Streamlining and harmonizing the global drug development pathway for Alzheimer's Disease treatment

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Failing trials in AD: few reasons why

- Insufficient scientific knowledge about the pathogenesis of this multi-factorial disease;
- Clinical trials performed when the disease was too advanced;
- Diagnostic uncertainty with heterogeneous dementia populations;
- Clinical trials performed with insufficient dosage to meaningfully impact disease processes;
- Lack of knowledge sharing across intervention trials;
- Lack of combination treatment approaches.

Possible solutions

- Invest more into Alzheimer's Disease research;
- Address AD in earlier stage of history disease even when asymptomatic;
- Share knowledge from failed trials, optimize PoC trials design;
- Improve AD diagnosis to enrich clinical trials with specific patient population;
- Combined treatment approach;
- Identify preventive factors to defeat the known risk factors linked to AD.


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2nd Lausanne Workshop (2015): Global Action to Drive Innovation in Alzheimer's Disease and Other Dementias: Connecting Research, Regulation and Access
On December 15-16, experts convened in Lausanne to define an action plan to speed effective treatments and diagnostics for Alzheimer's disease by 2025. This year's two-day meeting under the auspices of the Organisation for Economic Co-operation and Development (OECD), entitled "Global Action to Drive Innovation in Alzheimer's Disease and Other Dementias: Connecting Research, Regulation and Access," focused on the drug development process critical to both bringing a drug to market and delivering treatment to patients. It comes at an important time as the expected completion of several rigorous research programs offers new hope for innovative treatments that could be on the market in the coming years. Read the Press Release
GLOBAL CEOINITIATIVE
ON ALZHEIMER'S DISEASE
Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra
Swiss Confederation
Federal Department of Economic Affairs, Education and Research EAER
State Secretariat for Education, Research and Innovation SERI
Alzheimer's Disease International
The global voice on dementia

Guidance for Industry

Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2013
Clinical/Medical

The underlying anatomical and pathophysiologic changes in AD begin many years before clinical symptoms emerge. A variety of biomarker measures have shown some promise with respect to their ability to reflect reliably the biological hallmarks of AD well before there is any evidence of clinical impairment. Levels of β-amyloid and tau proteins in the brain and cerebrospinal fluid, as well as markers of neuronal degeneration, are among the leading candidates in this respect. In the earliest clinical stages of AD, subtle cognitive deficits may be evident only through use of sensitive measures of neuropsychological performance. Thereafter,

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 January 2016
EMA/CHMP/539931/2014
Committee for Medicinal Products for Human Use (CHMP)

Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias

Draft

The field of AD research and development witnessed a recent paradigm shift in the diagnostic framework of AD which is now considered a continuum with a long-lasting presymptomatic phase, with evidence of AD neuropathology, which precedes 10-20 years the onset of dementia. As the biomarker field is evolving, the possibility to detect disease changes and progression *in vivo*, opens new regulatory scenarios including the possibility to intervene directly on the neuropathology before the appearance of symptoms.

FDA Clinical outcome measures	EMA Clinical outcome measures
Prodromal AD or MCI: Improvement in functioning and cognition This dual approach may be impractical Clear evidence of an effect on delaying cognitive impairment may provide sufficient evidence Composite endpoint	Prodromal AD/MCI due to AD: Dual outcome approach ideal but difficult to establish Cognitive domain preferable versus function domain Composite scale assessing cognition and functioning of daily living New tools
Preclinical AD: Single primary efficacy measurement with a valid and reliable cognitive assessment scale Accelerated approval mechanism Long efficacy still to be proven afterwards Time to diagnosis Biomarkers, proven a real clinical benefit	Preclinical AD: cognitive decline, cognitive function New but not validated neuropsych. tests Time to event Biomarkers not yet defined as real surrogate measure of treatment effect
AD: Co-primary outcome • Cognitive and functional assessment scale • Global assessment scale	Mild/moderate AD: Co-primary outcome • cognitive • functional domain • global domain (either co-primary or secondary) Secondary outcomes: neuropsychiatric and behavioral symptoms Care-giver evaluation

Science AAAS

Why the big change to Lilly's Alzheimer's trial is not evidence its drug has failed again

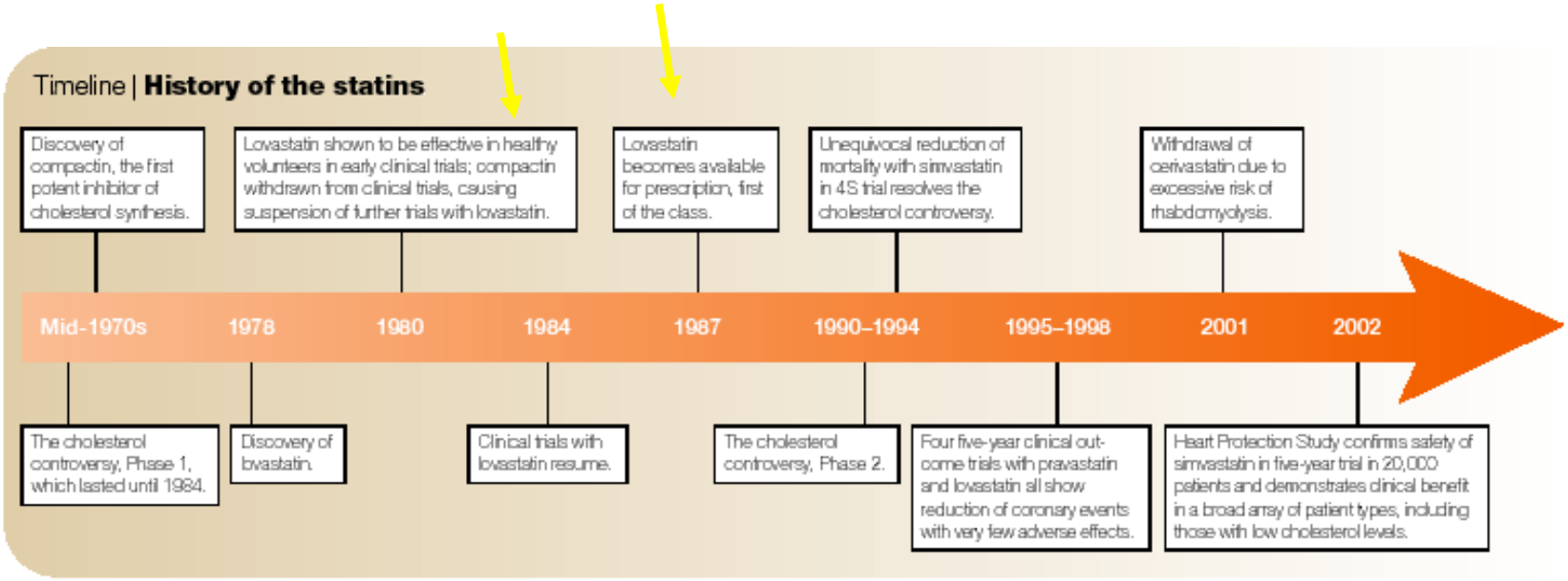
By Emily Underwood | Mar. 21, 2016 , 1:30 PM

In solanezumab trials EXPEDITION and EXPEDITION II both a cognitive test and a functional measurement were used for mild and moderate Alzheimer's disease

Both trials failed to show significant benefits over placebo in either measure. A trend to a significant effect was observe for cognition

EXPEDITION III with 2100 people and with only mild Alzheimer's will assess only cognition

Learning from Statins



J.A. Tobert 2003
Nature Reviews Drug Discovery

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2013
EMA/CHMP/748108/2013
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment of lipid disorders

4.2.1. Evaluation of morbidity and mortality

To show a beneficial effect on CV morbidity and mortality, the preferred primary endpoint should be a composite of major cardiovascular events (CV or all-cause death, non-fatal myocardial infarction and non-fatal stroke) adjudicated by a blinded, independent committee. If cardiovascular instead of all-cause mortality is chosen, effects on non-cardiovascular mortality should also be taken into account.

4.1.2. Lipid levels

A relative reduction in LDL-C level is acceptable as a primary efficacy endpoint in patients with primary hypercholesterolemia, provided that claims in the label are restricted to a lipid lowering effect.

In principle, an isolated effect on TG or HDL-cholesterol is not expected to be the sole basis for the demonstration of the efficacy of a new lipid-modifying agent, but should be seen in conjunction with the effect on non-HDL cholesterol and the underlying pharmacological mechanisms of actions (see section 4.2.2).

There is limited experience with clinical studies investigating medicinal products which qualitatively modify dyslipidaemias. Scientific advice could be requested to specifically address such developments.

4.1.3. Vascular damage (target organ damage)

Target organ damage of heart, brain, kidneys and, in particular, blood vessels is presumably and plausibly associated with morbidity and mortality. Vascular damage is an integral part of atherosclerosis. Imaging modalities such as IMT (intima media thickness) measurement, IVUS (intravascular ultrasound), and MRI (magnetic resonance imaging), have evolved over the past few years as indicators of vascular (or target organ) damage and atherosclerotic burden. Amongst various modalities available, cIMT (carotid IMT) and IVUS may have sufficient validity and weight of evidence for use in phases of drug development including dose finding studies as markers of atherosclerotic process. However they lack the evidence base to suggest that small changes in these parameters influence outcome (that is, to be considered as surrogate markers).

Future: drugs to treat AD

Present: stakeholders working together

Past: always a learning

Thank you!

Clinical trial efficiency
From «Big Data» to Design Thinking?