NEW DATA PRESENTED AT THE 2015 ALZHEIMER’S ASSOCIATION INTERNATIONAL CONFERENCE INCLUDE THREE REPORTS OF CLINICAL TRIALS TARGETING COGNITION, AGITATION, PATIENT MANAGEMENT

WASHINGTON, DC, July 22, 2015 – Results of three clinical trials reported at the Alzheimer’s Association International Conference® 2015 (AAIC® 2015) in Washington, D.C. show positive evidence of efforts to attack the disease from multiple angles – targeting the underlying causes and some of the most pernicious symptoms, and developing tools to determine an appropriate treatment plan.

The trials include:
- A 24-week, double-blind, phase 2b placebo-controlled clinical trial, and a 24-week blinded extension study, of a once-daily oral 5-HT6 serotonin receptor blocker as an add-on to stable donepezil treatment. (RVT-101, Axovant)
- A 10-week, double-blind, placebo-controlled study of a combination of dextromethorphan and quinidine in people with Alzheimer’s and symptoms of agitation. (AVP-923, Avanir)
- A year-long study of brain amyloid PET scans (florbetapir, Avid/Lilly) to see if they can influence physicians to change medical management of their patients.

“It’s exciting to see significant advances in therapies for the prevention and treatment of Alzheimer’s disease, and it’s also important to see innovation in the management of behavioral symptoms,” said Maria Carrillo, PhD, Alzheimer’s Association Chief Science Officer. “Hard-to-manage care situations, wandering off and challenges with the bathroom are the primary reasons families are forced to move their loved ones into institutional care centers. Treatment advances that support family caregiving and enable people to stay home longer can have a tremendous emotional and economic impact.”

Alzheimer’s disease is devastating to families physically, emotionally and financially. In 2014, friends and family of people with Alzheimer's and other dementias provided an estimated 17.9 billion hours of unpaid care, a contribution to the nation valued at $217.7 billion. This is approximately 46 percent of the net value of Walmart sales in 2013 and nearly eight times the total revenue of McDonald's in 2013.

Medicaid pays for a significant portion of the nation’s residential care costs for those with Alzheimer’s and other dementias. On average, per-person Medicaid costs for those with Alzheimer’s and other dementias compared with $574 for individuals without Alzheimer’s in 2015. Alzheimer’s Disease Facts and Figures 2015 Alzheimer's Association.
These figures reinforce the value of reaching the goal of preventing and effectively treating Alzheimer’s by 2025, as set by the National Plan to Address Alzheimer’s Disease. Promising research is in the pipeline, and leading scientists believe the national goal is attainable if we accelerate federal funding.

**A Neurotransmitter-Targeted Therapy Boosts Efficacy of Standard Alzheimer’s Treatment**

RVT-101 (Axovant Sciences) is an investigational once-daily oral 5-HT6 serotonin receptor antagonist in development for Alzheimer’s disease and other forms of dementia. It is believed that RVT-101 promotes the release of acetylcholine and other neurotransmitters important for memory and cognitive function. RVT-101 is being developed to be co-administered with donepezil (Aricept, Pfizer), a member of the class of drugs that is the current standard of care for mild-to-moderate Alzheimer’s disease.

At AAIC 2015, Lawrence T. Friedhoff, MD, PhD, FACP, Chief Development Officer of Axovant Sciences, Inc., shared results from a 48-week Phase 2b placebo-controlled clinical trial, which included a 24-week double-blind phase followed by a 24-week double-blind extension phase. 684 participants with mild to moderate Alzheimer’s were randomized to receive 35 mg RVT-101, 15 mg RVT-101, or placebo as an add-on to stable donepezil treatment. Multiple endpoints were used to assess cognition and function, including the ADAS-cog which evaluates memory, attention, orientation and language; ADCS-ADL which captures activities of daily living such as feeding and bathing; and CDR-SB which assesses both cognition and function.

Results included participants with complete data at each time point (i.e., completer analysis) and showed that people receiving 35 mg of RVT-101 once per day in combination with donepezil had statistically significant improvements in cognition (ADAS-Cog) and daily living activities (ADCS-ADL) compared to subjects receiving donepezil alone, at 12, 24, 36 and 48 weeks of treatment. The researchers also report that RVT-101 was well tolerated.

<table>
<thead>
<tr>
<th>Week</th>
<th>ADAS-cog benefit</th>
<th>ADCS-ADL benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1.29 (p=0.008)</td>
<td>1.72 (p=0.016)</td>
</tr>
<tr>
<td>24</td>
<td>1.63 (p=0.007)</td>
<td>2.11 (p=0.016)</td>
</tr>
<tr>
<td>36</td>
<td>1.35 (p=0.039)</td>
<td>2.20 (p=0.029)</td>
</tr>
<tr>
<td>48</td>
<td>1.82 (p=0.018)</td>
<td>2.34 (p=0.048)</td>
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Participants who received 35 mg RVT-101 achieved a statistically significant benefit on CDR-SB only at 12 weeks after initiation of treatment. Mean ADAS-cog, ADCS-ADL and CDR-SB values for the 15 mg group were not statistically significantly different from the placebo group.

“RVT-101 is a promising potential new symptomatic therapy for the treatment of Alzheimer’s disease,” stated Friedhoff, who previously led the development of Aricept. “We believe these results justify its advancement into a confirmatory Phase 3 program that we intend to start later this year.”

**New Use of an Already-Approved Treatment Reduces Agitation**

Agitation (shouting, cursing, hitting, kicking, pacing) occurs in many people with Alzheimer’s disease. Agitation is a major reason that people with Alzheimer’s are moved into residential care, and the symptoms considerably decrease the quality of life for patients and create significant burden and distress for families and caregivers. There are no drugs approved by the FDA for these symptoms in Alzheimer’s disease.
At AAIC 2015, Jeffrey Cummings, MD, of the Cleveland Clinic Lou Ruvo Center reported results from a double-blind, placebo-controlled study of AVP-923 (a combination of dextromethorphan 20mg and quinidine 10mg) in people with probable Alzheimer’s and agitation symptoms. AVP-923 is FDA-approved for treating pseudobulbar affect (PBA), a condition characterized by sudden and uncontrollable outbursts of laughing and/or crying associated with certain neurological diseases or brain injury. The drug was observed to have a beneficial effect on agitation in past trials for other indications.

According to Cummings, a specially designed two-stage study utilizing a Sequential Parallel Comparison Design (SPCD) was used to minimize the “placebo-effect” commonly seen in neuropsychiatric studies. The researchers randomly assigned patients (4:3) to either receive placebo or AVP-923 (20/10 mg QD titrated to 30/10 mg BID) in stage 1 (weeks 1-5). In stage 2 (weeks 6-10), patients randomized to AVP-923 continued at 30/10 mg BID while those initially on placebo were stratified on the basis of their response (since some improved on placebo, indicating a “placebo effect”) and then re-randomized 1:1 to placebo or AVP-923 (titrated as in stage 1). The primary study analysis combined data from stage 1 and stage 2. Additional analysis, similar to what is conducted in a standard parallel comparison trial, assessed data from patients who received only AVP-923 (N=93) or only placebo (N=66) during the 10-week trial.

Results from this 10-week analysis were consistent with the primary analysis (SPCD) and showed that AVP-923 significantly reduced agitation within one week of treatment, an effect that was sustained for the 10 weeks of the trial. In addition, at the end of the trial, clinicians deemed 45 percent of the study participants who received AVP-923 to be “much improved or very much improved” compared to 27 percent of patients receiving placebo.

In the full study group, the most common side effects in AVP-923 vs placebo were falls (8.6 percent vs 3.9 percent), diarrhea (5.9 percent vs 3.1 percent), and urinary tract infection (5.3 percent vs 3.9 percent).

“Our study suggests that AVP-923 has meaningful effects in reducing agitation, and further studies are warranted,” said Cummings. “If future studies support these findings, we believe this type of pharmacological approach may play a useful role in the management of Alzheimer’s.”

**Brain Amyloid PET Scans May Change Patient Diagnosis and Management**

When the cause of a patient’s cognitive impairment is uncertain, doctors often struggle to provide a diagnosis and determine an appropriate treatment plan. Brain amyloid imaging PET scans can detect the accumulation in the brain of amyloid “plaques” – a hallmark feature of Alzheimer’s disease. The FDA has approved three “radiopharmaceuticals” to use with PET scanners for this purpose.

However, the appropriate role of amyloid PET scans in clinical practice remains controversial. In the U.S., the Center for Medicare and Medicaid Services (CMS) has questions about the ability of PET amyloid imaging to improve health outcomes. Only recently has CMS consented to paying for an amyloid PET scan in a CMS-sanctioned clinical trial to develop evidence (known as “coverage with evidence development”) to help evaluate this specific diagnostic tool.

At AAIC 2015, Michael Pontecorvo, Ph.D., Vice President, Clinical Development for Avid Radiopharmaceuticals (a subsidiary of Eli Lilly and Company) and colleagues presented data from a study of physicians in France, Italy and the U.S. treating 618 patients being diagnosed for mild cognitive impairment (MCI) or dementia where Alzheimer’s disease was considered a possible cause.
Following initial examination of each study participant, physicians in the study recorded a working diagnosis and a management plan. Patients then underwent a PET scan using an imaging agent called florbetapir (Avid/Lilly) and were randomly placed into one of two groups: 1) an immediate feedback group whose physicians received results from the scan at a 3-month visit (n=308) or 2) a delayed feedback group whose physicians were given the scan results one year after the first patient visit (n=310).

Patients returned 3 months after initial examination. The physician updated their diagnosis and recorded a patient management summary, including tests performed, follow-up/referral visits, and medications used to treat cognitive impairment since the post-scan visit. Those in the immediate feedback group had received the amyloid PET scan results; those in the delayed feedback group had not. The researchers examined the impact of immediate feedback versus delayed feedback on diagnosis and medical management. While analyses are currently ongoing, preliminary results demonstrate that knowledge of amyloid status altered patient diagnosis and management.

“Changes in patient management were greater in the group who received immediate amyloid PET scan results than among those who were delayed for one year,” Pontecorvo said. “This was driven primarily by medication changes, particularly cholinesterase inhibitor use.”

The researchers found no group differences in cognitive performance or health outcomes at one year, and changes in medical history, psychotropic drug use, and psychiatric-related events were not significantly different between the immediate and delayed feedback groups. There was no evidence of increased safety risk associated with early disclosure of amyloid status.

To develop more definitive answers regarding the ability of amyloid PET scans in Alzheimer’s to change health outcomes, the Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) Study, a four-year $100 million study was recently launched by the Alzheimer’s Association and the American College of Radiology, with the bulk of funding coming from CMS. Starting in early 2016, more than 18,000 Medicare beneficiaries age 65 and older will be enrolled at roughly 200 sites throughout the United States.

About AAIC
The Alzheimer’s Association International Conference (AAIC) is the world’s largest gathering of researchers from around the world focused on Alzheimer’s and other dementias. As a part of the Alzheimer’s Association’s research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2015 home page: www.alz.org/aaic/
AAIC 2015 newsroom: www.alz.org/aaic/press.asp

About the Alzheimer’s Association®
The Alzheimer’s Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer’s disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer’s. Visit alz.org or call 800.272.3900.

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• Ilise Lombardo, MD; Lawrence T. Friedhoff, MD, PhD; et al. The Efficacy of Rvt-101, a 5-HT6 Receptor Antagonist, As an Adjunct to Donepezil in Adults with Mild-to-Moderate Alzheimer’s Disease: Completer Analysis of a Phase 2b Study. (Funder: Axovant Sciences, Inc.)

• Jeffrey Cummings, MD, ScD, et al. Dextromethorphan/Quinidine (AVP-923) for Treatment of Agitation in Patients with Alzheimer’s Disease: Analysis of Week 10 Results for Patients Treated Only with AVP-923 Versus Patients Receiving Only Placebo (NCT01584440). (Funder: Avanir Pharmaceuticals)

• Michael Pontecorvo, PhD, et al. A Randomized, Controlled, Multicenter, International Study of the Impact of Florbetapir (18F) PET Amyloid Imaging on Patient Management and Outcome. (Funder: Eli Lilly and Company)
The Efficacy of Rvt-101, a 5-HT6 Receptor Antagonist, As an Adjunct to Donepezil in Adults with Mild-to-Moderate Alzheimer’s Disease: Completer Analysis of a Phase 2b Study

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Background: RVT-101 is a 5-hydroxytryptamine 6 (5-HT6) receptor antagonist for the treatment of dementia with a number of favorable properties including once daily dosing, lack of food effect, and low potential for drug interactions. We present the results of an analysis of observed data from a randomized, double-blind, placebo-controlled Phase 2b study.

Methods: In this study, 684 subjects with mild to moderate Alzheimer’s disease were randomized to receive 35 mg RVT-101, 15 mg RVT-101, or placebo as an adjunct to stable donepezil treatment. The study included a 24-week double-blind randomized phase and an optional, additional 24-week blinded extension. An analysis of covariance (ANCOVA) method was used to evaluate multiple endpoints on cognition and function based on observed data, including the ADAS-cog, CDR-SB, and ADCS-ADL at weeks 12, 24, 36, and 48.

Results: The proportion of subjects completing the study ranged from 86-89% from week 0 to week 24 and from 87-89% from week 24 to week 48. On ADAS-cog and ADCS-ADL respectively, subjects who received 35 mg RVT-101 achieved a 1.29 (p = 0.008) and 1.72 (p = 0.016) point benefit at week 12; a 1.63 (p = 0.007) and 2.11 (p = 0.016) point benefit at week 24; and a 1.82 (p = 0.018) and 2.34 (p = 0.048) point benefit at week 48, all compared to donepezil alone. Subjects who received 35 mg RVT-101 achieved a statistically significant benefit on CDR-SB compared to subjects who received donepezil alone only at 12 weeks after initiation of treatment. Mean ADAS-cog, ADCS-ADL and CDR-SB values for the 15-mg group were generally numerically superior to placebo but the differences were not statistically significant.

Conclusions: In this analysis of subjects completing a Phase 2b study in subjects with mild-to-moderate Alzheimer’s disease, the 35 mg dose of RVT-101 was shown to be effective in improving cognition and function as an adjunct to stable donepezil at multiple time points. Given the low drop-out rate, this analysis provides an accurate representation of the study. The 35 mg dose of RVT-101 will be advanced into a Phase 3 study in the second half of 2015.
Dextromethorphan/Quinidine (AVP-923) for Treatment of Agitation in Patients with Alzheimer’s Disease: Analysis of Week 10 Results for Patients Treated Only with AVP-923 Versus Patients Receiving Only Placebo (NCT01584440)

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Background: Neuropsychiatric symptoms such as aggression/agitation are common in AD, adversely impact patients and caregivers, and have no FDA-approved treatments. AVP-923 (dextromethorphan and quinidine), is being investigated for AD-related agitation.

Methods: This double-blind, placebo-controlled, 2-stage study used Sequential Parallel Comparison Design (SPCD) methodology. Patients with probable AD and clinically meaningful agitation were randomized (4:3) to placebo or AVP-923 (20/10 mg QD titrated to 30/10 mg BID) in stage 1 (weeks 1-5). In stage 2 (weeks 6-10), patients randomized to AVP-923 continued at the same dose; those initially on placebo were stratified by response, then re-randomized 1:1 to placebo or AVP-923 (titrated as in stage 1). Here we analyzed primary and key secondary outcomes, comparing change from baseline to week 10 for patients treated only with AVP-923 versus only placebo during both trial stages.

Results: The primary analysis was significant for AVP-923 vs placebo (P≤0.001). In this secondary analysis of patients receiving only AVP-923 (N=93) or only placebo (N=66), mean (SD) baseline NPI Agitation/Aggression domain scores were 7.1 (2.6) and 7.2 (2.5), respectively; mean [SD] change from baseline at week 10 was -3.6 [3.5] vs -1.9 [3.6] (P=0.001; standard effect size [SES] -0.48). Significant improvements from baseline favoring AVP-923 vs placebo were also seen for NPI total score (-16.0 vs -10.1; P=0.024; SES -0.336); NPI composite domains including Agitation/Aggression, Irritability/Lability, and Aberrant Motor Behavior with Disinhibition (NPI-4D; P=0.022; SES -0.356), or Anxiety (NPI-4A; P=0.014; SES -0.379); Aberrant Motor Behavior (P=0.026) and Sleep/Nighttime Behavior (P=0.013) domains; Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC; P=0.015); Patient Global Impression of Change (PGI-C; P=0.007); Caregiver Strain Index (P=0.044) and Cornell Scale for Depression in Dementia (P=0.031). Changes in quality of life, activities of daily living, and MMSE favored AVP-923 but were not significant. In the full subject cohort, the most common AEs in the AVP-923 vs placebo groups included falls (8.6% vs 3.9%), diarrhea (5.9% vs 3.1%), and urinary tract infection (5.3% vs 3.9%).

Conclusions: AVP-923 provided significant improvement in agitation in patients with AD, based on both primary SPCD analysis and this comparison simulating a conventional parallel design.
A Randomized, Controlled, Multicenter, International Study of the Impact of Florbetapir (18F) PET Amyloid Imaging on Patient Management and Outcome

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Background: Previous studies of PET amyloid imaging impact on patient diagnosis and treatment have been limited in size or design (retrospective or hypothetical outcomes, lacking a control group that does not receive PET results). This is the first prospective, multicenter, randomized, controlled study of amyloid PET impact on actual patient diagnosis, management and outcomes.

Methods: Physicians in France, Italy and the US identified patients seeking diagnosis for MCI or dementia, where AD was considered a possible cause (<85% certain). They recorded a working diagnosis, and a management plan including any planned diagnostic and neuropsychological testing, plans for follow-up and referral visits, and any medication planned to improve cognition. Patients underwent a florbetapir PET scan and were then randomized to either immediate or delayed (1 year) feedback regarding PET amyloid status (positive: $A_{\beta}^+$, negative: $A_{\beta}^-$). Patients returned after 3 months and the physician updated the diagnosis and recorded a summary of actual management, including neuropsychological and diagnostic testing actually performed, follow-up/referral visits that occurred and medications actually used to treat cognitive impairment since the post-scan visit. Patients returned one year post baseline for assessment of patient and caregiver outcomes including change in cognitive status (ADAScog), health outcomes/resource utilization, mood, function and quality of life. Analyses examined the impact of immediate feedback versus delayed feedback of amyloid status for diagnosis and management changes at 3 months, and outcome measures at 12 months.

Results: A total of 618 subjects were randomized to the immediate (308) or to the delayed (310) amyloid PET feedback arms, including 174 subjects in France, 221 in Italy and 223 in the US. 599 completed the 3 month and 560 completed the one-year follow-up visits. Analyses are currently ongoing. Preliminary results indicate that the percentage of patients for whom the actual management composite recorded at 3 months was different from the baseline management plan (protocol specified primary outcome) was significantly greater for the group that received immediate feedback regarding amyloid status than for those with delayed feedback.

Conclusions: This randomized controlled trial supports the hypothesis that knowledge of amyloid status as determined by florbetapir PET imaging alters patient management.

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