via: 1) chest physical therapy/ airway clearance; 2) hydration to reduce mucosal buildup; 3) acute or chronic antibiotics and anti-inflammatory agents to address infections and PEs "flare-ups", and 4) bronchodilators, although their efficacy is debated (see our Insmed initiation for greater detail).

However, our experts stressed these options are on one hand difficult to tolerate and at the same time not especially effective—with disease progression still common. For these reasons, our KOLs estimated only ~80% of patients ultimately receive treatment, with the regimen largely based on disease severity. Not surprisingly, compliance is relatively low—with lifestyle and financial burdens also weighing on rates, estimated to be 52% for medications and 40% for airway clearance methods. Indeed, all told, only ~16% of patients overall are estimated to adhere to their regimens, further limiting efficacy (Thornton CS, 2022).

At the same time, our KOLs did not foresee challenges prescribing an agent like brenso, especially in community settings given 1) its once a day oral formulation and 2) relatively benign safety profile. Indeed, our experts pointed to increasing use of high-cost,

potentially complex treatments in the space—including notably Amgen's (Geoff Meacham) and Astra's (Jain/ Parry's) asthma treatment Tezspire or Insmed's own Arikayce. Ultimately, combined with the almost inevitable progression of NCFB patients, none of our experts felt prescribers would be hesitant to use brenso, should it demonstrate a benefit in ASPEN.

Select KOL feedback

airway clearance methods… during the process they actually make you feel worse, because you are jiggling up mucus, you're costing more… you just have to trust that they are working… they can have a benefit, but it's a huge pain and compliance Is an issue… and they ultimately don't usually prevent disease progression…

Given financial burden, KOLs expect limited pushback from payers with supportive economic argument for a disease modifying agents

With regards to likely payer responses—with implications for access—our experts were quick to emphasize the economic burden of bronchiectasis is high for both individual patients as well as the overall system. Most of these costs are associated with pulmonary exacerbations (PE), i.e., the hallmark "flare ups" of the disease. Especially in more advanced cases, PEs can drive some to seek in-patient care to manage symptoms including hypoxemia (low blood oxygen levels) and hemodynamic instability (abnormal blood flow affecting blood pressure) (Macfarlane L, 2021).

Indeed, a systematic review of NCFB patients found that more frequent exacerbators had higher rates of hospitalizations and annual costs than those with few/ no PEs. Indeed between 2008-2011, this review estimated the average annual treatment cost for a patient with PEs at $37,030, meaningful above those not suffering from PEs, $26,284. Further, costs associated with addressing individuals with >2 PEs per year were ~2X greater than patients with ≤2 (Geominne PC, 2019).

We note brensocatib reduced exacerbation-related hospitalizations as well as severe exacerbations vs placebo in WILLOW, providing, in our view, economic support for use. Recall specifically, exacerbation-related hospitalizations were 8% in the placebo arm vs 5.9% in both treatment cohorts, with severe exacerbations also lower: 0.19/ person/ year in the 10mg arm and 0.11 in the 25mg vs 0.30 for those on placebo (Chalmers DJ, 2020) (Chalmers DJ H. C., 2020).

Despite likely strong uptake in frequent exacerbators, use in earlier-stage patients and non-exacerbators less clear

In our conversations with Insmed, the team expected limited payor pushback, especially for established, frequent exacerbators. That said, they acknowledged use earlier in the treatment paradigm was an open question. While the value of preventing pulmonary damage from becoming more severe makes theoretical sense, it's unlikely we'll get insights into the clinical relevance of early intervention absent longer-term data. Indeed, our KOLs thought it may be difficult to detect a benefit in less frequent exacerbators, those with 0-1 PEs/year, over ASPEN's 52-week study period. That said, they intuitively saw benefit in treating patients earlier, as prophylaxis may ultimately limit the cycle of pulmonary degradation.

Similarly, while PEs are a hallmark of disease, our experts acknowledged only ~50% of their patients fit the ASPEN enrollment criteria (i.e., ≥2 exacerbations in the past 12 mos). When we caught up with management, they acknowledged an EU label would likely include language with similar restrictions, though the US label would be unlikely to. Still, they expect initial focus at launch to be on more frequent exacerbators, with potential to move earlier/ target less severe patients over time.

Here, our experts felt evidence of benefit beyond PE reduction—namely PROs and pulmonary function—could facilitate uptake. Indeed, most thought stat sig improvements in QoL-B and FEV1 would help make brenso relevant for treatment of these symptomatic patients without PEs. Admittedly while there were not minimally clinically important improvements in any of the symptom-based endpoints in WILLOW, our experts were encouraged by at least the positive trends in FEV1, with, in their view, the longer duration in ASPEN also potentially needed to reveal benefits.

Select KOL feedback

it's very likely that insurance will mandate that you've had two exacerbations, but I think it's part and parcel to the strength of the data... as well as those secondary endpoints... if those secondary endpoints are really positive, like specifically lung function, that will make physicians more excited to prescribe this...

and also exacerbations can be a very soft criteria... it's like remember last week when you were a little shorter of breath and coughing a bit... that was an exacerbation... it's a lot easier than other circumstances where you need an actual test... they will enforce the trial definition of an exacerbation, but people will find ways around it...

but, I don't really think prescribing is going to be a challenge, because, in contrast to the PAH space, there's no standard of care... it's like tell me what I need to try first, oh nothing, ok great, we've done that...

Competitive landscape expanding, although NT threats unlikely

In terms of the competitive landscape, despite a growing pipeline of candidates, our KOLs didn't foresee any near-term threats. Rather, most felt brensocatib's first-mover advantage would be significant, with solid formulary positioning and prescriber familiarity—with most other candidates still in phase 2. Moreover, our experts similarly flagged DPP-1 inhibitors from Boehringer Ingelheim and Chiesi (both private) as the more interesting candidates—but then admitted, that there was a chance both would be viewed as more "me-too" drugs (Exhibit 1).

Exhibit 1: Current pipeline products in development for NCFB
Two other inhibitors of the DPP-1 pathway are in development, though the first is likely 3+ years behind

Candidate	Lead Company	Target	Phase
Promixin*	Zambon	Protein synthesis	3
BI-1291583	Boehringer Ingelheim	DPP-1; CatC, CTSC	2
AP-PA02	Armata Pharma	*P. aeruginosa*	2
ARINA-1	Renovion	GSH synthesis	2
CHF-6333	Chiesi Farmaceutici S.p.A	Inhaled NE inhibitor	1b

Source: BofA Global Research, Biomedtracker, Company presentations
*private company, development plans unclear

BofA GLOBAL RESEARCH

Potential commercial synergies with Arikayce, other brenso targets

From a commercialization standpoint, we suspect investors are largely overlooking the synergies with Arikayce. Indeed, NTM-PD is thought cause ~10% of bronchiectasis, with an infection often leading to NCFB progression. At the same time, NCFB patients are more susceptible to developing NTM infections, with ~60% of patients testing positive at some point (Kowk N, 2020).

More critically, many pulmonologists treat both NCFB and NTM-PD, with implications regarding commercial infrastructure, specifically the sales force and medical liaisons—many of whom already have established relationships. Indeed, Insmed believes the current Arikayce salesforce (~70-75), along with ~125 additional FTEs, would likely be sufficient to support brenso's launch, with positive readthroughs to gross margins. We similarly note meaningful overlap between bronchiectasis and other pulmonary and I&I disorders Insmed is targeting. Between 40-80% of bronchiectasis patients also have CRS, the target of phase 2 BiRCh (CRSsNP; 2025e topline), with co-incidence a marker of more severe disease (Chalmers JD, 2023).

Deep Dive: What does the market opportunity look like for brensocatib?

Ultimately, our pulmonologist KOLs felt brenso's uptake in NCFB would largely depend on magnitude of PE reduction—and to a lesser extent on other functional endpoints, namely QoL-B and FEV1—given its impacts on prescriber/ patient interest, price, payor pushback/ GTN, and compliance. Leveraging their qualitative feedback, we therefore reviewed four distinct ASPEN outcomes: a 1) a miss on the primary outcome; 2) 15% to low 20s% reduction in PEs (corresponding to an p value ≤0.05 but > 0.01; 3) low 20s to a 35% reduction, representing a p ≤0.01; and 4) a best-case outcome of (35%+ reduction in PEs) (Exhibit 2).

For each case, we forecasted brenso's likely revenues, with impact on stock price and company valuation. In our view, the third scenario is most likely given our analysis, including our deep dive of the underlying MoA (see our science-focused deep-dive). With the upside dependent on the magnitude of benefit, we see a range of implications to the stock, with ultimate peak sales likely to range between $4.2B and $5.2B, we think.

Following management's comments, pricing floor likely ~$40k/ year; impact on compliance potentially more modest

At Insmed's investor event at the January healthcare conference (see our discussion takeaways), management stressed consensus projections for brenso's price were too "low" (~25K in 2025). But while stopping short of providing specific guidance, they stressed AstraZeneca's Fasenra offered an appropriate benchmark of ~$40K/yr gross as a floor. That said, in our direct discussions with the team, they admitted robust data could warrant premiums, with our KOLs forecasting a higher level threshold given historical precedents.

For this reason, for this exercise we assume an annual gross price of $40k for scenario II vs $45k and $50k for III and IV, respectively. We don't doubt robust outcomes (i.e., outcomes >30%) could well push these amounts meaningfully higher but opted for a more conservative approach. At the same, we assume compliance rates of 70%, 72.5%, and 75% for the three scenarios as we see a clear reduction in PE frequency over time likely improving general QoL and increasing adherence vs current SoC therapies.

Scenario I: Non-stat sig reduction in PEs (<15%) likely to leave shares trading ~$16/share

Largely on the basis of encouraging brenso's phase 2 data—along with positive KOL feedback—we currently estimate a 30% chance ASPEN misses. Based on our discussions with investors, we expect the market is pricing in a higher chance of failure (35-45%) due to uncertainties surrounding the MoA. That said, given the favorable updates thus far, including the DSCM's recommendations, exacerbation rates in-line with expectations, and management's thoughtful phase 3 design (including its powering/ size and overall duration), we see reasons to be optimistic (see our ASPEN deep-dive).

Should the trial fail however, management stressed there was no "plan B", with the company planning to discontinue further development. In this case, we would remove brenso from our models, leaving us with a valuation of ~$16 primarily driven by Arikayce ($12/share) and TPIP ($6/share), with more modest contributions from the translational medicine platform (~$.50/share).

Scenario II: Stat sig on the primary (0.01 < p ≤ 0.05), with 15% to low 20s% PEs reduction likely to offer more modest boost to shares: ~$31-33

In lieu of running two separate phase 3s—usually the standard for securing FDA approval—the agency permitted Insmed to conduct a single study provided it generated a p value ≤0.01. It was thus somewhat of a surprise to us investors reacted negatively to the follow-up the agency would a permit a filing if ASPEN's p value exceeded 0.01 but was still ≤0.05, allowing the inclusion of the WILLOW data in the application. We suspect

many interpreted this as an indication ASPEN was likely to underperform, and for this reason, we think the market is still pricing in the likelihood of this scenario as relatively high.

But while we think many would see this outcome as a disappointment, given the lack of options in the space/ the low bar for entry, our experts felt a 15% reduction in PEs would still be clinically and commercially meaningful. Admittedly, we think it would limit brenso's gross price to ~$40k/year, with payors likely to be more restricted with authorizations. That said, even under our more conservative outlook, we think peak NCFB sales could reach $2.8B—with, given readthroughs to its outlook in CRSsNP and HS—would likely leave shares trading at $31-33.

Select KOL feedback

it all comes down to the risk benefit, and in this case it's like if you have a side effect profile that is completely benign, you have a drug that's free from side effects, even with a 1% benefit why wouldn't you use it, right?

but the second you incorporate costs... side effects, you start to be a bit more exclusive on discerning who this would be beneficial for... so I think 15% would be the lower limit for physicians to be excited...

Scenario III: Base-case, PEs reduction low 20s-35% with a p≤0.01: likely solid momentum in shares to ~$43-45

In contrast to the Street, we are more bullish, and look for ASPEN to reach p≤0.01 on the primary outcome, implying a reduction in PEs from the 20s-35%—largely replicating the outcomes of WILLOW (recall the 25mg dose, which at 25%, did not reach stat sig). Admittedly much of this reflects our positive view on the trial design, where we'd highlight comments from Insmed's CMO Martina Flammer, who during our Boston Bus Tour last year noted it was statistically more difficult to hit on two independent trials even at a higher p-value (p ≤0.05) (see our tour takeaways).

Our KOLs acknowledged a benefit in this realm would be exciting and likely to drive robust early uptake. And assuming the safety profile is in-line with the phase 2—i.e., low rates of skin, dental, or infection related AEs—they didn't see any reason not to prescribe the drug to patients who would likely benefit.

As we noted above, we suspect there may be some pushback for non/low-exacerbating patients, particularly if there aren't meaningful improvements in QoL endpoints, (i.e. QoL-B) or pulmonary function (FEV1), which are largely absent from our forecasts. Still, we note use in this population could well push forecasts further up. More critically for our analysis, we think a magnitude of benefit at this level would de-risk the platform—and in this scenario, we increase our LoS for CF and other I&I indications +5% in our models for scenarios III and IV (vs our current forecast of 20% LOS in CF/ 15% in other indications).

Select KOL feedback

I think every doctor who treats patients with bronchiectasis who fit this criterion, meaning two or more exacerbations, will easily prescribe this drug... there may be headaches with prior authorization... but because there is no other therapy, I think people will still go for it...

Scenario IV: Best-case (p ≤ 0.01; PEs reduction 35%+), home-run scenario, likely not priced-in to current forecasts, shares likely to ~$50-52

While treatment with brenso evidenced up to a 36% reduction in PEs in WILLOW, we doubt many expect this benefit to hold up in a phase 3. Still, while we acknowledge

attenuation is typical in moving from a phase 2 to a phase 3, we think COVID could act as a tailwind, screening for patients who continued to experience multiple exacerbations even in a period where infections/ exacerbations were less common. Additionally, we expect the longer duration of follow-up (52 weeks vs 24 weeks) to potentially offer greater resolution in PE rates, given the high variability of events. And, while recognizing trial dynamics at play (i.e. longer duration of follow up), we would view a magnitude of benefit above the benchmark set by WILLOW (36%), as most likely an indication of longer-term, durable benefits for brenso.

In this best-case scenario, we think the addressable market meaningfully expands. In fact, we'd argue this magnitude of PE reduction may be enough for use in all-comers, and we conservatively forecast ~37K treated patients by 2030. Further, while yet to define the quantitative benchmarks, management has suggested a potential pricing premium for a more robust primary endpoint. Therefore, we see pricing ≥ $50k/ yr for PE reductions > 35% (Exhibit 2).

Select KOL feedback

what we really care about is preventing further collateral damage to the airways… if you limit PEs you're preventing the vicious cycle from accelerating out of control… if you start treatment earlier, your outcomes will be better… so, the ideal patient would be someone with normal lung function who has exacerbations…

I think it's 100% disease modifying. it's not just that you're reducing exacerbations, but you're altering lung function, lung structure, you're preventing progression of disease over time… and I honestly see that as more of a marker…

Ultimately, while management sees potential to reach 50-60% of the market, assuming the market is uncontested, we remain more conservative. Indeed, we forecast ~15% penetration of the addressable NCFB population (i.e. patients with ≥ 2 PEs/ yr) for our base-case, p ≤0.01. Thus, we leave room for many outcomes to drive a re-rating as the commercial story materializes. Ultimately, while we outline above a range of scenarios with implications to the stock, our $40 PO is based predominantly on the third scenario adjusted by a 70% likelihood of success for a positive readout on the trial.

Select KOL feedback

I am not an expert on pricing, but 40K, I don't think that's terrible at all, I was expecting more like 100K if something like this is positive… if you look at other drugs… like Tyvaso is close to 200K, Uptravi is up there… there are other oral drugs that are probably around 30K or 40K, that were higher when they first came out…

Exhibit 2: INSM NPV analysis for brensocatib
We expect the efficacy profile to fall most in-line with scenario III, supporting our $40/sh PO

						Revenue Expectations (2031)							
	Expected p-value	Reduction in Pes	LoS Market (%)	LoS Street (%)	LoS BofA (%)	GTN (%)	$/yr (000s)	compliance (%)	treated NCFB Patients	unadj. sales BofA	unadj. sales cons	unadj. BofA peak sales (2035)	Shares likely to trade
I	p > 0.05	< 15%	35-45	low (50) mean (65) max (70)	30	--	--	--	--	--	low ($2.3B) mean ($2.9B) max ($3.7B)	--	$18
II	0.01 < p ≤ 0.05	15-low 20s%	30-35		15	30	40	70	~32K	$1.9B		$2.8B	$31-33
III	p ≤ 0.01	low 20s-35%	20-25		40	35	45	72.5	~36K	$3.0B		$4.2B	$43-45
IV	p ≤ 0.01	35%+	5		15	40	50	75	~37K	$3.6B		$5.2B	$50-52

Source: BofA Global Research

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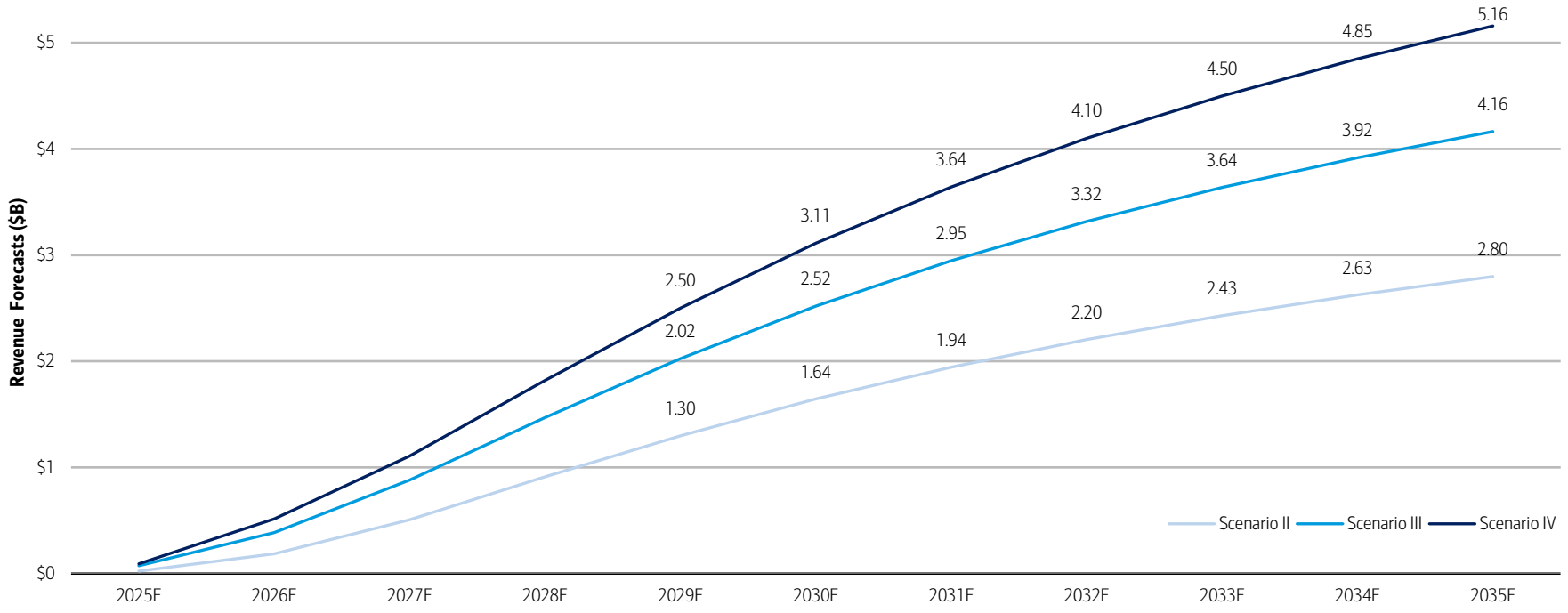
Exhibit 3: Brensocatib revenue forecasts
Market opportunity/ penetration clearly differentiated based on magnitude of reduction in annual PEs



Source: BofA Global Research

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Abbreviations:
AEs: adverse events
CF: cystic fibrosis
CMO: Chief Medical Officer
CRSsNP: chronic rhinosinusitis without nasal polyps
CT: computed tomography
DPP-1: dipeptidyl peptidase-1
DSCM: drug supply chain management
FDA: food and drug administration
FDA: Food and Drug Administration
FEV1: forced expiratory volume
FTE: full time employees
GTN: gross to net
HS: hidradenitis suppurativa
I&I: inflammation and immunology
KOLs: key opinion leaders
LOS: likelihood of success 4.2
MoA: mechanism of action
NCFB: Non-cystic fibrosis bronchiectasis
NE: neutrophil elastase
NSPs: neutrophil serine proteases
NTM-PD: non-tuberculosis mycobacterial pulmonary disease
PEs: pulmonary exacerbations
PRO: patient reported outcome
QoL-B: quality of life bronchiectasis
TAM: total addressable market
TPIP: treprostinil palmitil inhalation powder

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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: 70%), 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 14%, 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, $23/sh for Brensocatib, $6/sh for TPIP, $0.50/sh for the early pipeline, and $-2/sh for net cash, resulting in $40/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.

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	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
	Gilead Sciences Inc.	GILD	GILD US	Geoff Meacham
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US - Biopharmaceuticals Coverage Cluster

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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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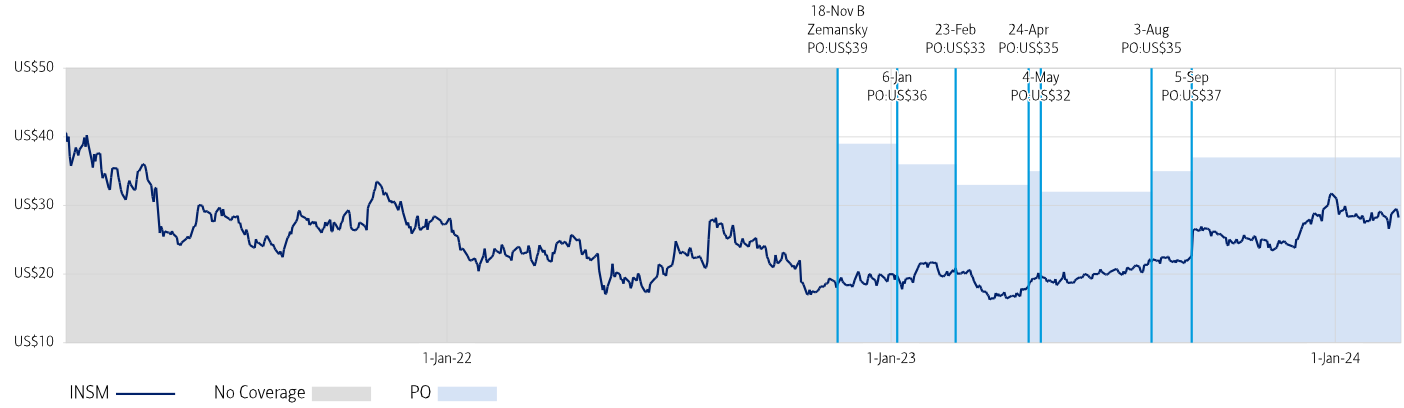
Insmed (INSM) Price Chart



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Hold	80	20.83%	Hold	36	45.00%
Sell	70	18.23%	Sell	29	41.43%

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