

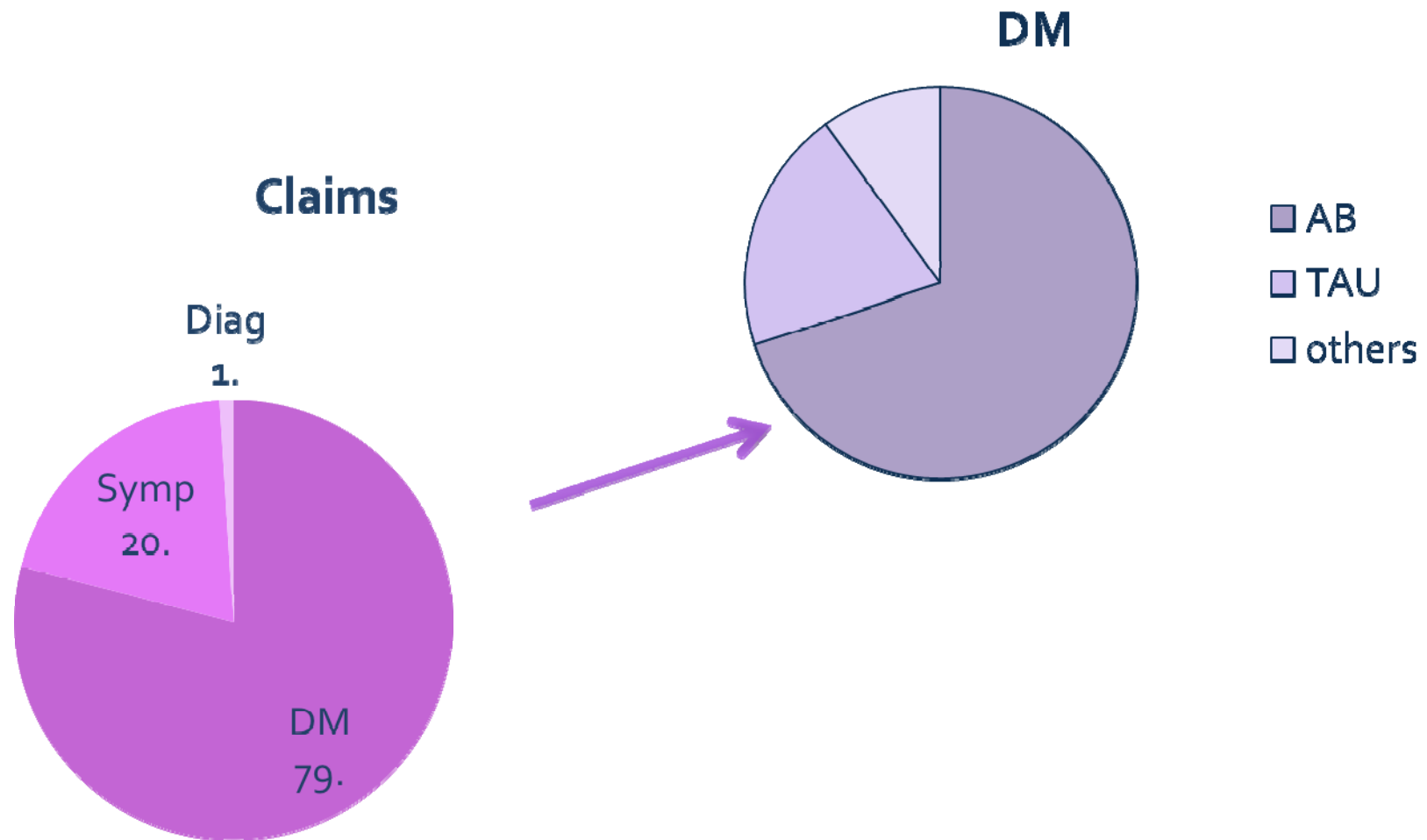
COMMON DIFFICULTIES
in the CLINICAL
DEVELOPMENT OF
ALZHEIMER DISEASE
MEDICINES

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Summary

- + Revision of the bottlenecks most often identified in the clinical development of AD Medicines
 - + Disease-modification claims
 - + Dosing strategy
 - + Trial Design
 - + Statistical analysis
 - + Biomarkers
 - + Symptomatic claims
 - + Feasibility of placebo controlled trials/ Add-on trials
 - + Choice of outcomes
 - + Responder definition
 - + Progression rates under placebo
 - + Diagnostics

ALZHEIMER DISEASE





DiSEASE MODIFICATION...

Dosing strategy

- + **It is an important bottleneck**
- + One weakness for drugs that do not have symptomatic effect.
 - + *Eventually, it can become biomarker based.*
- + For the moment DOSING is mostly based
 - + On pre clinical data
 - + Safety data.
 - + If this does not impose a cap, the optimal dose might be elusive.
 - + Particularly risky if response is U shaped.

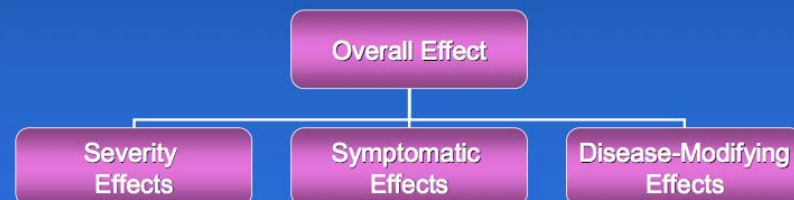
Trial design

- + Mechanistic approaches as:
 - + **Delayed start and randomized withdrawal**
 - + are seen as too cumbersome and uncertain
- + Other alternatives like:
 - + Staggered design

Suzanne Henderix

“Natural History Staggered Start”

- A suggested alternative is a parallel-group design that adjusts for differences due to severity – using baseline disease status – allowing separation of disease modification and symptomatic effects



Trial Design

- + Still based on a treatment versus placebo difference comparing changes at endpoint from baseline in the 2 co-primary endpoints.
- + Slope analysis complementary

Statistical analysis

- + LOCF clearly abandoned. Although might be considered in sensitivity analysis.
- + RMMM accepted.
 - + Assumptions debatable.
 - + Sensitivity analysis required.
- + Different tendencies
 - + The proposal for staggered designs calls for a mix severity at baseline.
 - + The use of linear imputation methods, studied in a particular case, shows a different behaviour in mild and moderate cases what imply different trials in these 2 populations.

BIOMARKERS

- + In phase II, an exploratory approach is very reasonable.
- + In phase III a pre-specified hypothesis and plan of analysis is expected.
- + Biomarkers should be disease-related and not drug-related



SYMPTOMATIC.....

Feasibility of placebo controlled trials.

- + In principle they are possible;
- + Multi-arm trials;
- + Superiority versus active comparator;
 - + Not strictly necessary.
- + Eventually, adaptive designs.

CHOICE OF OUTCOMES

- + 2 co-primary endpoints
 - + ADAS-cog; NBT
 - + Functional: DAD, ADCS-ADL

- + Eventual conflict with FDA requirements

Symptomatic RESPONDER standard definition

- + The most frequently applied responder definition in past studies of symptomatic treatment of mild to moderate AD has been the requirement for at least a 4-point improvement in ADAS-Cog, and no worsening at the functional and global domains.

**No major deviations
are expected!**

PLACEBO RATE OF PROGRESSION

- + Presumption that more recent studies have “better-off “ patients which do not deteriorate under placebo....
- + Data do not support
 - + J Clin Psychiat 2007; 68:430-438
 - + Publication year is not a factor;
 - + With time populations got older and trials longer
 - + MMSE at entry, mild deteriorate less
 - + More evaluations and investigational sites are also related with less deterioration



DIAGNOSTICS....

REQUIREMENTS FOR DIAGNOSTICS

- + Phase II
 - + Ability to separate well-defined categories;
- + Phase III
 - + Longitudinal studies
 - + Ability to discriminate among uncertain cases.



CONCLUSIONS

EVOLUTION OF THE DIFFICULTIES

- + In 2 years: from 2006 to 2008 – NBT (Harrison et al) become an accepted, validated scale.
- + Trials tend to become segmented according:
 - + Baseline severity
 - + ApoE 4 status.
- + Imputation of missing data
 - + Definitively moved out LOCF