CERTARA

Quantify AD
Clinical Outcomes Database

Summary Information

The current version of the database includes clinical safety and efficacy information on all symptomatic drugs as well as newer Abeta drugs currently approved or in development for Alzheimer 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 or web-based platform
indications	AD + MCI, AD, probable AD, dementia + probable AD, AD + dementia, AD + CVD or mixed dementia, AD or dementia, probable AD or AD + CVD
references	178
trials	152
trial.arms	400
patients	50,273
data.rows	9,673
compounds	an1792, atorvastatin, avagacestat, azd3480, bapineuzumab, cad106, celecoxib, cerebrolysin, cerebrolysin , choline alphoscerate, citalopram hbr, coenzyme q, conjugated equine estrogen, dimebolin, donepezil, galantamine, ginkgo biloba, hrt, immunoglobulin, kami-untan-to, ly450139, melissa oil, memantine, naproxen, pbt2, perphenazine, phenserine, pioglitazone, placebo, ponezumab, quetiapine, risperidone, rivastigmine, rofecoxib, rosiglitazone, sb-742457, semagacestat, sertraline, silymarin, simvastatin, solanezumab, tacrine, tarenflurbil, tramiprosate, vitamin e
key.efficacy.endpoints	adas-cog, adas-cog-11, adas-cog <=-4, adas-cog <=-7, adas-cog <=0, adcs-adl, adcs-adl >=0, cdr-sob, cgic, cgic 5-7, cibic-plus, cibic-plus = 1, cibic-plus = 2, cibic-plus = 3, cibic-plus = 4, cibic-plus = 5, cibic-plus = 6, cibic-plus = 7, cibic-plus 1-3, cibic-plus 1-4, cibic-plus 5-7, dad, gds, mmse, npi, npi-cd, sib
key.safety.endpoints	abdominal pain, accidental/inflicted injury, ae serious, ae total, agitation, anorexia, confusional state, death, depression, diarrhea, dizziness, dropout, dropout ae, dropout efficacy, fatigue, headache, hypertension, insomnia, muscle cramps, nausea, rhinitis, somnolence, upper respiratory infection, urinary tract infection, vomiting

Features and Benefits

Key Features

- **Comprehensive:** includes information for marketed drugs; data sources include journal publications, conference posters, regulatory reviews, etc.
- **Ease of tracking:** all clinical trial publications are listed in a separate 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.

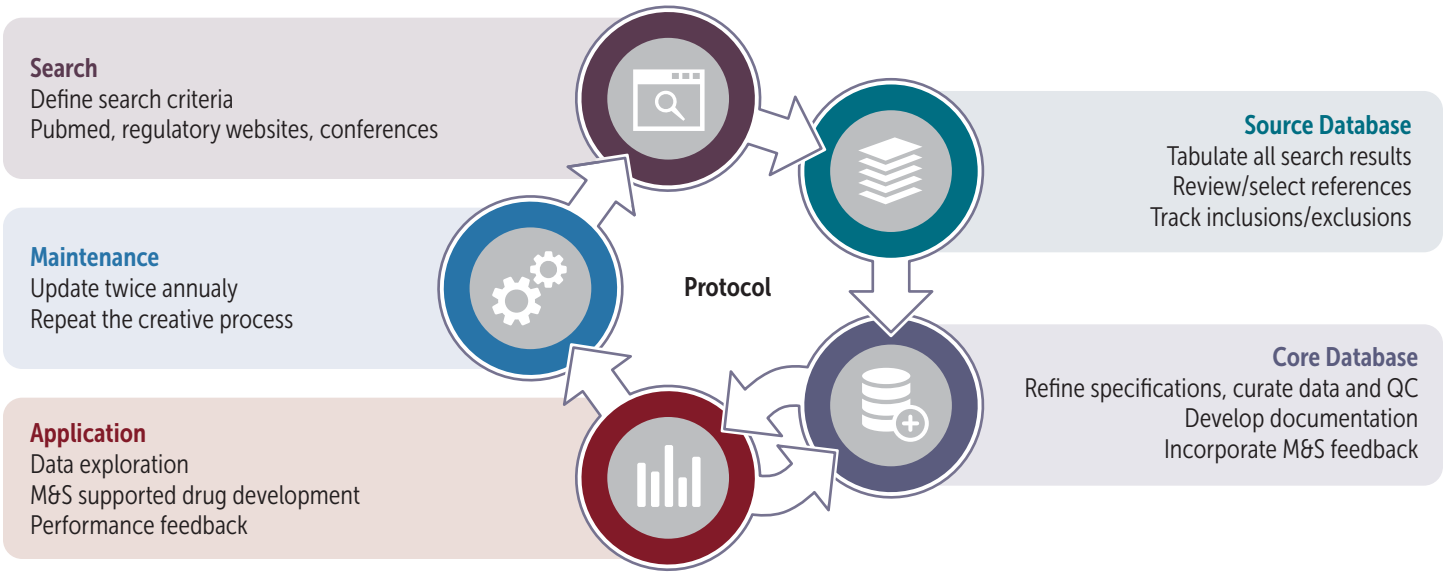
Why Use Our Databases

- Designed and managed by experienced modelers
- Provides most relevant data to support clients' needs for quantitative decision making
- Contains 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 and custom curation services (by our partner, GVK Bio)

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.



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, all trials for the treatments of interest were reviewed and data available on ClinicalStudyResults.org was evaluated.

581 references were identified and documented in the source database, of which a total of 178 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.

Overview of the Alzheimer's Clinical Outcomes Database

The clinical outcomes database contains information from 152 trials, representing 400 unique treatment arms and about 50,273 patients. There are a total of 9,673 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 by drug

randomized.drug	trials	arms	patients
an1792	1	1	64
an1792+qs-21	1	1	299
atorvastatin	2	2	346
avagacestat	1	4	167
azd3480	1	3	244
bapineuzumab	4	11	1624
cad106	1	2	46
celecoxib	1	1	285
cerebrolysin	1	1	70
cerebrolysin+donepezil	1	1	72
choline alphoscerate+donepezil	1	1	92
citalopram hbr	1	1	25
coenzyme q	1	1	26
conjugated equine estrogen+micronized progesteron	1	1	29
dimebolin	1	1	89
donepezil	45	54	6099

donepezil+ginkgo biloba	1	1	32
donepezil+hirudin	1	1	42
donepezil+perphenazine	1	1	6
galantamine	17	28	4202
ginkgo biloba	2	2	56
hrt	1	1	59
immunoglobulin	1	6	41
kami-untan-to	1	1	18
ly450139	2	3	71
melissa oil	1	1	38
memantine	21	23	2570
memantine+donepezil	1	1	73
memantine+rivastigmine	1	1	88
naproxen	1	1	118
pbt2	1	2	49
perphenazine	1	1	6
phenserine	1	1	10
pioglitazone+vitamin e	1	1	14
placebo	122	123	17042
placebo+donepezil	2	2	164
placebo+ert	1	1	9
placebo+lecithin	1	1	41
placebo+placebo	1	1	89
placebo+rivastigmine	1	1	84
placebo+vitamin e	1	1	15
ponezumab	2	9	41
quetiapine	1	1	31
risperidone	1	1	12
rivastigmine	24	44	6356
rivastigmine+fluoxetine	1	1	41
rofecoxib	3	3	1193
rosiglitazone	4	8	2300
sb-742457	1	1	68
semagacestat	1	2	1036
sertraline	1	1	124
silymarin	1	1	110
simvastatin	3	3	257
solanezumab	3	6	1069
tacrine	9	11	1093
tacrine+ert	1	1	37
tacrine+lecithin	2	2	129
tacrine+placebo	1	1	41
tarenflurbil	2	3	1001
tramiprosate	2	5	744
vitamin e	2	3	50
vitamin e+vitamin c with alpha lipoic acid	1	1	26
TOTAL	**152**	**400**	**50273**

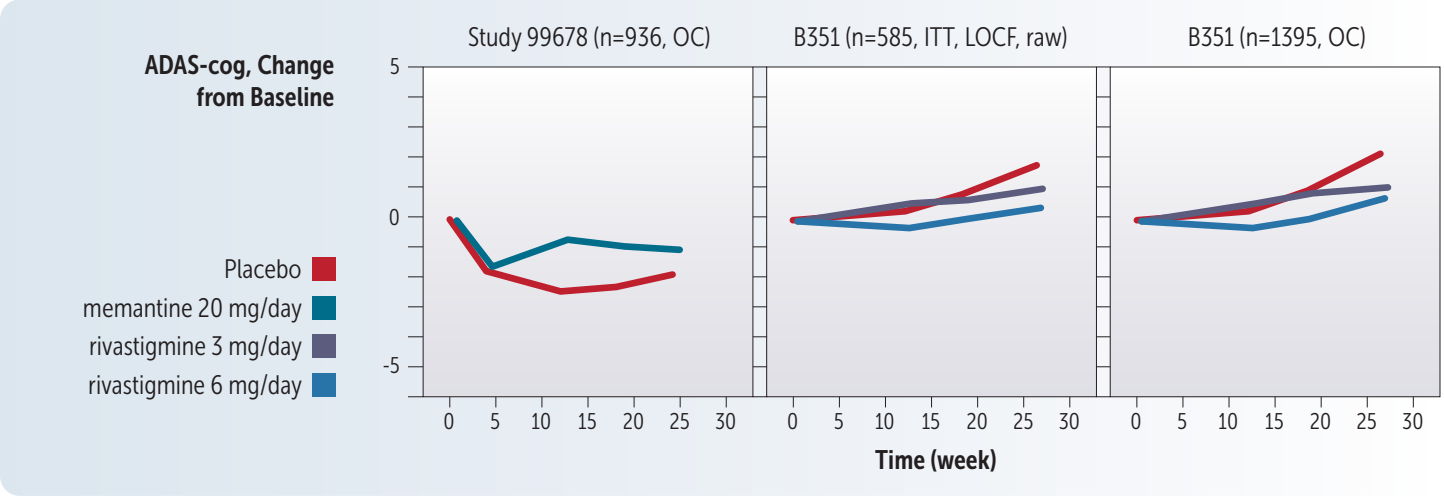
Table 3. Overview of efficacy endpoints in the AD database

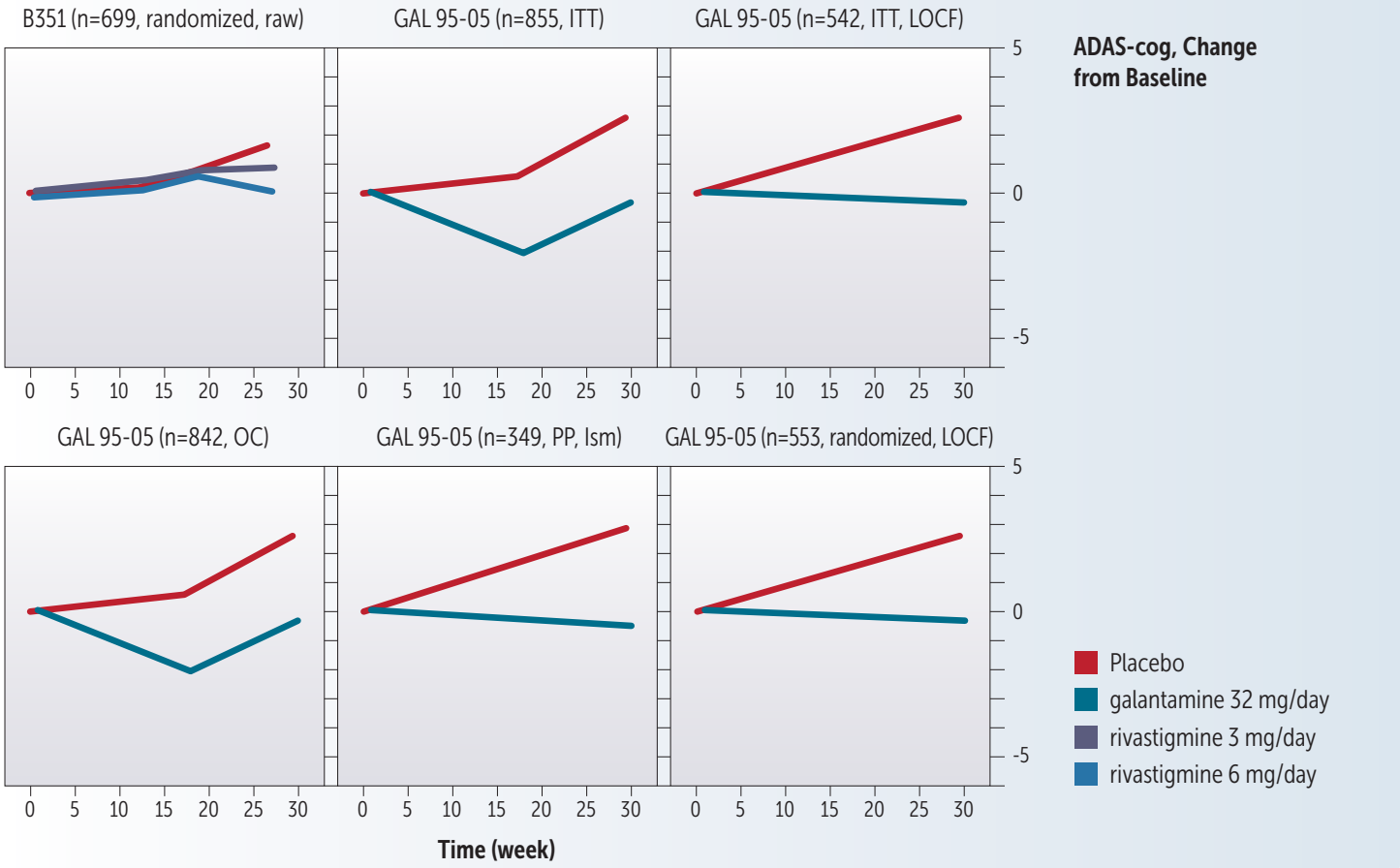
endpoint	trials	arms	patients
abdominal pain	24	61	7922
abdominal pain/diarrhea	1	2	100
accidental/inflicted injury	17	38	4711
adas-cog	38	101	9264
adas-cog-11	44	118	25159
adas-cog-11 slope	1	2	1684
adas-cog-12	3	10	2594
adas-cog-13	2	4	404
adas-cog-14	4	12	2321
adas-cog <=-10	4	12	2988
adas-cog <=-4	16	43	8383
adas-cog <=-7	8	20	4081
adas-cog <=0	12	30	6752
adas-cog brazilian version	1	2	23
adas-cog japanese version	1	2	268
adas-cog korean version	1	4	300
adas-cog slope	1	2	1684
adcs-adl	40	103	19442
adcs-adl-severe	2	5	668
adcs-adl >=0	6	13	3254
adcs-adl >=2	1	3	892
adcs-adl >=4	2	5	1296
adcs-adl >=6	1	3	892
adcs-adl >=8	2	5	1296
adcs-adl slope	1	2	1684
ae clinical	1	2	640
ae lab	2	3	93
ae serious	69	172	30295
ae severe	5	13	1438
ae total	74	189	33837
agitation	48	120	20842
anorexia	32	79	13751
cbq	2	4	1928
cdr-sob	22	62	13602
cdr-sob slope	1	2	1684
cgic	17	43	4651
cgic = 1	4	12	1894
cgic = 1 japanese version	1	2	268
cgic = 2	4	12	1894
cgic = 3	4	12	1894
cgic = 3 japanese version	1	2	268
cgic = 4	5	17	2463
cgic = 4 japanese version	1	2	268
cgic = 5	3	10	1728
cgic = 5 japanese version	1	2	268
cgic = 6	4	12	1894
cgic = 7	4	12	1894
cgic = 7 japanese version	1	2	268
cgic 1-2	1	3	402
cgic 1-3	3	10	857
cgic 1-4	4	12	778
cgic 1-4 japanese version	1	2	268
cgic 4	1	3	122
cgic 4-7	1	2	166
cgic 5-7	6	20	1469
cgic 5-7 japanese version	1	2	268
cgic caregiver rated	1	2	154
cgic clinician rated	2	4	307
cgis	3	7	354
cibic-plus	27	68	13025
cibic-plus = 1	10	28	5322
cibic-plus = 2	10	28	5322
cibic-plus = 3	10	28	5322
cibic-plus = 4	12	32	5848
cibic-plus = 5	10	28	5322
cibic-plus = 6	10	28	5322
cibic-plus = 7	10	28	5322
cibic-plus 1-3	11	31	5506
cibic-plus 1-3 korean version	1	4	300
cibic-plus 1-4	7	15	3048
cibic-plus 5-7	6	14	2754
cibic-plus nyu version	1	2	252
confusion	1	2	153
confusional state	26	66	9229
csf abeta1-40	4	18	139
csf abeta1-42	5	21	197
csf abeta40	6	14	2295
csf abeta42	8	19	2430
csf abetan-42	1	3	58
csf abetax-40	1	3	58
csf abetax-42	1	3	58
csf drug concentration	2	3	48
dad	14	35	5619
dad korean version	1	4	300
death	71	187	35398
depression	26	59	13044
diarrhea	75	204	33248
dizziness	60	167	24829
dose reduction	3	6	1550
dropout	124	312	44247
dropout ae	98	248	40624

dropout efficacy	35	88	15600
fatigue	15	48	4796
frs	1	2	290
gds	12	29	5609
headache	63	172	22354
hypertension	18	39	8309
iadl+	3	6	528
injury	1	2	592
insomnia	28	73	12284
mmse	84	211	29049
msms+	1	2	290
muscle cramps	7	16	1620
nausea	70	187	30483
nausea/vomiting	4	10	505
npi	49	111	21250
npi-cd	8	19	3794
npi behavioral and psychological subscale	1	2	244
npi nursing home version	2	4	473
pds	8	23	3502
plasma abeta1-40	4	21	151
plasma abeta1-42	2	13	107
plasma abeta40	4	8	1158
plasma abeta42	2	4	1072
plasma abetax-40	1	3	58
plasma abetax-42	1	3	58
plasma drug concentration	8	29	1248
qol-ad	4	12	1406
qol-ad caregiver	4	10	3897
qol-ad patient	4	10	3897
responders	8	23	4291
rhinitis	9	23	3218
serum drug concentration	1	3	22
sib	17	38	7592
sib change from baseline>=0	1	2	290
sib change from baseline>=10	1	2	290
sib change from baseline>=12	1	2	404
sib change from baseline>=4	1	2	404
sib change from baseline>=8	1	2	404
sib change from baseline>0	1	2	404
smmse	4	10	997
somnolence	10	23	3465
upper respiratory infection	17	45	6927
upper respiratory tract infection	1	2	1121
urinary tract infection	41	106	16811
vomiting	58	162	23315
TOTAL	**152**	**400**	**50273**

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.





Outcome Fields

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 40 and A 42 (Category is "A beta" for Aß40 and Aß42 levels and Category is "PK" for the Plasma drug concentrations)

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