

Quantify Schizophrenia Clinical Outcomes Database Release 1.0 March 31 2010

1. Summary Information

The current version of the database includes clinical safety and efficacy information on both second-generation antipsychotics (SGAs) currently approved or in development for the first-line monotherapy treatment of schizophrenia and on anti-psychotics used for the second-line treatment (monotherapy or add-on) in treatment-resistant or refractory schizophrenia patients. Information on first-generation antipsychotics (FGAs) such as haloperidol are included if they were used as active controls.

Table 1. Summary information

Parameter	Description
Format	Excel
Indications	schizophrenia
#Trials/References	114/114
# Patients	26,203
# Rows of Data	12,171
Last Updated	Sept 23, 2009
Compounds	risperidone, paliperidone, quetiapine, ziprasidone, asenapine, aripiprazole, olanzapine, chlorpromazine, haloperidol, sertindole, clozapine, iloperidone, remoxipride, zotepine, cariprazine, methotrimeprazine, zotepine, fluoxetine, sulpiride, estradiol, mirtazapine, fluvoxamine, fluphenazine, ginkgo biloba, dehydroepiandrosterone, celecoxib, perphenazine, lamotrigine, CX516, donepezil, LY2140023, selegiline, amisulpride, ritanserin, pregnenolone and lurasidone.
Key efficacy end points	PANSS, BPRS, BPRSd, CGI, GAF, SANS, NSA-16, Response, Relapse
Key safety end points	ESRS, SAS, AIMS, BARS, SWN, adverse event percentages, and treatment discontinuations/required medication

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:***Characterize relative (comparative) clinical safety and efficacy profile:***

Example:

- Analyze relative efficacy among drugs, taking into account impact of titration and drop out, as well as various imputations methods (last observation carried forward, baseline carried forward, observed cases, etc)
- Understand the correlation of placebo response versus active response as a function of time; determine optimal time points for measuring the drug effect
- Estimate the difference in magnitude of changes in efficacy outcomes across drugs and mechanisms of action

Characterize endpoint-to-endpoint relationships:

Example:

- Scale from different outcome measurements
- Explore potential differences or similarities in dose response relationship for a particular drug class

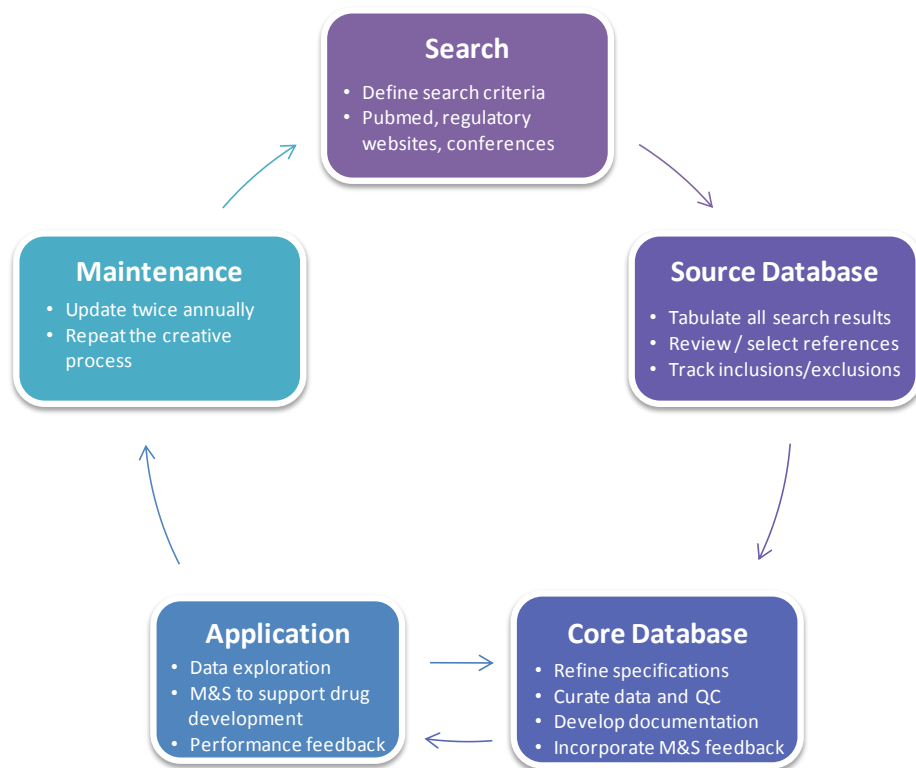
Ultimately, these analysis help drug companies to optimize trial design, improve trial outcomes, and strengthen product differentiation.**Why use our databases:**

- Designed and managed by experienced modelers. There is a strong emphasis to making it easy to extract analysis datasets from the database
- 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. In addition, a detailed documentation is provided with these databases.

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



4. Overview of the Schizophrenia Source Database

The primary data sources were controlled clinical trials published in the medical literature or available through the FIA from the FDA. A secondary source of information was published abstracts or presentations of clinical trial data from conferences and corporate websites.

796 references were identified and documented in the source database, of which a total of 102 references were selected for inclusion in the database after careful review of the

abstracts. The detailed reference information as well as reasons for exclusion is recorded to facilitate potential future expansion of the database. In addition, 12 additional trials were identified from review of pivotal trials in FDA and EMEA regulatory reports. The database contains information on 114 unique trials.

5. Overview of the Schizophrenia Clinical Outcomes Database

The following randomized controlled trials provided information on safety and efficacy that was used for the registration with the FDA and EMEA as primary or supportive evidence. No published reference was found for 12 of the trials mentioned in the FDA or EMEA reviews.

Table 2. List of registration trials in the database

Drug	Reg. Agency	Study
Risperidone	FDA	RIS-INT-3
	FDA	RIS-INT-2
Olanzapine	FDA	HGAP
	FDA	HGAD
	FDA	E003
	FDA	HGAJ
Quetiapine	FDA	6
	FDA	8
	FDA	12
	FDA	13
	FDA	4
Ziprasidone	FDA	104
	FDA	106
	FDA	114
	FDA	115
	FDA	303
Paliperidone	FDA	302
	FDA	303
	FDA	304
	FDA	305
Iloperidone	FDA	3000
	FDA	3004
	FDA	3005
	FDA	3101
	FDA	B202

Aripiprazole	FDA	93202
	FDA	94202
	FDA	97201
	FDA	97202
	FDA	138001
Asenapine	FDA	41004
	FDA	41021
	FDA	41022
	FDA	41023

The clinical outcomes database contains information from 114 trials, representing 325 unique treatment arms and about 26,000 patients. There are a total of 12,171 rows in the database. Each row contains the information for an endpoint in one arm of a trial at a specific point in time. The table below provides an overview of the available data for randomized treatments, i.e. treatments that were started at time of randomization and not present as background therapy.

Table 3. Number of trials, treatment arms and patients for each drug

Drug	# of trials	# of arms	# of patients
aripiprazole	8	14	1144
asenapine	4	6	579
chlor-promazine	5	5	457
clozapine	20	24	1341
haloperidol	36	38	4033
iloperidone	6	11	1712
olanzapine	22	30	3686
other ¹	25	27	910
paliperidone	8	16	1906
placebo	68	68	4212
quetiapine	10	17	1762
risperidone	27	43	3079
sertindole	3	7	514
ziprasidone	10	20	1528
Total	114	325	26203

¹ methotrimeprazine, zotepine, fluoxetine, sulpiride, estradiol, mirtazapine, fluvoxamine, fluphenazine, ginkgo biloba, dehydroepiandrosterone, celecoxib, perphenazine, lamotrigine, CX516, donepezil, LY2140023, selegiline, amisulpride, ritanserin, pregnenolone and lurasidone.

Table 4. Overview of efficacy clinical scale related endpoints

Endpoint	# of trials	# of arms	# of patients	# of drugs
Clinical Scale changes				
PANSS Total	74	219	21666	27
PANSS Positive	55	155	13566	26
PANSS Negative	63	185	17816	25
BPRS Total	44	127	8031	20
SANS Total	32	80	3989	19
Response rates				
>=20% improvement in BPRS Total	10	30	1332	10
>=20% improvement in PANSS Total	20	57	4822	10

Table 5. Overview of treatment endpoints

Endpoint	# of trials	# of arms	# of patients	# of drugs
Treatment Discontinuation				
Due to Any Reason	93	259	24892	31
Due to Lack of Efficacy	69	210	20669	21
Due to Adverse Events	73	212	21250	23
Required Medication				
Antiparkinsonian/ Anticholinergic Medication	39	124	12789	18
Benzodiazepines	25	75	6838	14

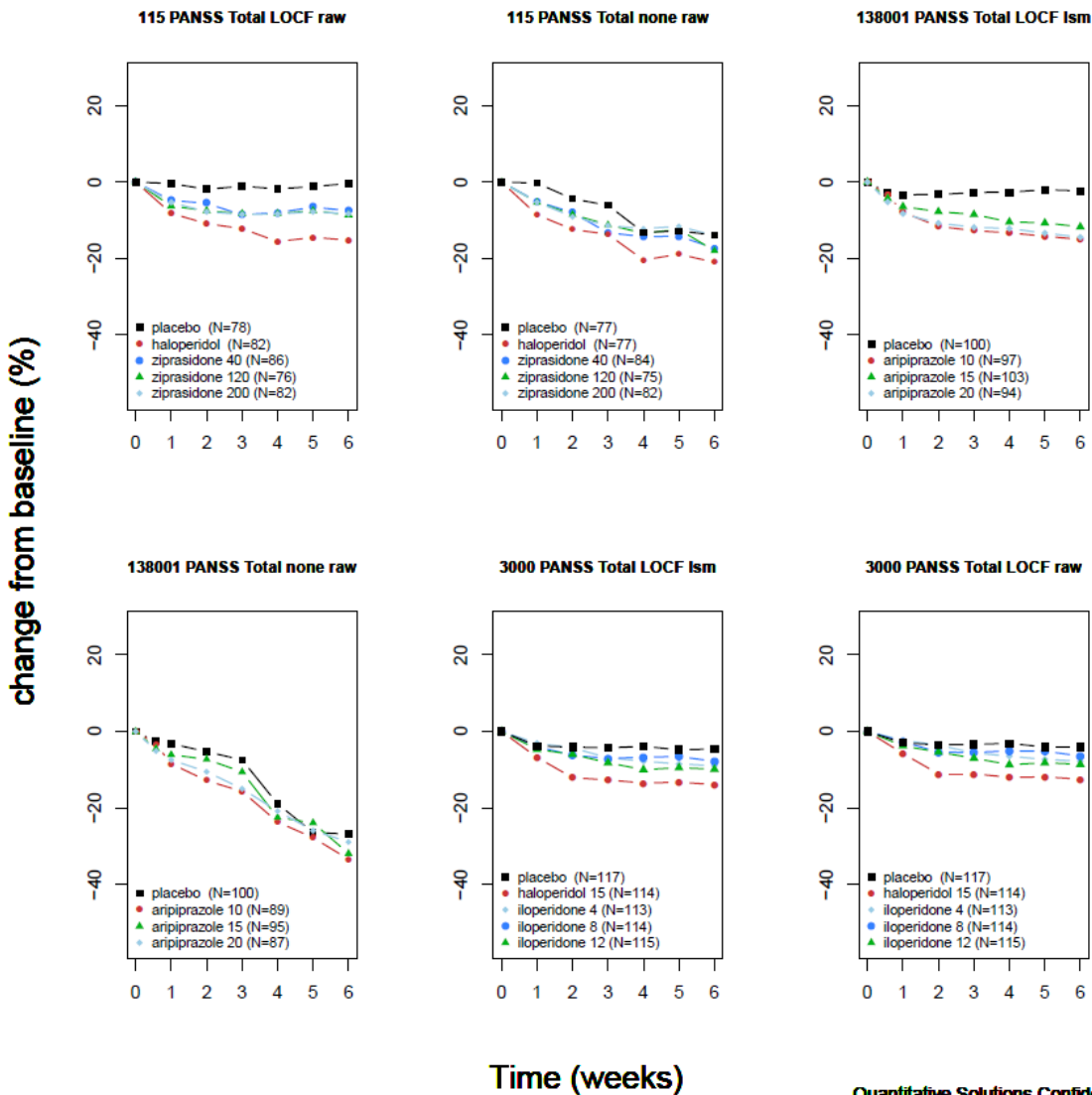
Table 6. Overview of tolerability endpoints

Endpoint	# of trials	# of arms	# of patients	# of drugs
Extrapyramidal Symptom Rating Scale (ESRS)	6	21	1911	6
AIMS	29	83	6019	19

SAS - Simpson-Angus Scale	39	105	6908	21
BARS – Barnes Akathesia Rating Scale	27	82	5968	17
SWN	2	4	200	4

6. Example plots of actual trial data

The following graph shows examples of the time course of PANSS 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

The following endpoints are recorded in the database. For binary outcomes, the number of patients, percent of patients or rate is recorded.

- Efficacy
 - PANSS (Positive and Negative Symptoms Scale)
 - BPRS (Brief Psychiatric Rating Scale)
 - BPRSd (BPRS derived from PANSS)
 - CGI (Clinical Global Impression- Severity or Improvement Scale)
 - GAF (Global Assessment of Functioning)
 - SANS (Scale for the Assessment of Negative Symptoms)
 - NSA-16 (Negative Symptom Assessment)
 - Response
 - Relapse
- Tolerability
 - ESRS (Extrapirimal Symptom Rating Scale)
 - SAS (Simpson Angus Scale)
 - AIMS (Abnormal Involuntary Movement Scale)
 - BARS (Barnes Akathisia Rating Scale)
 - SWN (Subjective Well-being on Neuroleptics Scale)
 - AE Response
- Adverse Response endpoints (AE)
 - fatigue
 - headache
 - insomnia
 - somnolence
 - dizziness
 - dyspepsia
 - rhinitis
 - weight gain
 - fasting plasma glucose
 - Prolactin
 - Tachycardia
 - QTc prolongation

- Treatment Endpoints (TX)
 - Antiparkinsonian /Anticholinergic Medication (eg benztropine, biperiden)
 - Benzodiazepines
 - StudyDisconAdverseEvents – total number of subjects who discontinued the study due to adverse events
 - StudyDiscon– total number of subjects who discontinued the study due to any reason
 - StudyDisconEfficacy – total number of subjects who discontinued the study due to lack of efficacy