LifeSci Capital KOL Series – Alzheimer’s Disease

At this year’s Alzheimer’s Association International Conference (AAIC), Biogen (NasdaqGS: BIIB, in BBH, BBP, FBT, IBB, PBE, XBI) is expected to report additional data from its Phase Ib trial of the anti-β amyloid antibody aducanumab for Alzheimer’s disease (AD). The upcoming presentation could affect all of the sector ETFs but is especially important for the weighted funds. Biogen has heaviest weighting in the iShares Nasdaq Biotechnology (NasdaqGM: IBB; 7.4%), and Market Vectors Biotech ETF (NYSE MKT: BBH; 7.4%). We hosted a Key Opinion Leader call with Dr. Frank Tarazi, an Associate Professor in Psychiatry and Neurology at Harvard Medical School, in advance of the conference to discuss the beta-amyloid hypothesis and clinical updates on monoclonal antibody programs from Biogen and Eli Lilly (NYSE: LLY). A recording of the call can be accessed at this link or by visiting www.lifescicapital.com.

- **Biogen and Eli Lilly are in the Spotlight at This Year’s AAIC Meeting.** Biogen is conducting a Phase I trial evaluating aducanumab, a monoclonal antibody targeting β-amyloid plaques, as a potential disease-modifying therapy for AD. Preliminary results, first announced in December 2014, garnered a lot of excitement due to a significant and dose-dependent slowing of cognitive decline with aducanumab compared to placebo treatment that was concomitant with a reduction in amyloid plaques. Other recent attempts at targeting amyloid, including Johnson & Johnson and Pfizer’s (NYSE: JNJ, PFE) bapineuzumab, Eli Lilly’s (NYSE: LLY) solanezumab, and Roche’s (VTX: ROG) gantenerumab, have failed to show statistically significant benefits in large randomized, controlled trials despite positive signs of efficacy in early-stage trials. However, Lilly is expected to present results from an additional Phase III trial that enrolled only mild AD patients.

At this year’s AAIC meeting in Washington DC, Biogen is expected to provide data on the 6 mg dose cohort and the associated 10 placebo patients after 54 weeks. The presentation is scheduled for Wednesday July 22nd at 2:00-3:30 PM. Investors are keen to see efficacy data with the 6 mg dose that is consistent with the dose correlation found with the 1, 3, and 10 mg doses of aducanumab. In addition, the inclusion of the 10 additional placebo patients could substantially alter the trial results due to the small size of the placebo arm reported in March.

Although some have raised concerns over the apparent high rates of amyloid-related imaging abnormalities (ARIA), Dr. Tarazi notes that this has been identified as a safety concern in many previous trials evaluating anti-amyloid antibodies. Within the 10 mg dose cohort, 55% of patients carrying the ApoE4 gene allele experienced ARIA, which led to a discontinuation rate of 35% among these patients. Among non-carriers of the ApoE4 allele, 18% of patients experienced ARIA and only 8% discontinued from the trial. The 6 mg dose cohort was introduced midway into the study upon recommendation from the independent Data Safety Monitoring Board (DSMB). The company hopes to find a better balance between therapeutic effect and ARIA incidence with the 6 mg cohort.

- **Potential Problems with Biogen’s Last Observation Carried Forward (LOCF) Analysis.** LOCF analysis is a widely used strategy in dementia research as a way to handle patient dropout during a clinical trial. For the intent-to-treat (ITT) analysis, this strategy uses the last available data for a patient who drops out of the trial as their final results. LOCF is widely recognized as a confounding factor in clinical trials that may potentially introduce bias and systematic error. In the case of Biogen’s trial, a patient dropping out after 26 weeks would have the changes in their cognitive scores at that time point treated as the final result at 54 weeks. Therefore, higher patient dropout necessarily underrepresents that extent of cognitive decline, since a shorter amount of time has elapsed than what is ultimately reported. This is particularly troubling in the context of Biogen’s trial because of the correlation between dose and dropout rate.

Biogen has reported some data on patient dropout rates, but not enough to form solid conclusions on the extent to which LOCF analysis may have altered the results. The higher dose cohorts experienced higher rates of ARIA and had higher rates of patient dropout due to these side effects. The highest dose cohort, the 10 mg group, had a 31% discontinuation rate overall, compared to a 10% dropout rate in the placebo group. In addition, patients possessing the APOE4 allele, which confers higher risk of developing Alzheimer’s disease and is associated with more rapid cognitive decline than non-carriers, were most prone to ARIA and accounted for this.
for nearly two-thirds of the dropouts in the 10 mg dose cohort. Thus, the treatment effects observed in the higher dose cohorts may have been substantially skewed by LOCF analysis in a dose-dependent manner. Without knowing when each discontinuation occurred, it is difficult to assess how this might have affected the statistical significance achieved in the interim analysis of the trial. We will be looking to Biogen to release more of this data at the conference to understand the extent of the LOCF bias.

- **Two-Year Extension Study Data Expected from Eli Lilly.** Eli Lilly is expected to present data from the EXPEDITION-EXT study of its anti-β amyloid monoclonal antibody solanezumab (sola), on Tuesday July 21st at 9:30 AM – 4:15 PM and Wednesday July 22nd at 8:00 AM – 9:30 AM. The EXPEDITION-EXT trial is a two-year, open-label extension study that enrolled 1275 AD patients who completed treatment in either the EXPEDITION 1 or EXPEDITION 2 Phase III trials. These Phase III trials failed to show a statistically significant difference between treatment with sola and placebo. The EXPEDITION-EXT data may be an important early indication of sola’s efficacy in the ongoing EXPEDITION 3 trial of sola in 2100 mild AD patients. Data from the trial are not expected until late 2016.

The extension trial is based on a retrospective, pooled analysis that identified a significant treatment effect in patients with mild AD. It was designed to compare the cognitive function of patients who started on drug at the onset of the 18 month Phase III trial and those that crossed over from placebo at the start of the study as a measure of the drug’s ability to slow the disease. The stakes are high for Eli Lilly as it recovers from earlier setbacks with sola.

Eli Lilly’s early setbacks with sola may highlight the need for early intervention in treating AD. The company’s retrospective, pooled analysis found that sola had a statistically significant treatment effect on mild but not moderate AD patients. This treatment effect could potentially result from sola’s preferential binding of soluble monomeric β-amyloid. Sola is thought to work by reducing system levels of amyloid and is unlikely to substantially affect existing β-amyloid plaques. Most of the other anti-β amyloid antibodies, including Biogen’s aducanumab, bind to the N-terminus, which confers a preference for binding plaques over soluble monomers. The antibody's binding profile may provide a scientific rationale to support Lilly’s retrospective findings and the need for early targeting of the disease.

**Risk to Investment**

Investors should consider the risk of any investment, including in the exchange traded funds mentioned here. These funds include stocks with high risk and high volatility. Clinical stage biopharmaceutical companies’ assets may not be successful in clinical trials or may fail to gain regulatory approval. If products are launched, it is possible that revenues will not meet investor expectations, or that the products will face unexpected competition. Overall market conditions may also affect the value of the underlying securities in these funds.
Analyst Certification

The research analyst denoted by an “AC” on the cover of this report certifies (or, where multiple research analysts are primarily responsible for this report, the research analyst denoted by an “AC” on the cover or within the document individually certifies), with respect to each security or subject company that the research analyst covers in this research, that: (1) all of the views expressed in this report accurately reflect his or her personal views about any and all of the subject securities or subject companies, and (2) no part of any of the research analyst's compensation was, is, or will be directly or indirectly related to the specific recommendations or views expressed by the research analyst(s) in this report.

DISCLOSURES

This research contains the views, opinions and recommendations of LifeSci Capital, LLC (“LSC”) research analysts. LifeSci Index Partners, LLC, an affiliate of LSC under common control, (or an affiliate of each), serves as the sub-adviser to the BioShares Biotechnology Products Fund and the BioShares Biotechnology Clinical Trial Funds (the BioShares funds) and receives compensation for acting in this capacity. A further description of the compensation arrangements can be found in the prospectuses for the BioShares funds, which are accessible at: http://bioshares.com/investor-materials.html.

LSC has provided investment banking and other broker-dealer services to companies that are constituents of one or more of the Exchange Traded Funds described in this report. LSC (or an affiliate) has also provided non-investment banking securities-related services, non-securities services, and other products or services other than investment banking services to one or more companies that are constituents of one or more Exchange Traded Funds described in this report, and received compensation for such services within the past 12 months. LSC does not make a market in the securities of any of the constituents of any of the Exchange Traded Funds described in this report. Please visit http://www.lifescicapital.com/equity-research/ for disclosures related to each issuer. LSC is a member of FINRA and SIPC. Information has been obtained from sources believed to be reliable but LSC or its affiliates (e.g., LifeSci Advisors, LLC) do not warrant its completeness or accuracy except with respect to any disclosures relative to LSC and/or its affiliates and the analyst's involvement with each issuer that is the subject of the research. Any pricing is as of the close of market for the securities discussed, unless otherwise stated. Opinions and estimates constitute LSC's judgment as of the date of this report and are subject to change without notice. Past performance is not indicative of future results. This material is not intended as an offer or solicitation for the purchase or sale of any financial instrument. The opinions and recommendations herein do not take into account individual client circumstances, objectives, or needs and are not intended as recommendations of particular securities, companies, financial instruments or strategies to particular clients. The recipient of this report must make his/her/its own independent decisions regarding any securities or financial instruments mentioned herein. Periodic updates may be provided on companies/industries based on company specific developments or announcements, market conditions or any other publicly available information. Additional information is available upon request. No part of this report may be reproduced in any form without the express written permission of LSC. Copyright 2015.