

Quantify AD Clinical Outcomes Database

1. Summary Information

The current version of the database includes clinical safety and efficacy information on all symptomatic drugs as well as newer AD drugs currently approved or in development for Alzheimer's Disease (AD).

This document describes the structure and content of two databases, the *source database* and the *clinical outcomes database*. The *source database* is a database that maintains the sources of information identified by searches and reviewed for inclusion or exclusion from the database. The *clinical outcomes database* contains the information on trial, treatment and patients characteristics and safety and efficacy results of the trials identified for inclusion in the database

Table 1. Summary information

Parameter	Description
Format	Excel
Indications	Alzheimer's Disease
#Trials/References	116/136
Last Updated	2-Mar-10
Compounds	Rivastigmine, galantamine, donepezil, memantine, tacrine, rosiglitazone, 3APS, AN1792, LY450139, PBT2, atorvastatin, celecoxib, dimebolin, naproxen, phenserine, rofecoxib, sertraline, simvastatin, tarenflurbil
Key efficacy end points	ADAS-cog, ADCS-ADL, CDR-sob, CGIC, CIBIS, CIBIC-plus, DAD, GDS, MMSE, sMMSE, NPI, NPI-CD, QOL-AD, PDS, responders, SIB, Plasma/CSF levels of Abeta40 and Abeta42
Key safety end points	Tolerability percentages, dropout percentages

2. Features and benefits

Key Features:

- **Comprehensiveness:** includes information for marketed drugs as well as drugs in development; data source includes journal publications, conference posters, regulatory reviews, etc.
- **Ease of tracking:** all clinical trial publications are listed in a separated source database and linked to unique clinical trial names
- **Flexibility:** the database design allows for quick updates as well as expansions to include additional indications/drugs/endpoints/trials
- **Model-friendliness:** designed and reviewed by experienced modelers to ensure highest quality and usability for modeling and simulation to support drug development strategies
- **Customizability:** can be augmented with clinical trial data proprietary to the client (this information goes into a separate proprietary database and will be owned by the client)

Potential Applications:

Understand relative efficacy and safety profiles

This type of analysis is important and frequently done, especially for compounds in crowded diseases. Population differences, design differences, and endpoint variability make direct numbers difficult to compare. Clinical outcomes databases capture a broad range of trial-specific information, which enables comparative efficacy and safety analysis NORMALIZED by variants such as existing therapy, placebo response, patient characteristics, etc.

Link/Scale different endpoints or indications

Clinical outcomes databases aggregate endpoint data from tens of thousands of patients, making it possible to make reasonable predictions of clinical outcomes from existing data. For example, clinical teams find it valuable to predict a compound's performance in late phase development based on early development biomarkers, or short-term efficacy studies.

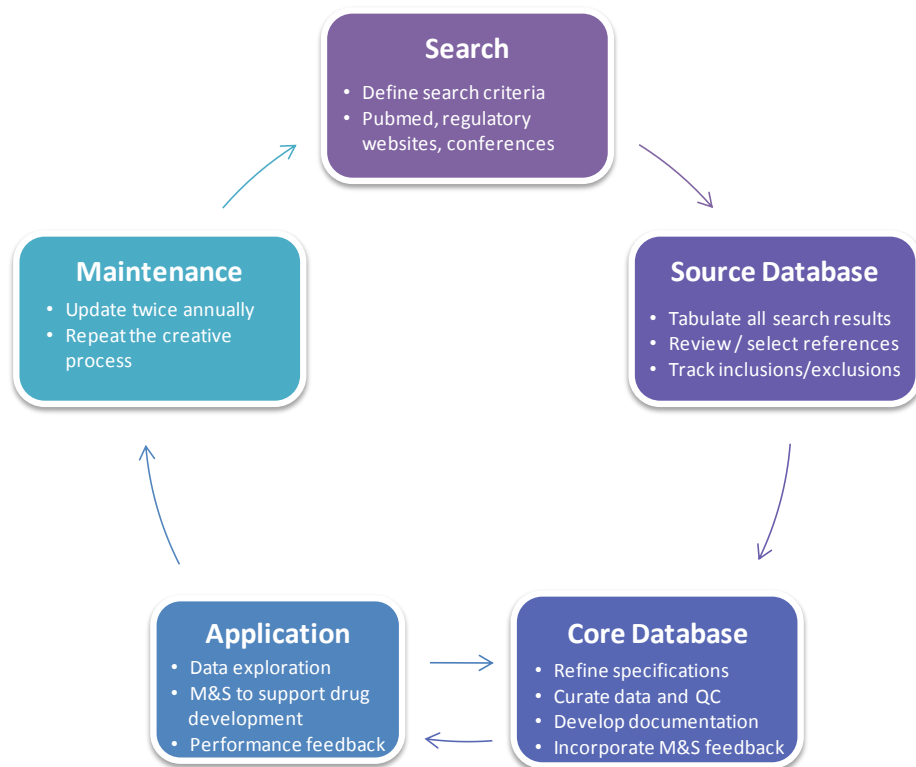
Why use our databases:

- Designed and managed by experienced modelers
- Provide most relevant data to support clients' needs for quantitative decision making
- Contain up-to-date and high quality data so that it is always readily available to provide timely analysis required to support critical clinical trial decisions
- Supported by additional services such as modeling and simulation consulting services (by QS) and custom curation services (by GVK Bio)

3. Organization and Structure

This product consists of two databases, the *source database* and the *clinical outcomes database* (core database). The *source database* is a database that maintains the sources of information identified by searches and reviewed for inclusion or exclusion from the database. The *clinical outcomes database* contains the information on trial, treatment and patients characteristics and safety and efficacy results of the trials identified for inclusion in the database.

The following is a flowchart showing the process with which databases are created, optimized and updated.



4. Overview of the Alzheimer's Source Database

The primary data sources were controlled clinical trials published in the medical literature or available through FDA and EMEA. A secondary source of information was ClinicalTrials.gov (<http://clinicaltrials.gov/>), all trials for the treatments of interest were

reviewed and data available on ClinicalStudyResults.org (<http://www.clinicalstudyresults.org/>) was evaluated.

581 references were identified and documented in the source database, of which a total of 136 were selected for inclusion in the database after careful review. The detailed reference information as well as reasons for exclusion is recorded to facilitate potential future expansion of the database.

5. Overview of the Alzheimer's Clinical Outcomes Database

The clinical outcomes database contains information from 116 trials, representing 291 unique treatment arms and about 32,408 patients. There are a total of 7249 rows in the database. Each row contains the information for an endpoint in one arm of a trial at a specific point in time.

Table 2. Overview of trials in the AD database

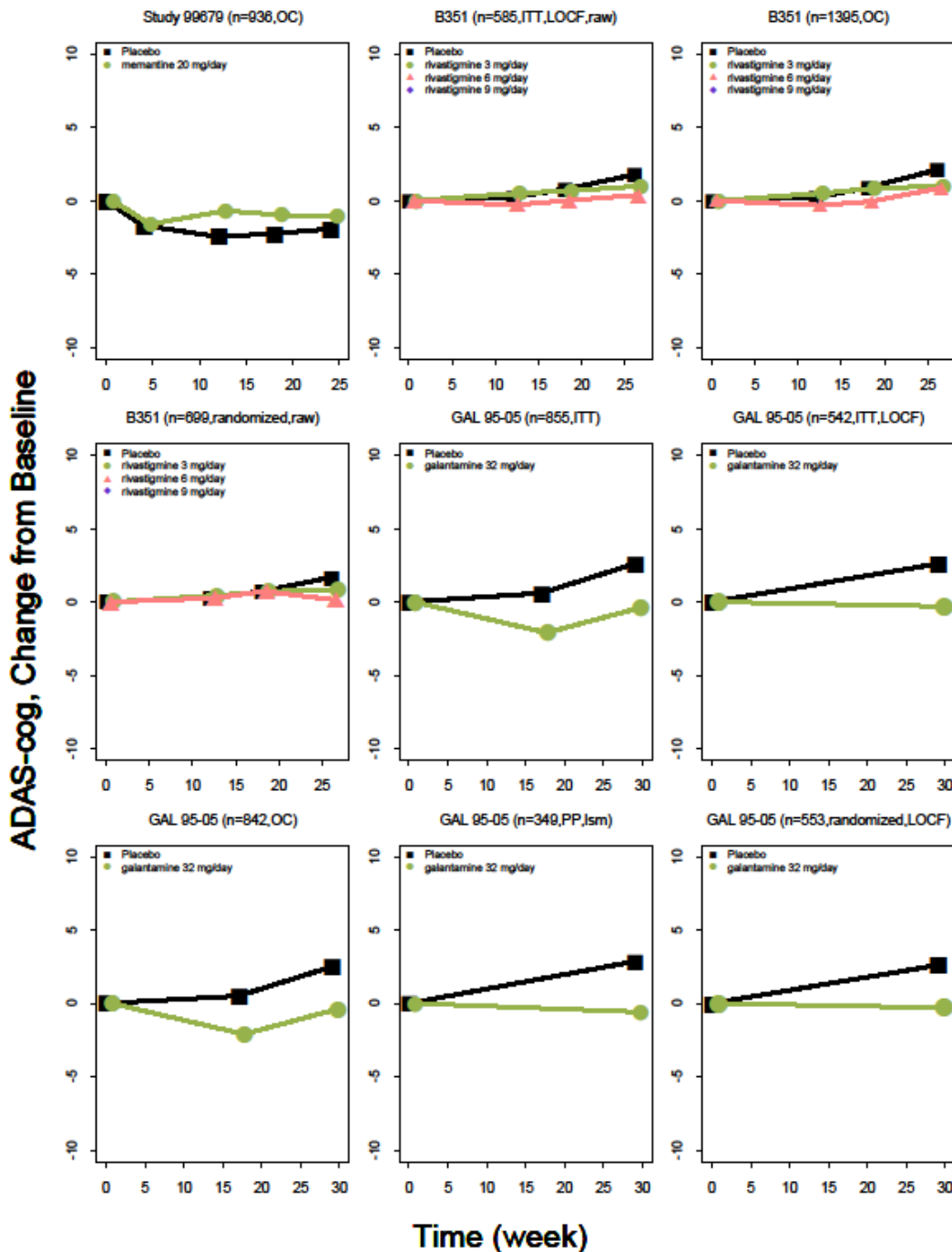
<i>Compound</i>	<i># of trials</i>	<i># of arms</i>	<i># of patients</i>
rivastigmine	25	57	6,646
galantamine	17	44	6,692
donepezil	43	83	7,788
memantine	13	27	3,406
tacrine	11	36	3,274
rosiglitazone	2	6	547
3APS	1	5	68
AN1792	1	1	64
LY450139	2	5	120
PBT2	1	3	78
atorvastatin	1	2	63
celecoxib	1	2	425
dimebolin	1	2	183
naproxen	1	1	118
phenserine	1	2	20
rofecoxib	3	5	2,271
sertraline	1	2	244
simvastatin	2	4	101
tarenflurbil	1	3	189
Total	116	291	32,408

Table 3. Overview of efficacy endpoints in the AD database

<i>endpoint</i>	<i># of trials</i>	<i># of arms</i>	<i># of patients</i>
ADAS-cog	65	178	21235
ADAS-cog <=-4	17	47	8300
ADAS-cog <=-7	10	25	4182
ADAS-cog <=0	12	31	5164
ADCS-ADL	25	63	9930
CDR-sob	9	24	4593
CGIC	16	43	3614
CGIC 1-4	6	18	1196
CGIC 5-7	7	21	1301
CGIC =4	6	18	2233
CGIC improvement	7	21	2564
CGIC worsening	6	18	2233
CIBIC-plus	24	60	11000
CIBIC-plus 1-3	13	37	5970
CIBIC-plus 1-4	9	21	3665
CIBIC-plus 5-7	7	18	2822
CIBIC-plus =4	12	30	5362
CIBIC-plus improvement	9	23	4559
CIBIC-plus worsening	9	23	4559
CSF Abeta42	6	13	281
DAD	9	20	2512
GDS	12	31	4816
MMSE	69	167	17891
NPI	37	85	11709
NPI-CD	8	20	3194
PDS	9	32	4260
QOL-AD	7	20	1522
SIB	13	31	4595
responders	8	23	3881

6. Example Plots of data in the Alzheimer's Database

The following graph shows examples of the time course of ADAS-cog as change from baseline. The graphs show the time course for each treatment arm and each trial that has information on this endpoint.



7. Outcome Fields

7.1. *Efficacy outcomes fields*

The following efficacy measurements are recorded in the database

- ADAS-cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale total score
 - includes different responder definitions: much improvement, improved, no change, worse, much worse
- CIBIS: Clinician's Interview-Based Impression of Severity
- CIBIC-plus: Clinician's Interview-Based Impression of Change Plus Caregiver Input total score
 - includes different responder definitions: much improvement, improved, no change, worse, much worse
- ADCS-ADL: the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory scale
- CGIC: Clinical Global Impression of Change
- MMSE: Mini-Mental State Examination
- sMMSE: standardized Mini-Mental State Examination
- NPI: Neuropsychiatric Inventory
- NPI-CD: NPI-caregiver distress scale
- SIB: Severe Impairment Battery
- CDR-sob: Clinical Dementia Rating sum-of-boxes
- QOL-AD: the quality of life-AD scale
- DAD: Disability Assessment for Dementia
- CBQ: Caregiver Burden Questionnaire
- GDS: Global Deterioration scale
- PDS: Progressive Deterioration Scale
- FRS: Functional Rating Scale
- IADL+: modified Instrumental Activities of Daily Living
- MSMS+: modified Physical Self-Maintenance Scale
- Plasma/CSF levels of A β 40 and A β 42 (Category is "A beta" for A β 40 and A β 42 levels and Category is "PK" for the Plasma drug concentrations)

7.2. Safety/tolerability Outcomes Fields

The following safety and tolerability information is recorded in the database. The number of patients, percent of patients or rate (events per patient year) is recorded. For each safety outcome the numeric values (mean, etc) is also extracted if available at baseline or during trial:

- Dropout: Total dropout/treatment discontinuation. This refers to all patients that did not complete the study or that did receive rescue therapy. In trials in which rescue treatment was provided also the dropout minus the patients that receive rescue is provided (dropout – rescue)
- Dropout AE: Dropout related to adverse events
- Dropout Efficacy: Dropout related to lack of Efficacy. Some trials provide rescue therapy for patients with lack of efficacy. The number of patients that rescue is captured from those trials. This can be compared to dropout due to lack of efficacy.
- Rescue: Patients receiving rescue treatment due to lack of efficacy (Category is “Rescue”)
- Death
- AE total: any adverse events
- AE clinical: clinical adverse events
- AE lab: laboratory adverse events
- AE serious: serious or severe adverse event
- dose increase, interruption, reduction or modification: AE resulting in changes in dose
- nausea
- vomiting
- dizziness
- diarrhea
- headache
- somnolence
- accidental/inflicted injury
- abdominal pain
- anorexia
- depression
- agitation
- infection upper respiratory: upper respiratory infection

- infection urinary tract: urinary tract infection
- insomnia
- confusional state
- hypertension
- fatigue
- rhinitis
- muscle cramps
- development of anti-drug antibodies