

## Morning Note – January 26, 2012

- Navidea Options Altropane® from Alseres for Parkinson's Disease Imaging
- Could Be Complimentary to AZD4694 Alzheimer's Imaging Program
- In-Licenses AstraZeneca's AZD4694  $\beta$ -amyloid Alzheimer's Imaging Agent

Please See Last 2 Pages For Important Disclosures And Analyst Certification

Company	Ticker	Price	Mkt. Cap.	Daily Volume	Rating	Target	Analysts
Navidea Biopharma	NAVB	\$2.70	\$253M	3-month 346,511 10-day 192,143	Strong Speculative Buy	\$5.75	Stephen M. Dunn Sr. Managing Director Research sdunn@LifeTechCapital.com (954) 240-9968

### Summary

After market close yesterday, Navidea announced that they entered into an option agreement with Alseres Pharmaceuticals (formerly Boston Life Sciences) to license Altropane® ( $^{123}\text{I}$ -E-IAFCT Injection), an Iodine-123 radiolabeled imaging agent, being developed as an aid in the diagnosis of Parkinson's disease and movement disorders. The option agreement provides for exclusive rights for 6 months (June 30, 2012) to perform final due diligence and prepare the documentation necessary to enter into a definitive license agreement. We note that both Mark Pykett, CEO and Dr. Thomas Tulip, EVP are previously from Alseres.

$^{123}\text{I}$ -E-IACFT is a patented, novel, small molecule radiopharmaceutical used with single photon emission computed tomography (SPECT) imaging to identify the status of specific regions in the brains of patients suspected of having Parkinson's disease. The agent binds to the dopamine transporter (DAT) on the cell surface of dopaminergic neurons in the striatum and substantia nigra regions of the brain. Loss of these neurons is a widely recognized sign of Parkinson's disease.

**We believe that this Parkinson's program would be complimentary to Navidea's recent acquisition of AZD4694, a radiopharmaceutical imaging agent for Alzheimer's disease (AD), from AstraZeneca (NYSE:AZN).**

## Diseases of the Brain | Progressive conditions affect the body and mind in different ways

### Alzheimer's symptoms

**Cognitive:** Memory loss and deterioration in thinking and planning functions.

**Physical:** In mid-stage, disease could include slowness, rigidity and tremors.

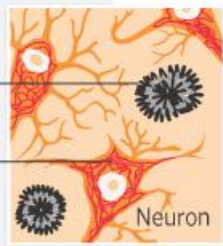
#### INSIDE THE BRAIN

The cortex, particularly the **hippocampus**, key to memory, shrinks.

**Ventricles** (fluid-filled spaces within the brain) enlarge.

**Plaques** (amyloid deposits) cluster between neurons.

**Tangles** (twisted proteins) are found within neurons.



### Parkinson's symptoms

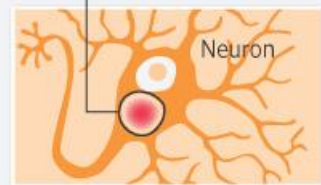
**Cognitive:** Loss of executive functions, including planning, decision-making and controlling emotions.

**Physical:** Tremors, stiffness and slowed movements.

#### INSIDE THE BRAIN

Cells shrink in the **substantia nigra**, where dopamine is produced.

**Lewy bodies** (clusters of alpha-synuclein protein) accumulate inside neurons.



Sources: Alzheimer's Association, Parkinson's Disease Foundation and helpguide.org

## CLINICAL HISTORY

[<sup>123</sup>I]-E-IACFT has been administered to over 600 subjects to date. A Phase III Special Protocol Assessment (SPA) for [<sup>123</sup>I]-E-IACFT is already in place with the FDA (POET-2) and over 50 subjects have been enrolled to establish a training data base. Results from clinical trials (POET-1) have demonstrated that [<sup>123</sup>I]-E-IACFT has high affinity for DAT and rapid kinetics which enable the generation of clean images quickly, beginning within about 20 minutes after injection while other agents typically have waiting periods from 4 to 24 hours before imaging can occur. In addition to its potential use as an aid in the differential diagnosis of Parkinson's disease and movement disorders, [<sup>123</sup>I]-E-IACFT may also be useful in the diagnosis of Dementia with Lewy Bodies (DLB), a common form of dementia after Alzheimer's disease.

**POET-1:** In March 2006, Alseres (then known as Boston Life Sciences) ended the Phase III SPA trial named "POET-1" early with approximately 30% fewer patients than originally specified because non-blinded data indicated that the error rate of general practitioners in the trial was higher than had been anticipated in the trial design. On September 25, 2006, they announced statistically significant results for the primary endpoint from the Company's POET-1 (Parkinson's or Essential Tremor) trial for the ALTROPANE® molecular imaging agent. The POET-1 trial was designed to assess whether ALTROPANE imaging is more accurate than the clinical diagnosis of primary care physicians to distinguish between tremors caused by Parkinsonian Syndrome and those associated with other disorders, as judged by comparison to a definitive diagnosis by movement disorder specialists. ALTROPANE scans showed statistically significant superiority over the diagnosis of PCPs on measures of both specificity and sensitivity, the primary endpoint of the trial. Based on data analyzed to date, with the exception of one "possibly-related" urinary tract infection that resolved after treatment, there were no drug-related serious adverse events.

**POET-2:** After discussions with the FDA, the POET-2 program was designed as a 2-part Phase III program using the optimized ALTROPANE image acquisition protocol. The first part of the program, a multi-center clinical study in subjects to acquire a set of ALTROPANE images, was completed. This set of images will be used to train the expert readers as is the customary process for clinical trials of molecular imaging agents. The second part involves two concurrent, replicate, multi-center Phase III trials. These two concurrent trials, the final design of which is under discussion with the FDA, will be

initiated once final agreement on the design of the two trials is reached with the FDA. The completed image acquisition trial design can be found at <http://clinicaltrials.gov/ct2/show/NCT00596908> The 2 concurrent Phase III trials have not yet enrolled but the trial design can be found at <http://clinicaltrials.gov/ct2/show/NCT00724906>

### **Option Terms**

- 1.) Navidea paid Alseres an option fee of \$500,000 for the exclusive right to negotiate a definitive license agreement by June 30, 2012.
- 2.) Navidea can extend the option period from June 30, 2012, to July 31, 2012, for an additional \$250,000.

### **Anticipated License Terms**

- 1.) Navidea will issue Alseres 400,000 shares of Navidea common stock upon execution of the definitive license agreement.
- 2.) The option also anticipates that the license agreement will provide for contingent milestone payments of up to \$3.0 million, \$2.75 million of which will principally occur at the time of product registration or upon commercial sales, and the issuance of up to an additional 1.05 million shares of Navidea stock, 950,000 shares of which are issuable at the time of product registration or upon commercial sales.
- 3.) Royalties on net sales of the approved product which are consistent with industry-standard terms.

## **Other Recent News**

### **\$10M Debt Funding:**

On January 4, 2012, the company announced that Hercules Technology II, L.P would provide up to \$10M in debt financing. The first funding of \$7M closed on December 29, 2011 is in the form of a secured note which is repayable in installments over 30 months following an interest-only period of between 6 to 12 months. The note bears interest at a prime-based variable rate, currently at 10%. Up to \$1.5M of the principal of the note is convertible at the option of the company, and up to \$1.5M of principal is convertible at the option of Hercules, each at a conversion price of \$2.77 per share. In addition, Hercules received 333,333 warrants to purchase shares of common stock at an exercise price of \$2.10 per share. A second funding of \$3M is available upon FDA clearance to market Lymphoseek in the U.S.

### **Acquisition of AZD4694 Alzheimer's Disease Imaging Agent:**

On December 12, 2011, Navidea announced that they in-licensed the worldwide exclusive rights from AstraZeneca (NYSE:AZN) for AZD4694, a radiopharmaceutical imaging agent for Alzheimer's disease (AD). Specifically, AZD4694 is a Fluorine-18 labeled radiopharmaceutical that binds to  $\beta$ -amyloid deposits in the brain that can then be imaged using a PET (Positron Emission Tomography) scanner. Although there is debate as to whether  $\beta$ -amyloid plaque is the root cause of Alzheimer's disease, it is a broadly accepted biomarker for AD diagnosis. The use of AZD4694 will initially focus on determining which patients are shown as negative for  $\beta$ -amyloid pathology meaning they do not have Alzheimer's disease. Some of the key features of AZD4694 are the potential to detect low levels of amyloid (earlier stages of AD), to identify small changes in  $\beta$ -amyloid levels, as a companion diagnostic to AD therapy and the possibility for use as a cerebral blood flow co-marker of AD (instead of flurodeoxyglucose or FDG). Investors should note that the patents and patent applications related to AZD4694 are effective until 2028.

**Investment Summary:** Building on Navidea's in-house expertise in radiolabeled agents and in particular Dr. Thomas Tulip, the company has inexpensively acquired from AstraZeneca a credible candidate for the large, unmet and growing Alzheimer's disease market. While AZD4694 is currently behind other candidates in the space (*see Competition*) we believe the expected approval of Eli Lilly's Amyvid™ in 2012 will validate both the mechanism of action and market adoption in this diagnostic drug class. **Therefore, we believe the development of AZD4694, while behind others, has been de-risked as a result. Based on the favorable economics of the AZD4694 license with AstraZeneca addressing a large underserved market with a validated diagnostic drug class, we view this as a net benefit to investors. We strongly encourage investors to review the presentations for Amyvid made during the January 2011 FDA Advisory Committee meeting to better understand the Alzheimer's diagnostic space (*see Additional Research References*).** We have not yet added AZD4694 to our financial model as we await the finer development plan details.

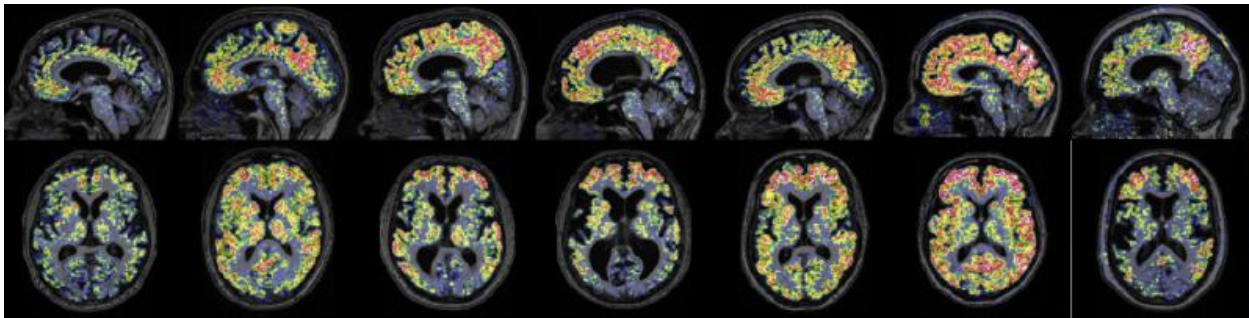
**Transaction:** Navidea paid \$5M upfront to AstraZeneca with future potential milestone payments including up to \$6.5M

on clinical development (\$2.5M) and regulatory filing (\$4M) milestones and up to additional \$11M following regulatory approvals and the initiation of commercial sales. **It should be noted that after the \$5M upfront payment, no milestones are due to AstraZeneca for at least two years.** In addition, Navidea will also pay undisclosed tiered royalties on net sales. AstraZeneca retains the right to use AZD4694 in their clinical trials to support the development of potential Alzheimer's therapies.

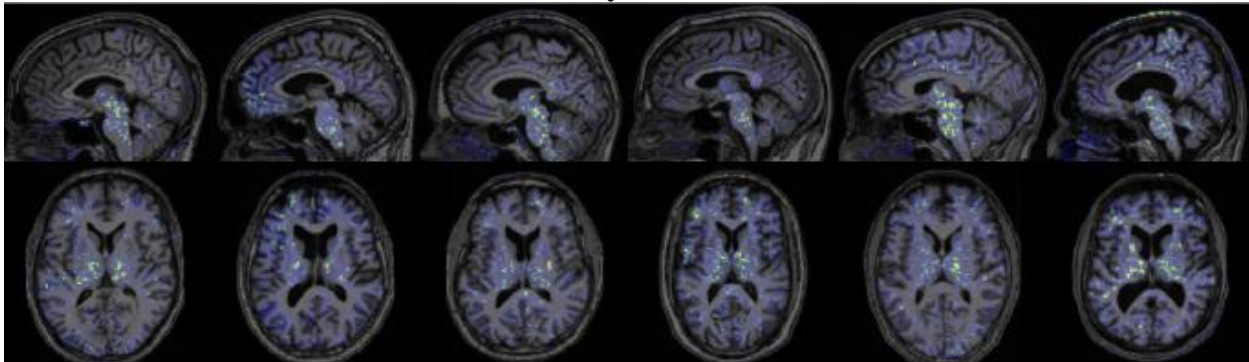
**Clinical Development:** Approximately 75 patients have been dosed to date in Phase I and Phase IIa human clinical trials with no significant adverse events. Navidea is expecting to conduct a 200-patient Phase IIb trial to collect data with the initiation of a 200-patient multi-country Phase III trial anticipated in early-2013 with regulatory submissions expect in 2015. Navidea expects the clinical cost related to these activities to be approximately \$16M. **Investors should note that due to the expected competition reaching the market before AZD4694, we believe Navidea will be required to perform comparative, non-inferiority trials for marketing purposes (see Competition).**

### AZD4694 Images

#### Alzheimer's Disease Patients



#### Healthy Patients



Source: Cselenyi, Z., et al., "Clinical validation of [<sup>18</sup>F]AZD4694, a novel amyloid beta specific PET radioligand" In press, J Nuc Med

### **COMPETITION:**

**Eli Lilly (NYSE: LLY) Amyvid™ florbetapir F18 injection:** Developed through wholly-owned Avid Radiopharmaceuticals, Amyvid (AV-45), was review on January 20, 2011 by the FDA Peripheral and Central Nervous System Drugs Advisory Committee who voted 16-0 in favor of recommending that Amyvid be approved for use. However, this was contingent on a training program as there was significant variability among the readers. On March 18, 2011 they received an FDA Complete Response letter primarily focused on the need to establish a reader training program ensure reader accuracy and consistency of interpretations of existing Amyvid scans. **Eli Lilly submitted their response in Q3 2011, which we believe eliminates the 5 point scale used in the autopsy readings in favor of a binary yes/no reading and we further expect FDA approval in 2012.** Investors should note that Eli Lilly acquired Avid Radiopharmaceuticals in Q4 2010 for \$300M in cash and up to an additional \$500M for milestones.

**GE Healthcare division of GE (NYSE:GE) flutemetamol 18-F:** The company is currently conducting Phase III clinical trials "Positron Emission Tomography (PET) Imaging of Brain Amyloid Compared to Post-Mortem Levels" <http://clinicaltrials.gov/ct2/show/NCT01165554> and "Assess the Prognostic Usefulness of Flutemetamol (18F) Injection for Identifying Subjects With Amnesic Mild Cognitive Impairment Who Will Convert to Clinically Probable Alzheimer's Disease" <http://clinicaltrials.gov/ct2/show/NCT01028053>

**Bayer (XETRA:BAYN) 18-F florbetaben:** The company is currently conducting a Phase III clinical trial “*Phase III Study of Florbetaben (BAY94-9172) PET Imaging for Detection/Exclusion of Cerebral  $\beta$ -amyloid Compared to Histopathology*” <http://clinicaltrials.gov/ct2/show/NCT01020838>

**AZD4694 COMPETITIVE ADVANTAGES:**

Although all clinical trials have not been completed, preclinical and Phase I & II data indicates that AZD4694 may have significantly better sensitivity with improved contrast resulting in a higher precision scan (and presumably earlier detection). It also may provide improved ease-of-use allowing for shorter imaging times. The reduced risk of head movement as a result may also improve scan quality. Finally, AZD4694 has potential to be used for measuring blood flow. In general the targeted advantages are:

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|---|--|
| <p><u>Clean images with less white matter uptake</u></p> <ul style="list-style-type: none"><li>• High sensitivity with better contrast</li><li>• Identification of lower levels of amyloid</li><li>• Earlier detection of amyloid</li></ul> <p>• <u>Excellent reader reproducibility</u></p> <ul style="list-style-type: none"><li>• Easy reader training</li><li>• Consistent test/re-test performance</li></ul> | <p><u>Rapid imaging procedure</u></p> <ul style="list-style-type: none"><li>• Patient-friendly</li><li>• High throughput at imaging site</li><li>• Minimal head movement enables high quality images</li><li>• Potential to replace FDG scans measuring blood flow</li></ul> |
|---|--|

**ADDITIONAL RESEARCH REFERENCES**

**Avid Presentations for the January 20, 2011 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee:**  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240951.pdf>

**FDA Presentations for the January 20, 2011 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee:**  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240949.pdf>

**Alzheimer’s Background for the January 20, 2011 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee:**  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240952.pdf>

**DISCLOSURES**



Ratings and Price Target Changes over Past 3 Years  
Initiated March 25, 2011 – Strong Speculative Buy - Price Target \$5.75

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Ratings Distribution	% of Total	% of Total	Ratings Distribution	% of Total	% of Total
Strong Buy	17%	0%	Buy	75%	33%
Strong Speculative Buy	58%	43%	Hold/Neutral	8%	100%
Buy	0%	0%	Sell	17%	0%
Speculative Buy	0%	0%	Total	100%	33%
Neutral	8%	100%			
Avoid/Sell	17%	0%			
Under Review	0%	0%			
Not Rated	0%	0%			
Restricted	0%	0%			
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