RESEARCH UPDATE BULLETIN – SEPTEMBER 2012

Exclusive to Alzheimer’s disease Therapy Trends clients, Impact Assessments are dynamic analyst bulletins evaluating the impact of events over the next 12 months. Impact Assessments convey views of key opinion leaders delivered within days of a significant event happening, providing a continuous updated report.

**Bapineuzumab trials fail – Phase III trials discontinued**

- **What’s new?** Top-line results for bapineuzumab’s Phase III clinical studies that it failed to meet either of the co-primary endpoints in cognition and function

In August 2012, Pfizer and Johnson & Johnson announced the discontinuation of the bapineuzumab following disappointing results in the Phase III trial in patients with mild-to-moderate Alzheimer’s disease who do not carry the ApoE4 genotype. It was announced the drug failed to meet the co-primary clinical endpoints in cognition and function signalling the end of the intravenous formulation. Given the previous Phase II results in the non-carriers that demonstrated some efficacy, key opinion leaders had marginally higher hopes for this study than for the first bapineuzumab study in ApoE4 genotype. However, this failure represents a huge disappointment and highlights the difficulties in Alzheimer’s drug development. Key opinion leaders are disappointed in the result and reflect on the issues that led to discontinuation.

1 Marketwatch, Pfizer Announces Co-Primary Clinical Endpoints Not Met In Second Phase 3 Bapineuzumab Study In Mild-To-Moderate Alzheimer’s Disease Patients Who Do Not Carry The ApoE4 Genotype, August 2012

For more information on Therapy Trends: Alzheimer’s Disease, please [CLICK HERE](#) or [CONTACT US](#) to request additional details including an executive summary and full details of the KOLs who participated in this research.

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“Bapineuzumab’s failure is a major disappointment to the Alzheimer’s disease research. Discontinuation raises a number of questions, whether this is drug specific, a class issue or a population issue.”

Professor Lutz Frölich (EU Key opinion Leader)

“My first reaction to bapi’s discontinuation is disappointment; secondly it’s not a huge surprise. I think the promising results that were available before Phase III begun they were sub group based and that is always kind of makes us a little bit suspicious about the overall efficacy.”

Professor Dag Aarsland (EU Key opinion Leader)

“It seemed like that bapineuzumab Phase II trial and the theory behind the treatment approach made good sense but unfortunately in Phase III trials like this sometimes the results don’t follow the hypothesis or the earlier phase data so bapi’s discontinuation is hugely disappointing certainly for the field, and I’m sure for those who’ve been involved in the development of the compound.”

Professor David Sultzer (US Key Opinion Leader)

■ Phase III trial in failed to meet two primary endpoints in patients with Alzheimer’s disease who carry the ApoE4 genotype

A month earlier, Pfizer and Johnson & Johnson announced bapineuzumab’s failure to change cognitive and functional endpoints compared to placebo in patients with mild-to-moderate Alzheimer’s disease who carry the ApoE4 genotype.2

2 Reuters, Pfizer, J&J Alzheimer’s drug fails one of 4 big trials, July 2012
However, these results came as no surprise as the probability of success in these carriers were lower than in non-carriers based on the Phase II results. Key opinion leaders speculate a lack of benefit for the drug in any potential sub-group and that the side effect profile led to total discontinuation of the bapineuzumab intravenous (IV) formulation.

“My guess is that the primary end points were not met, plus there was no trend towards efficacy. From a regulatory and commercial point of view this is obviously a challenge. Also, in the development of bapineuzumab over time, there have been dosing issues and the side effect profile that have caused concern so I believe the combination of those issue the discontinuation of bapi was a business decision as much as a medical one.”

Professor David Sultzer, MD, PhD. Professor, Columbia University Medical Center, Departments of Psychiatry, Neurology, and Pharmacology, New York, US

“I think the combination of no signal and the tolerability in terms of adverse effects probably resulted in this discontinuation in both patients with the ApoE4 genotype and without.”

Professor Dag Aarsland (EU Key opinion Leader)

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■ Further takeaways: Ongoing Phase II study will continue looking at the subcutaneous (SQ) formulation of bapineuzumab

Pfizer and Johnson & Johnson have announced all intravenous bapineuzumab Phase III studies have been discontinued, including two currently ongoing in Europe. However, the Phase II study investigating the subcutaneous formulation of bapineuzumab is expected to continue. A possibility is Pfizer,
Johnson & Johnson and Elan will eventually take the subcutaneous formulation into a Phase III pre-Alzheimer’s population, contingent on the companies seeing positive biomarker data in Phase II (this is the primary endpoint in the Phase II trial).

“There maybe something in the bigger non ApoE4 trial, although that study led to the discontinuation. It may be a dosing issue or it may lead to some benefit for another sub group, maybe of less value but is important in understanding what the drug is doing in further development”

Professor David Sultzer, MD, PhD. Professor, Columbia University Medical Center, Departments of Psychiatry, Neurology, and Pharmacology, New York, US

“The Phase III data suggests that the IV formulation, at least for people with mild to moderate Alzheimer disease didn’t meet the primary endpoints, so that leaves a couple of different options for that drug as well as therapies in general. For bapineuzumab the continued interest in the subcutaneous form could be related to just ease of administration; should the drug be at least mildly efficacious obviously the subcutaneous administration has advantages over an IV just from a practical point of view. My feeling is that the companies may be poised for further development in earlier stage and want to get more information, everything from pharmacokinetics to some other population as well as some adverse effects so should they want to pursue earlier treatment they’ve got a stronger base to operate.”

Professor David Sultzer (US Key Opinion Leader)

“It’s possible that some of the secondary end points showed benefit or there is benefit in sub group. There maybe something in the bigger non ApoE4 trial, although that study led to the discontinuation, a dosing issue or it may lead to some benefit for a sub group maybe of less value but is important in understanding what the drug is doing in further development perhaps.”

Professor David Sultzer (US Key Opinion Leader)
“Subcutaneous application is much cheaper than IV infusion line, so this might affect the willingness of the company to advance further on this type of application. It also might be that the immunogenicity of subcutaneous approach may be even better than just IV.”

Professor Lutz Frölich (EU Key opinion Leader)

“The continuation of the subcutaneous formulation is a bit surprising because according to the press release there was not even a signal for efficacy and in earlier trials there were side effect problems. So whether there is something in the different administration routes that could kind of influence either the efficacy or the side effect in a positive way, then there might be something there for Pfizer. It would make sense for the subcutaneous bapi if they treated in earlier stage patients, such as the pre Alzheimer’s population. But from a pragmatic view it might be more difficult really so people that are either healthy or close to healthy to treat these patients, they are not patients.”

Professor Dag Aarsland (EU Key opinion Leader)

Opinion leaders believe there will be a trend towards earlier intervention of the disease, before the mild-to-moderate patient population used in the bapineuzumab trial.

*If bapineuzumab was a very strong efficacious compound then effects might have been shown up even in patients with this mild to moderate AD which have been studied in those large trials involving more than almost 2,000 patients. But since this very dramatic strong efficacy is not to be expected it is much more important to reshape the timing of the intervention, the way how to
assess the outcomes and all other aspects of trial design and here one would say we need to wait until the new studies with antibodies directed against amyloid peptide in a prodromal AD trial population and this should not discourage the field of medicine and the patient.

Professor Lutz Frölich (EU Key opinion Leader)

**Further takeaways: bapineuzumab’s failure further dims the prospects for solanezumab**

The disappointing bapineuzumab results cast a shadow over the imminent data for solanezumab. Given the both therapies target beta amyloid, albeit different regions on the peptide, expectations for Eli Lilly’s solanezumab have dampened. However, key opinion leaders do not believe solanezumab is inevitably going to fail based on the bapineuzumab data, and eagerly awaiting the Phase III results.

“I still think immunotherapies have an opportunity, the question is when in the course of illness to start them and what’s the mechanism by which other anti-amyloid strategies work and their links to memory as well. With regard to solanezumab, it is a different antibody than bapineuzumab, there are reasons to think they would have different effects that could be translated into clinical benefit, we’ll just have to see.”

Professor David Sultzer (US Key Opinion Leader)

“I must admit my expectations for solanezumab have dampened. Because of the bapineuzumab discontinuation it is difficult to have a really high relevant expectation as they have a similar mechanism of action.”

Professor Dag Aarsland (EU Key opinion Leader)
“Solanezumab is directed towards the mid domain of the amyloid peptide and not against the end terminals which bapineuzumab targets. Actually most hypotheses have thought that end terminal targeting is better than mid terminal targeting as it’s more exposed. We need to wait and see when the Solanezumab data comes out but bapineuzumab discontinuation is not positive.”

Professor Lutz Frölich (EU Key opinion Leader)

Impact on funding: KOLs suggest focus should switch to improving diagnosis

Key opinion leader’s state Alzheimer’s disease research is at a crossroads, focus over the last decade has been concentrated too much the beta-amyloid theory and more focus should be identifying patients earlier in addition to understanding more about the disease.

“There is a big trend focusing on diagnostic markers and much less on novel immunotherapy at the moment. It’s a pity that there are few trials with new disease modifying therapies but it’s good the diagnostic markers are coming and I think there we have learned a lot and there’s still a lot to learn and that is also certainly needed in terms of moving the trials into earlier stages of disease and we need better diagnostic markers.”

Professor Dag Aarsland (EU Key opinion Leader)

“There will be an increasing interest in prevention and early or pre symptomatic treatment. Obviously to treat pre symptomatically you either have to treat the entire population which is not practical or identify those who are at high risk and that’s where biomarkers come into play. Alzheimer’s disease is really unique illness in that some of the neuropathologic components and
the pathophysiologic cascade is fairly well known, it's just understanding interactions with things and what it leads to memory difficulty. However, it is still a little unclear, but there's a lot of different things to look at so it’ll be interesting to see, and there are nano-biomarkers should it be spinal fluid or plasma, which is a lot easier to get at and imaging of the brain to look at amyloid burden, and that's taught us a lot already. Those kind of studies, the biomarker studies will be key in drug development in the future, everything from proof of concept, about the mechanism to perhaps predicting those who are more likely to respond to treatment rather than just treating everybody.”

Professor David Sultzer (US Key Opinion Leader)

“From a more medical or patient view we need to refine the diagnosis and define the diagnostic tools. This is the future even if this does not affect the drug development. In a certain way the definition of dementia is backdated, we still identify dementia when the ability to perform basic activities of daily living or activities of daily living fails and this needs to be refined.”

Professor Lutz Frölich (EU Key opinion Leader)