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Emerging Company Profile

SeneXta: Slow in the brain is OK

By Stephen Hansen
Staff Writer

SeneXta Therapeutics S.A. believes its acetylcholinesterase inhibitor could improve on marketed drugs in the class because the compound irreversibly binds AChE. Because turnover of the target is slow in the brain and faster in the peripheral tissues where side effects occur, the company expects SNX-001 should have a more prolonged therapeutic effect and a better toxicity profile in patients with Alzheimer's disease.

According to Donald Moss, a professor in the department of psychology at the **University of Texas at El Paso** who discovered SNX-001, marketed AChE inhibitors such as Aricept donepezil and Exelon rivastigmine have limited efficacy for two reasons: short duration of action and dose-limiting toxicities.

Aricept and Exelon are reversible inhibitors of AChE. According to its label, Aricept's half-life in the blood is 70 hours. But according to Moss, the amount of time that Aricept is bound to AChE in the brain is very short, because it binds AChE non-covalently. The non-covalent bond means it is in constant competition with acetylcholine for the AChE catalytic site.

Aricept's label does not indicate how long the AChE inhibition lasts, because it

SeneXta Therapeutics S.A.

Lugano, Switzerland

Technology: Long-acting AChE inhibitor

Disease focus: Neurology

Founded: 2008 by Enrico Braglia and Federica Pericle

University collaborators: University of Texas at El Paso

Corporate partners: None

Number of employees: 2 unpaid

Funds raised: CHF1.6 million (\$1.5 million)

Investors: Enrico Braglia and Federica Pericle

CEO: Enrico Braglia

Patents: 2 issued covering methods of use of SNX-001

is dependent on the amount of drug present.

Exelon binds AChE covalently. The drug's label says its half-life in the blood is one hour, but that AChE inhibition lasts 8-10 hours.

According to the SeneXta, such a duration of action means that high levels of drug are required in the blood to achieve

a therapeutic effect, which in turn results in high levels in peripheral tissues. This causes nausea, vomiting and diarrhea due to AChE inhibition in the smooth muscle.

As a result, higher doses that could achieve greater AChE inhibition in the brain can't be reached.

In contrast, SNX-001 is an irreversible inhibitor that covalently binds AChE until the drug-enzyme complex is destroyed or reabsorbed by the body. As a result, the amount of inhibition of AChE is affected by the turnover of new AChE synthesized in the brain and other tissues. According to Moss, the turnover rate in peripheral tissues is fast, so that AChE inhibition never reaches toxic levels.

"The half-life of AChE replacement in the intestines is about one day compared to 11-12 days in the brain. Therefore, a very large increase in AChE inhibition can be accumulated in the brain, while the effect of SNX-001 is being washed out of the intestines by the normal, rapid replacement of AChE," Moss told BioCentury.

"SNX-001 is essentially exploiting a property of the brain itself, slow AChE turnover, to selectively target the brain," he said. "No other AChE inhibitor product available takes advantage of this property of the brain."

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SeneXta,

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CEO Enrico Braglia told BioCentury that he and COO Federica Pericle in-licensed SNX-001, despite the difficulty of tackling AD as a small company, because of results from a Mexican trial conducted by Moss in collaboration with the **Autonomous University of Chihuahua**.

In 15 AD patients, those given SNX-001 had a 6-point improvement in ADAS-cog scores vs. placebo after eight weeks.

According to its label, Aricept trials demonstrated a 2-3 point improvement in ADAS-cog vs. placebo. For Exelon, a 26-week U.S. Phase III trial showed improvements of 1.9 points for the low dose and 4.9 points for the high dose, and a 26-week international Phase III trial showed improvements for the low and high doses of 0.2 points and 2.6 points, respectively.

According to their labels, Aricept dosages are 5 mg and 10 mg once daily; Exelon capsule dosages are 1.5 mg, 3 mg, 4.5 mg and 6 mg once daily. By com-

parison, in the Mexican Phase II trial, the dose of SNX-001 was 0.18 mg/kg three times per week.

However, the Mexican study was not conducted under GCP standards or the guidance of any regulatory agencies, so SeneXta is starting from scratch with a German Phase I trial in 24 healthy volunteers assessing safety and tolerability. Data are expected in 2Q10.

SeneXta needs to either partner its compound or raise CHF14 million (\$13 million) to start a Phase II trial this year. The company does not expect to take SNX-001 into Phase III due to the complex nature and high costs of the studies.

SNX-001 also is in preclinical development to treat cognitive impairment secondary to stroke.

SeneXta doesn't have a composition of matter patent for SNX-001 because the compound has been used for industrial purposes. But Pericle said method of use patents cover its medicinal use until at least 2017. Pericle expects that SNX-001 will receive five additional years of patent

protection from a supplementary protection certificate (SPC).

SeneXta also has filed patent applications for SNX-001's dosing regimen, which is undisclosed.

If a partner takes over development of SNX-001, Braglia said, SeneXta could shift its focus to SNX-002, an undisclosed compound in discovery for pain and inflammation.

Aricept is marketed by **Pfizer Inc.** and **Eisai Co. Ltd.**, while **Novartis AG** markets Exelon.

COMPANIES AND INSTITUTIONS MENTIONED

Autonomous University of Chihuahua, Chihuahua, Mexico

Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan

Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland

Pfizer Inc. (NYSE:PFE), New York, N.Y.

SeneXta Therapeutics S.A., Lugano, Switzerland

University of Texas at El Paso, El Paso, Texas