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Reason for report:

PROPRIETARY INSIGHTS

BIOPHARMA / NEUROSCIENCE

MEDACorp Alzheimer's Panel Takeaways

S&P 500 Health Care Index: **1,075.66**

Companies Highlighted:
ACAD, BIIB

• **Bottom Line:** We hosted two MEDACorp KOLs on an Alzheimer's disease panel as part of the SVB Leerink Global Healthcare Conference 2020. Key takeaways from our KOL panel include: (1) The panel was more negative than expected regarding Biogen's (BIIB, OP) aducanumab clinical data for Alzheimer's disease (AD) and intent to use the product, and neither physician thinks the FDA will approve the product based on existing data; (2) Skepticism regarding the amyloid hypothesis; (3) Concerns that Tau could turn out to be like amyloid (i.e., mostly disappointing); (4) A belief that more variables probably are coming into play regarding AD (e.g., neuro-inflammation, oxidative stress, glucose, infection, mitochondria disease, sleep disorders); and (5) Both KOLs were impressed by Acadia's (ACAD, OP) Nuplazid data for dementia-related psychosis (DRP), have used the product off-label already with some success, and plan to use the product significantly more for these patients if the indication gets approved.

• **Both KOLs are cautious about aducanumab's upcoming NDA in AD: (1)** EMERGE showed significant treatment effect, but there is a lack of consistency across doses and studies; **(2)** One KOL noted that he does not think the FDA would give it a broad label if approved, as it only seems to be working in a sub-population of AD patients, and it may be hard to find these patients in practice; **(3)** One KOL indicated that post-marketing studies may be needed to confirm the long-term treatment effect in practice. **(4)** Regarding probability of success (POS), one KOL offered a 2% POS of a positive advisory committee (AdCom) and potential FDA approval, and the other KOL offered a 10-20% POS for a positive AdCom but only a 2-5% POS for FDA approval.

• **Regarding aducanumab's market potential: (1)** One KOL thinks that aducanumab's treatment benefit has been marginal based on current data; therefore, he expects significant payer pushback regarding the value proposition of aducanumab vs current standard of care (SOC) drugs. **(2)** The other KOL was also concerned about aducanumab's risk-benefit given its marginal effect and modest safety profile. He noted that many patients in the real world are older and more severe vs those in the trials; thus, adverse events like ARIA (which seem to be manageable in clinical trials) could be more prominent and more of an issue in practice. **(3)** One KOL indicated that aducanumab's use in practice may be limited to a small subset of AD patients, as asymptomatic patients may not get insurance reimbursement. But KOLs would encourage patients to try aducanumab based on their disease status (high amyloid, low-to-no Tau). **(4)** Aducanumab's adoption would be highly depend on the its pricing strategy and amyloid-PET testing availability. One KOL thinks that payers may want aducanumab to be priced <$10K/month to give it broad coverage.

• **Both KOLs are skeptical regarding both amyloid and Tau hypotheses: (1)** The two KOLs think the association between amyloid and cognition has not been well established yet given that a majority of anti-Abeta antibodies have failed in large clinical trials, and they are

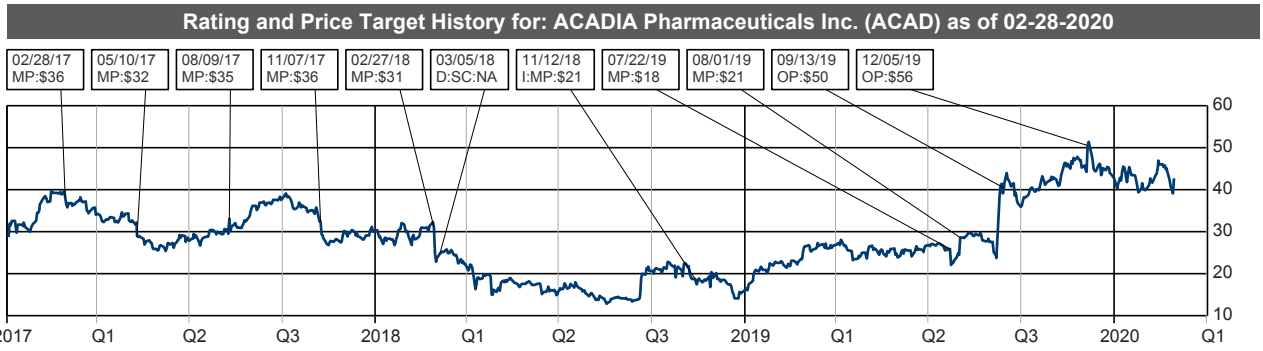
waiting for more data to validate the amyloid hypothesis. One KOL noted that he was also concerned about anti-Tau therapy given that it also works on targeting misfolded proteins. **(2)** The treatment effect of anti-Abeta antibodies may depend on several factors, including amyloid level, cognitive status, body mass index (cholesterol and other metabolism markers), etc. **(3)** One KOL indicated that there may be a critical treatment window in patients with minimal or no cognitive symptoms, i.e. late amyloid and early Tau (Tau seems to drive the symptoms), and that each individual patient may need a customized treatment solution. **(4)** KOLs want to see new animal models and subgroup biomarkers (e.g., genetic-defined DIAN-TU study) in future translational studies.

• **Regarding other pipeline products in Alzheimer's disease: (1)** KOLs are skeptical about the ongoing studies for anti-Abeta antibodies (solanezumab/gantenerumab, crenezumab, etc.) in treating early, sporadic AD, but they remain hopeful for success with prevention trials in asymptomatic Alzheimer's (e.g., crenezumab's Colombia trial). **(2)** One KOL thinks that there are many variables potentially involved in AD's pathology (glucose, oxidative stress, neuro-inflammation, infection, mitochondria disease, sleep disorders), and that a combination of multiple targets may be needed to effectively treat AD. **(3)** Regarding diagnosis, KOLs look for both biomarker signatures (Abeta, ApoE, age, etc.) and cognitive outcome measures. With that said, one KOL indicated that a vast majority of cases are still diagnosed based on clinical history, pending better amyloid testing coverage. One KOL thinks that blood tests for amyloid and Tau may be available in a few years and episome tools are moving closer to a breakthrough. **(4)** Regarding Nuplazid in DRP, both KOLs think the Phase 3 HARMONY design and data are impressive, and the drug has been very safe. One KOL noted that he has tried Nuplazid off-label with good success; thus, he would like to use this drug in more DRP patients upon approval.

Disclosures Appendix

Analyst Certification

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



Valuation

Our $56 PT is based on a SOTP analysis that forecasts cash flows into the 2030s, with a 10% discount rate.

Risks to Valuation

- Nuplazid Rxs don’t accelerate as much as expected with the new DTC campaign.
- Nuplazid's following pivotal trials in Schizophrenia Negative Symptoms or MDD don’t work.
- Payer pushback is significantly higher than we expect for Nuplazid's potential new DRP indication.
- Trofinetide in Rett syndrome has many new competitors that may steal share.

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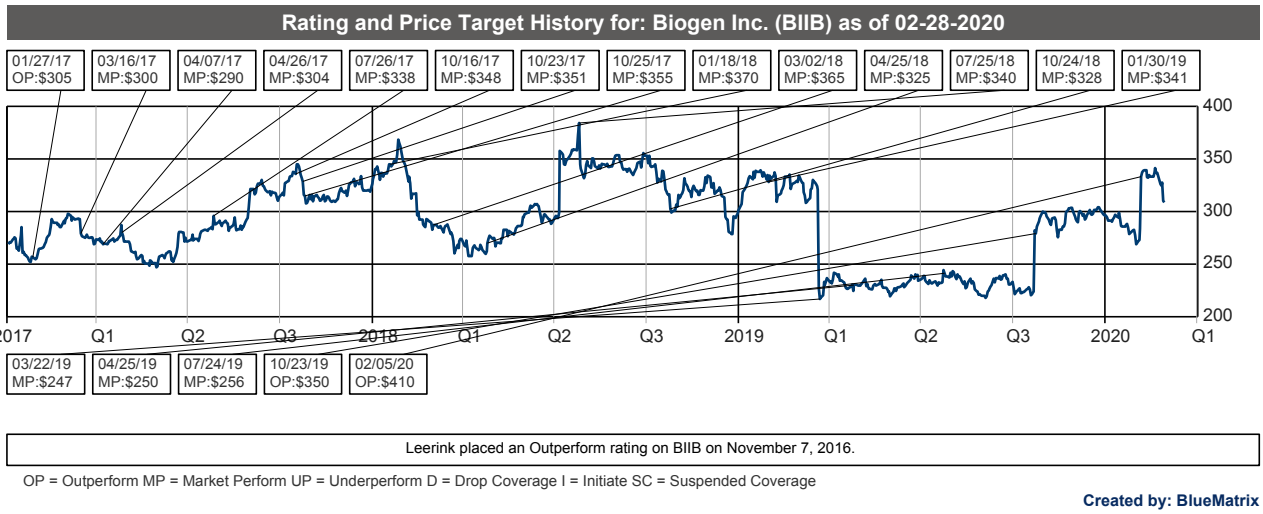

Valuation

Our $410 PT is based on a sum-of-the-parts (SOTP) analysis that forecasts cash flows into 2035E, with an 8% discount rate.

Risks to Valuation

Key risks to our investment thesis:

- Aducanumab is not approved by the FDA
- Aducanumab faces significant payer push-back
- New safety signal for aducanumab is detected in practice hindering commercial uptake
- Base business deterioration is worse than expected
- Tecfidera generic entry happens before 2028
- Spinraza declines even faster than our forecasts
- Early-stage pipeline products fail in late-stage studies

Distribution of Ratings/Investment Banking Services (IB) as of 12/31/19

			IB Serv./Past 12 Mos.	
Rating	**Count**	**Percent**	**Count**	**Percent**
BUY [OP]	153	73.9	59	38.6
HOLD [MP]	53	25.6	4	7.5
SELL [UP]	1	0.5	0	0.0

Explanation of Ratings

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

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

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

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

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

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