9th Clinical Trials on Alzheimer’s Disease (CTAD)
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The 9th CTAD was held once again in the pleasant and scenic environment of the Marriott Marquis Marina, San Diego CA, USA, December 8-10, 2016. This latest conference followed the tradition of the successful 1st CTAD meeting in 2008 (Montpellier, France), followed by 2nd meeting in Las Vegas (2009), the 3rd in Toulouse, France (2010), the 4th in San Diego (2011), the 5th in Monte Carlo (2012), the 6th again in San Diego (2013), the 7th in Philadelphia (2014) and the 8th in Barcelona, Spain (2015). The CTAD series continues to draw participants from academia, industry, hospital management and nursing, as well as students from diverse disciplines. The 9th meeting welcomed more than 1500 delegates to share their findings on improving therapeutic strategies for treating Alzheimer disease (AD) and/or alleviate its symptoms in AD patients for improved quality of life.

Collectively, this conference hosted 5 keynote presentations, 5 symposia, 1 workshop, 64 oral presentations and 135 posters over a 3-day period. This report presents an overview of salient new developments and novel research findings that emerged during the conference.

Thursday December 8

The 1st day of the congress began with a welcoming address by the organizing committee comprised of Paul Aisen (San Diego), Jacques Touchon (Montpellier) and Bruno Velas (Toulouse) and a presentation of the CTAD Lifetime Achievement Award to Neil Buckholtz (National Institute of Ageing, of the National Institutes of Health, Bethesda, MD). The 1st Keynote address was given by Maria Carrillo (Chicago, IL) discussing Alzheimer’s association and its contribution to public health perspectives. This was followed by 4 oral communications. Lon S. Schneider (Los Angeles, CA) discussed a phase 3 trial of tau aggregation inhibitor therapy with leuco-methylthioninium in mild AD. Maria Carrillo emphasized sharing of data from AD research groups for better understanding. Ruolun Qiu (Cambridge MA) discussed a novel gamma secretase modulator PF-06648671 on cerebrospinal fluid (CSF) beta amyloid peptide levels after oral administration in healthy subjects. A Phase 3 study with a BACE inhibitor LY3314814/AZD3239 in patients with early AD was presented by John R. Sims (Indianapolis, IN, USA). Helen Lin (San Francisco, CA) shared phase IB double-blind, placebo-controlled data of crenerzumab in patients with mild to moderate AD.

In the 1st Symposium entitled, “Time-to-event Endpoints for Clinical Trials in AD”, 3 speakers presented their findings. Mary Sano (New York, NY) discussed the history of time-to-event in AD clinical trials. Value of Time-to-Event was presented by José L Molinuevo (Barcelona). Suzanne Hendrix (Salt Lake City, Utah) argued clinical relevance and statistical utility for Time-to-Event endpoint definitions.

This was followed by 2 oral communications in which R. Scott Turner (Washington DC) showed resveratrol’s ability to regulate neuroinflammation and adaptive immunity in AD. Results of a phase 1 clinical trial of the active vaccine against amyloid beta 40 (ABvac40) was presented by Pedro Pesani (Zaragoza, Spain).

In the 2nd keynote address, Paul Aisen discussed continued progress in AD trial design. This was followed by 6 oral communications. Automated pre-screening of patients for clinical trials in AD was presented by Sulantha Mathotaraachchi (Montreal, Canada). Michael Rosenblum (Baltimore MD) discussed adaptive enrichment trial design for exploring subpopulations that could benefit from treatments based on ApoE4 carrier status. Automated classification of adverse events in clinical studies of AD was advocated by Gustavo A. Jimenez-Maggiora (San Diego). Phillip Schelten (Amsterdam, The Netherlands) presented a quantitative positron emission tomography (PET) study on p38-alpha kinase inhibitor VX-745 on brain amyloid plaque load in
early AD patients. Outcome from preventive studies of AD using vitamin E and selenium trial was discussed by Erin L Abner (Lexington, KY, USA). Finally, Reme Raman (San Diego) presented a statistical approach for risk-based monitoring of AD clinical trials.

The 3rd keynote address was given by David Michelson (Kenilworth, NJ) on industry perspectives for drug development in AD. This was followed by 5 oral communications. Allopregnanolone as regenerative therapy for AD Phase 1a/2a was discussed by Roberta Diaz Brinton (Tucson, AZ). Philippe Ciuciu (Gif-Sur-Yvette, France) showed effects of S47445 on functional connectivity and glutamate concentration in elderly subjects during rest and task performances. Dual phase to dual biomarker imaging using Florbetapir [F18]PET was discussed by Sergey Shcherbinin (Indiapolis), Guoqiao Wang (Saint Louis, MO) presented a novel disease progression model for clinical trials in dominantly inherited AD. Optimal reference region to measure longitudinal amyloid beta peptide changes with [F18]-flobetaben PET was presented by Susan De Santi (Melbourne, VIC, Australia).

Non-pharmacological intervention in populations at high risk of AD was the theme of Symposium 2 covered by 3 speakers. Sandrine Andrieu (Toulouse, France) presented the Multidomain Alzheimer Preventive Trial (MAPT) study on cognitive performance in amyloid beta subjects. Tobias Hartmann (Homburg, Germany) discussed LipiDiDiet program on multi-nutrient intervention in prodromal AD. New results of a 24-month study on LipiDiDiet that investigated the effects of Fortasyn Connect in prodromal AD was discussed by Hikka Soininen (Kuopio, Finland). This was followed by a panel discussion and appraisal of the new data and mingling with leaders during a grand welcome reception at Coronado Terrace of Marriott Marina Hotel overlooking beautiful San Diego Bay.

**Friday December 9**

The 2nd day of the congress started with 3 oral communications. Petr Novak (Graz, Austria) discussed the safety profiles of the active vaccine AADvac1 against AD tau protein in a long-term follow up study (AC-AD-002). Clinical pharmacology of the p38-alpha MAP kinase inhibitor Neflamapomoid (VX-745) was discussed by John Alam (Cambridge, MA) in mild cognitive impairment caused by AD. Vissia Viglietta (Zurich, Switzerland) presented 12-month interim analyses of Aducanumab titration dosing from a double-blind, placebo-controlled phase 1B study in patients with prodromal or mild AD.

These were followed by 27 oral communications divided into 2 parallel sessions. Six presentations were selected for the session on animal models. Preclinical development of GMP-1, a compound that protects mitochondrial function of neurons was discussed by Bengt Winblad (Huddinge, Sweden). Jacques Hugon (Paris, France) presented early prevention approaches for targeting amyloid beta lowering kinase inhibition in AD. Aruna Sharma (Uppsala, Sweden) showed new roles of TiO2-nanowired cerebrolysin in potentiating neuroprotective effects of anti-tau (PHOSPHO S422) antibody in AD. Exogenous infusion of nephrylsin together with nanowired cerebrolysin results in superior neuroprotection, as described by Hari Sharma (Uppsala, Sweden). Andrew Amer (San Diego) described increased hippocampal vulnerability in transgenic mice overexpressing amyloid precursor protein and triple repeat tau. Amyloid imaging in a mouse model of AD to evaluate reduction in beta amyloid plaques after irradiation was discussed by James Fontanesi (Royal Oak, MI). Ulf Neumann (Basel, Switzerland) showed evidence for the BACE inhibitor CNP520 in AD prevention. The salient new findings in another 23 oral communications include drug interaction between Intepiridine (RVT-101) and a histamine 5-HT6 receptor antagonist and memantine in healthy subjects (Ilise Lombardo (New York, NY); a 24-month Phase 1B trial of Aducanumab in AD (Samantha B Haebelnein, Cambridge, MA); Pharmacokinetics of the monoclonal anti-tau antibody ABBV-B in a Phase 1 ascending dose trial in AD (Diana Kerwin, Dallas, TX); NILVAD-European multicenter phase III trial of Nilvadipine in mild to moderate AD (Brian Lowler, Dublin, Ireland); Xanamem-an 11beta-HSD1 inhibitor in development for the management of AD (Craig Ritchie, Edinburgh, UK); and Effect of APOE genotype and low CSF amyloid beta 42 on docosahexaenoic acid bioavailability in AD (Hussein N Yassine, Los Angeles, CA).

Symposium 3 on the 2nd day focused on stem cell therapeutics for AD therapeutics covered by 3 speakers. Stem cells for AD in relation to amyloid beta amyloidosis, tau pathology and gut microbiota was discussed by Tristan Belmont (Lausanne, Switzerland). Barry Baumel (Miami, FL) presented clinical advancement of mesenchymal cells, while Almee Pierce (Irvine, CA) presented a Phase 2 trial of allergic human mesenchymal stem cells for AD. Nick Fox (London) delivered the 4th Keynote address on ‘What have we learned and what can we expect from brain imaging for Alzheimer trials?’.

The 4th Symposium was based on the European Prevention of Alzheimer’s dementia (EPAD) program with 3 speakers. Craig Ritchie discussed EPAD readiness cohort remains “fit for purpose”. The EPAD proof of concept-master protocol for increasing efficiency was discussed by Scott Berry (Austin, TX). Richard Milne (Cambridge, UK) presented parent cohort to clinical trial in EPAD and ethics.

A workshop on new trends in clinical trial designs in the search of next generation treatment was organized by Paul Aisen who discussed potential disease-modifying effects on delayed start, design and analysis. Steve Ruberg (Indianapolis, IN) emphasized controlling false positive finding among primary and secondary outcomes in a multiple testing procedures paradigm. The day concluded with 3 key communications on clinical trials in chronic traumatic encephalopathy: moving ahead (Charles Bernick, Cleveland, OH); computerized cognitive testing using NIH toolbox and Cogstate C3 for clinical trials (Dorene M Rentz, Boston, MA, USA); and Alan J. Lemer (Cleveland) on the functional activity questionnaire in the systolic pressure reduction intervention trial (SPRINT) and SPRINT-MIND.

**Saturday December 10**

The 3rd and final day of the conference started with 6 oral communications. Thirty-six weeks of treatment with PXT-864 in mild AD from the PLEODIAL extension study was
presented by René Goedkoop (Moulineaux, France). Lynne Shinto (Portland, OR) showed unique methodology for a phase 2 clinical trial evaluating omega-3 fatty acids for the prevention of vascular cognitive impairment. Rober A. Rissman (La Jolla, CA) demonstrated prediction of conversion from mild cognitive impairment to dementia with neuronally-derived blood exosome profiling. Outcome of a 3-year multicenter randomized, double-blind placebo-controlled phase 2 trial to assess safety and efficacy of low dose LADOSTGIL in patients with mild cognitive impairment was discussed by Lon S. Schneider. Identification of asymptomatic individuals at risk of AD using Chariot-Pro observational study as a true historical control to identify risk factors for amyloid pathology was presented by Ziad Saad (Teaneck, NJ). Stephen Macfarlane (Melbourne, Australia) showed 9- and 12-month safety and efficacy data of ANAVEX 2-73 in a phase 2a study in mild to moderate cognitively impaired AD patients.

Zaven Khachaturian (St. Louis, MO) delivered the 5th Keynote address on AD from proteinopathy to prevention. This was followed by 4 oral presentations. Removal of subjects with “false positive” diagnosis of mild cognitive impairment from the AD co-operative study donepezil trial that strengthens positive effects was presented by Emily C. Edmonds (San Diego). Kaycee M. Sink (Winston-Salem, NC) discussed Montreal cognitive assessment in 8724 SPRINT participants and implications for screening in clinical trials. Effect of symptoms on tau pathology in asymptomatic elderly individuals and individuals with early AD symptomology was described by Duygu Tosun (San Francisco). Finally, Michael Egan (Kenilworth, NJ) discussed baseline characteristics for participation in the phase II/III EPOCH AD trial of the BACE inhibitor verubecestat (MK-8931).

Symposium 5 on collaborative efforts to prevent AD was the final deliberation of the conference on the last day, and comprised of 3 speakers. Maria Isaac (London) presented efforts on Alzheimer’s prevention trial based on prevention regulatory scientific advices. Alzheimer's Disease Neuroimaging Initiative to build AD prevention trials was discussed by Mile Weiner (San Francisco), while Bruno Vellas (Toulouse) talked about MAPT trials in relation to MAPT-2 and MAPT-3 prevention trials.

Apart from oral communications, keynote addresses, symposia and workshops, 3-day poster presentations made up an important aspect of novel ideas and data display. A total of 135 posters were presented over the 3 days of the conference. The salient novel findings of these posters are summarized below.

Nine posters from the 1st day merit special mention. Niels D. Prins (Amsterdam) reported on an innovative phase II study design for exploring the glutaminylcyclase inhibitor PQ12 in early AD. Age reportedly increases the rate of amyloid beta and APOE4-related memory declines in preclinical AD, as shown by Paul Maruff (New Haven, CT). Brigitte Haas (Berlin) presented SIMAMCI- a randomized, controlled trial of simvastatin in amnestic mild cognitively-impaired patients for the prevention of conversion to AD. Amnon Katz (Tel-Aviv, Israel) presented results of phase 2 trial of piromelatine for mild AD (The ReCOGNITION Trial). Microstructural damage of white matter in the frontal aslant tract for visual spatial disturbances in AD was discussed by Laura Serra (Rome, Italy). A novel confrontational, phosphor-threonine 231 specific assay for CSF tau protein in AD was detailed by Eugeen Vanmechelen (Ghent, Belgium). Niklas Mattsson (Lund, Sweden) discussed tau pathology measurement by [F18]-AV1451 PET techniques in the CSF of AD patients. An electroencephalographic marker of cholinergic activity in the living brain in AD cases was displayed by Kristinn Johnsen (Reykjavik, Iceland).

On the 2nd day, 11 posters exhibited novel data for the advancement of our knowledge in AD. Anne Catrien Baakman (Leiden, The Netherlands) showed predicting response to a 6-month treatment with galantamine in patients with mild to moderate AD after single dose of pharmacological challenge. Intepirdine (RVT-101), a 5-HT6 receptor antagonist as an adjunct to donepezil efficacy and activities of daily living domain in mild to moderate AD patients were presented by Geetha Ramaswamy (New York, NY). In his poster, Alexei Lukashy (Lausanne, Switzerland) described testing combined with neuronal and mesenchymal stem cell therapy in a Phase 1 study for patients with dementia. John A. Hey (Farmington, MA, USA) discussed ALZ-801 - a novel produg of trampisolate with improved tolerability in a phase 1 program for AD patients. Pharmacokinetics, pharmacodynamics, safety and tolerability of piromelatine for AD therapy were presented by Amnon Katz. Tiffini Voss (Kenilworth, NJ) showed negative results of MK7622- a positive allosteric modulator of the acetylcholine M1 receptor on symptoms of AD in clinical trials. Neurophysiological effects of PXT864 in mild AD patients were discussed by Karim Bennys (Montpellier, France). The potential of protostasis-directed therapies of AD was the topic of John Alam (Washington DC). Glen Wunderlich Burlington, ON, Canada) described the pharmacokinetics of a single dose of BI 425809 in a double-blind placebo-controlled trial in healthy Chinese subjects. Phase 3 efficacy, safety and tolerability of AVP-786 (deuterated (D6)-dextromethorphan hydrobromide plus quinidine sulfate) for the treatment of agitation in AD was presented by Jeffrey Cummings (Las Vegas, NV). John A. Hey described efficacy and bioequivalence studies for the produg ALZ-801 in phase 3 trials in AD patients.

On the 3rd day of the meeting, 12 of the posters presented basic and clinical strategies aimed at modifying AD processes. Jun Li (Chengdu, China) described the impact of diabetes on caregiver stress in patients with AD, as taken from the ICTUS study. Sebastian Gonfrier (Nice, France) showed how environmental light therapy can improve sleep and psychiatric symptoms in dementia. Amyloid pathology in the progression of mild cognitive impairment was shown by Phillip Insel (Lund, Sweden). Tristan Bolmont (Lausanne, Switzerland) presented findings to show that amelioration of gastro-intestinal microbiota following stem cell treatment in a mouse model resulted in the reduction of cerebral amyloidosis. BI425809- a novel GlyT1 inhibitor increases glycine levels in CSF as shown by Glen Wunderlich. Kohji Fuku-
naga (Sendai, Japan) presented preclinical studies of an SAK-3-a type of calcium channel stimulator in APP23 mice and rats. Ramkrishna Nirogi (Hyderabad, India) demonstrated the safety and tolerability in healthy subjects of SUVN-502, SUVN-G3031 (a potent and selective histamine H3 receptor inverse agonist) and SUVN-D4010 (a selective histamine 5-HT4 receptor partial agonist). A randomized, double-blind placebo-controlled study for safety and tolerability of S-47445 in AD patients was shown by Pueyo Maria (Suresnes, France). Oneeb Majid (London) described a dose-related reduction of CSF amyloid beta (1-x) by E2609-a novel BACE inhibitor in patients with mild cognitive impairment due to AD. Krishna Prasad Pathak (Thessaloniki, Greece) discussed therapeutic links between anticancer drug (Bexarotene) and AD.

Overall, the 9th CTAD witnessed many novel advancements for AD therapy that, no doubt, merit further investigation. The 10th CTAD meeting is scheduled from November 1-4, 2017 at the Boston Park Plaza, Boston, MA, USA. All interested are very welcome!