

Quantify Schizophrenia Clinical Outcomes Database Release 2.0 September 30, 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	137
# Patients	32,704
# Rows of Data	13,624
Last Updated	July 9, 2010
Compounds	risperidone, paliperidone, Paliperidone palmitate, quetiapine, ziprasidone, asenapine, aripiprazole, olanzapine, olanzapine pamoate, risperidone LAI, 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

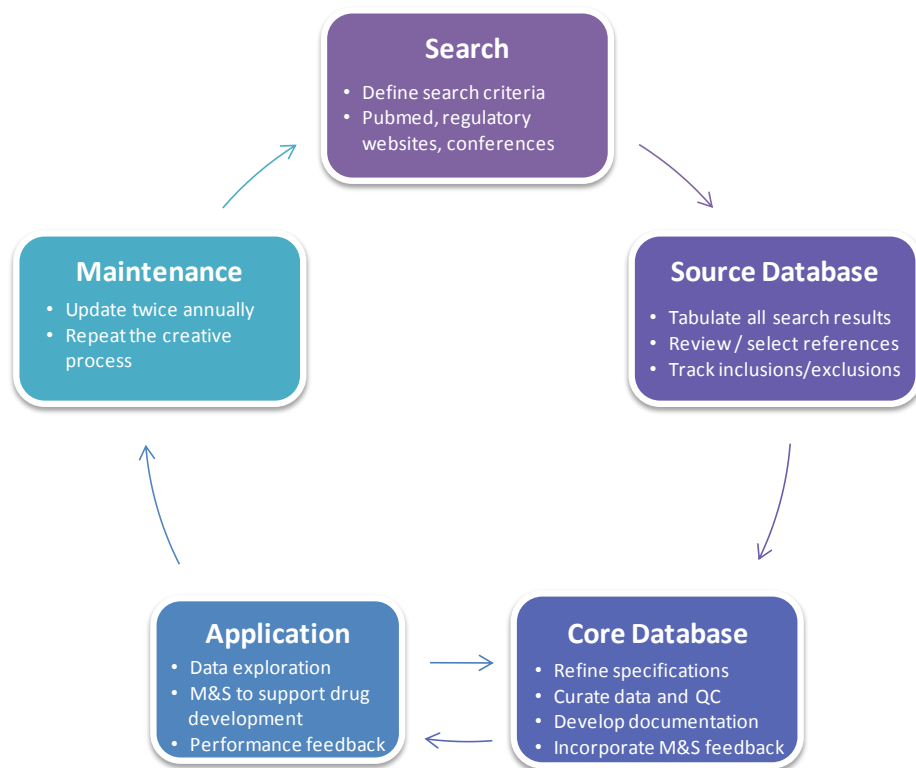
Ultimately, these analysis help drug companies to optimize trial design, improve trial outcomes, and strengthen product differentiation.**Why use our databases:**

- 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.

871 references were identified and documented in the source database, of which a total of 118 published articles 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. In addition, 15 unpublished trials were identified from review of pivotal trials in FDA and EMEA regulatory reports, and seven abstracts were selected from the abstract books of the Annual meetings of the American Association of Psychiatry (APA) in 2009 and 2010. The database contains information on 137 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 as primary or supportive evidence. No published reference was found for 15 of the trials mentioned in the FDA 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
Lurasidone	FDA	

(Long-acting injectables)

Drug	Reg. Agency	Study
Risperidone microspheres (Risperdal CONSTA)	FDA	RIS-USA-1213
Olanzapine Pamoate (ZYPREXX RELPREVV)	FDA	HGJZ
	FDA	HGKA
Paliperidone palmitate (INVEGA-SUSTENNA)	FDA	3001
	FDA	3003
	FDA	201
	FDA	3004
	FDA	3007

The clinical outcomes database contains information from 137 trials, representing 390 unique treatment arms and about 32,700 patients. There are a total of 13,624 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 presents for each drug the total number of trials, the number of trial arms and the total number of patients. In addition, the number of mono- or add-on therapy (augmentation-AUG) trials are represented for each drug. For each drug the median (range) dose, age, duration of the disease and baseline PANSS score is also shown.

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

Drug	# of trials	# of arms	# of patients
aripiprazole	9	15	1312
asenapine	4	6	579
chlorpromazine	5	5	457

clozapine	20	24	1341
haloperidol	35	37	3373
iloperidone	6	11	1712
lurasidone	3	5	426
olanzapine	25	33	4166
olanzapine pamoate	2	7	1049
Other	32	34	976
paliperidone	9	18	2115
paliperidone palmitate	5	12	1540
placebo	88	88	5692
quetiapine	10	17	1762
risperidone	30	47	3541
risperidone LAI ²	2	4	621
sertindole	3	7	514
ziprasidone	10	20	1528
total	137	390	32704

¹ methotrimeprazine, zotepine, fluoxetine, sulpiride, estradiol, lamotrigine, mirtazapine, fluvoxamine, fluphenazine, topiramate, ginkgobiloba, dehydroepiandrosterone, celecoxib,perphenazine, CX516, donepezil, LY2140023, selegiline, amisulpride, ritanserin, pregnenolone, modafinil, minocycline and memantine.

² Risperidone Long Acting Injectable

Table 4. Overview of efficacy clinical scale related endpoints

Endpoint	# of trials	# of arms	# of patients	# of drugs
Clinical Scale changes				
PANSS Total	92	273	25838	34
PANSS Positive	71	201	18208	33
PANSS Negative	76	225	20391	31
BPRS Total	47	133	8161	22
SANS Total	35	86	4118	21
Response rates				
>=20% improvement in BPRS Total	10	30	1332	10
>=20% improvement in PANSS Total	23	64	5052	12

Table 5. Overview of treatment endpoints

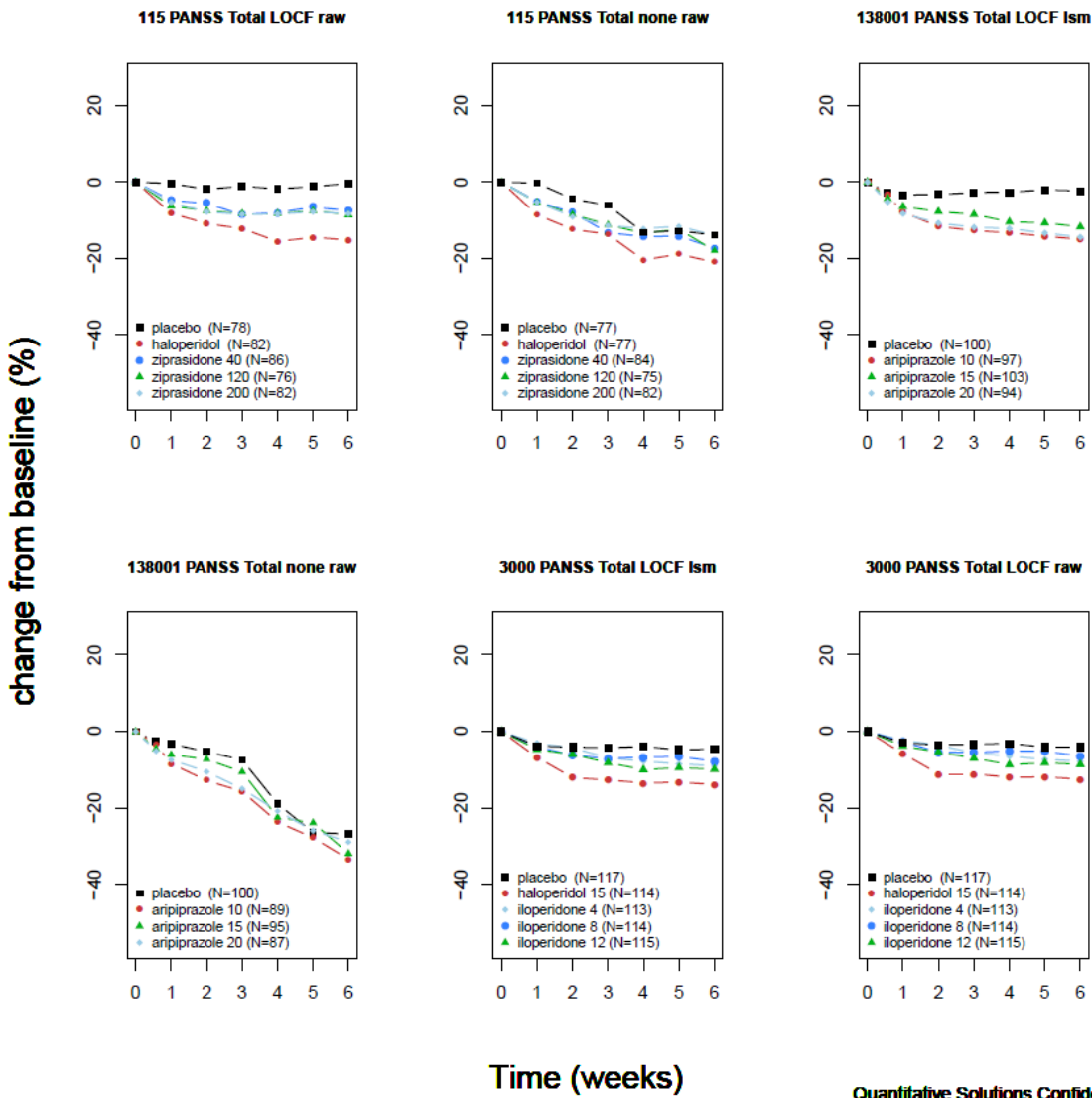
Endpoint	# of trials	# of arms	# of patients	# of drugs
Treatment Discontinuation				
Due to any Reason	109	302	26952	38
Due to Lack of Efficacy	82	247	24215	28
Due to Adverse Events/ Tolerability	87	250	25171	28
Required Medication				
Antiparkinsonian/ Anticholinergic Medication	44	141	15620	21
Benzodiazepines	32	97	10017	18

Table 6. Overview of tolerability endpoints

Endpoint	# of trials	# of arms	# of patients	# of drugs
AIMS- Abnormal Involuntary Movement Scale	32	92	6906	20
BARS – Barnes Akathesia Rating Scale	30	91	6855	18
SAS - Simpson-Angus Scale	43	116	7817	23
Extrapyramidal Symptom Rating Scale (ESRS)	7	23	1965	7
SWN	3	6	523	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.



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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