

## Quantify Pain Clinical Outcomes Database

### 1. Summary Information

The current version of the database includes clinical safety and efficacy information on treatment options currently approved or in development for painful diabetic neuropathy (DPN), post herpetic neuralgia (PHN), or fibromyalgia. Information on older treatment options (such as tricyclic antidepressants) was included if they are used as active controls.

**Table 1. Summary information**

Parameter	Description
<b>Format</b>	Excel
<b>Indications</b>	neuropathic pain
<b>#Trials/References</b>	57/64
<b># Patients</b>	17,390
<b># Rows of Data</b>	5,973
<b>Last Updated</b>	Nov 12, 2008
<b>Compounds</b>	Amitriptyline, amitriptyline fluoxetine, desipramine, duloxetine, fluoxetine, gabapentin, gabapentin morphine, lacosamide, lamotrigine, morphine, nortriptyline, oxycodone, oxycodone gabapentin, placebo, pregabalin, topiramate, tramadol, tramadol acetaminophen, venlafaxine
<b>Key efficacy end points</b>	Pain Intensity, Brief Pain inventory, Short Form McGill, FIQ, Global Impression of Change, Sleep (65 endpoints in total)
<b>Key safety end points</b>	Tolerability percentages (22 endpoints in total)

### 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, safety and speed of onset 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 pain scores across drugs and mechanisms of action
- Analyze differences in speed of onset across drugs

***Characterize endpoint-to-endpoint relationships:***

Example:

- Scale from different pain measurements
- Explore potential differences or similarities in dose response relationship for a particular drug or drug class across pain indication such as DPN, PHN and fibromyalgia
- Predict drug performance in another pain indication based on consistency of dose response across indications in drugs of the same class

***Ultimately, these analysis help drug companies to optimize trial design, improve trial outcomes, and strengthen product differentiation.***

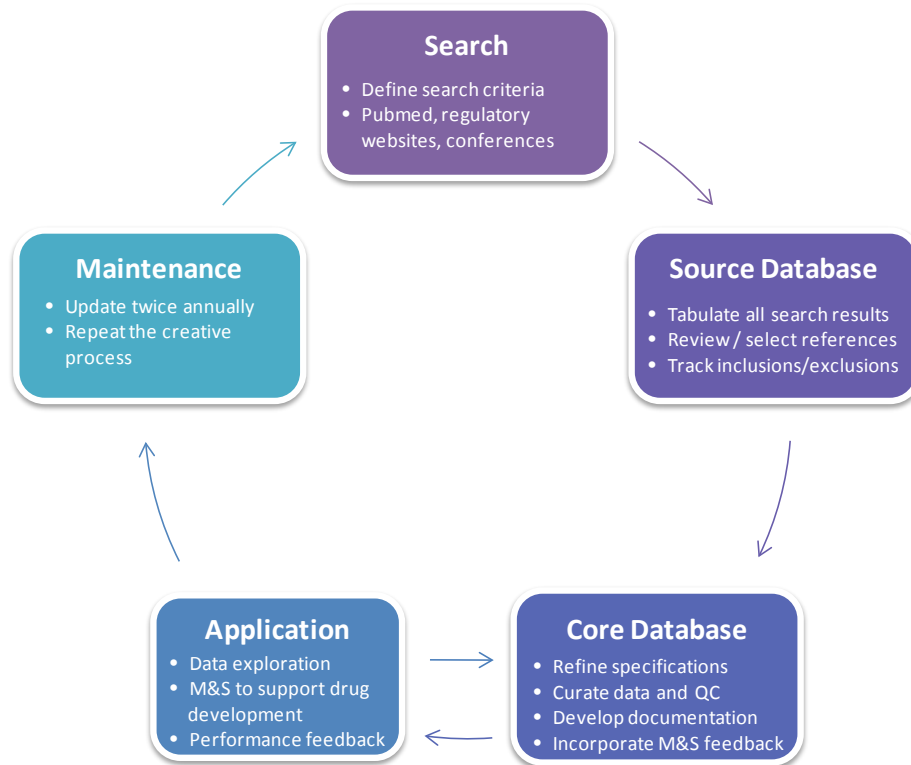
**Why use our databases:**

- Designed and managed by experienced modelers
- 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 and custom curation services (by our partner, GVK Bio)

### 3. Organization and Structure

This product consists of two databases, the *source database* and the *clinical outcomes database (core database)*, developed for RA. 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 Pain 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.

148 references were identified and documented in the source database, of which a total of 64 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. The 64 references selected for inclusion in the database provide information on 57 unique trials.

## 5. Overview of the Pain 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 5 of the trials mentioned in the FDA or EMEA reviews. Two of the 5 trials were stopped early. Two other trials for pregabalin that were not published did not show a significant effect of the drug. Detailed outcome information is available from the trials that were not published and will be included in the database. The primary reference for the other 16 registration trials is listed in the table.

**Table 2. List of registration trials in the database**

Drug	Study	Indication
Duloxetine	HMAV	DPN
Duloxetine	HMAW	DPN
Duloxetine	HMBT	DPN
Duloxetine	HMBO	fibromyalgia
Duloxetine	HMCA	fibromyalgia
Duloxetine	HMCJ	fibromyalgia
Duloxetine	HMEF	fibromyalgia
Gabapentin	945-211	PHN
Gabapentin	945-295	PHN
Pregabalin	1008-014	DPN
Pregabalin	1008-029	DPN
Pregabalin	1008-040	DPN
Pregabalin	1008-131	DPN
Pregabalin	1008-149	DPN
Pregabalin	1008-173	DPN
Pregabalin	1008-030	PHN
Pregabalin	1008-045	PHN
Pregabalin	1008-127	PHN
Pregabalin	1008-132	PHN
Pregabalin	1008-196	PHN
Pregabalin	1008-155	DPN/PHN

The clinical outcomes database contains information from 57 trials, representing 154 unique treatment arms and about 16,500 patients. There are a total of 5,973 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**

<b>Name of Drug</b>	<b># of trials</b>	<b># of arms</b>	<b># of patients</b>
amitriptyline	4	4	189
amitriptyline fluoxetine	1	1	31
desipramine	1	1	15
duloxetine	7	15	1963
fluoxetine	4	4	97
gabapentin	7	8	790
gabapentin morphine	1	1	57
lacosamide	1	1	60
lamotrigine	4	6	442
morphine	1	1	57
nortriptyline	1	1	38
oxycodone	3	3	177
oxycodone gabapentin	1	1	169
placebo	53	55	5717
pregabalin	19	41	5005
topiramate	5	11	1942
tramadol	2	2	129
tramadol acetaminophen	2	2	318
venlafaxine	2	3	194
<b>total</b>	<b>57</b>	<b>161</b>	<b>17390</b>

**Table 4. Overview of pain-related endpoints**

Endpoint	# of trials	# of arms	# of patients	drugs
<b>Pain Intensity</b>				
<b>30% reduction</b>	21	64	7843	/duloxetine/gabapentin/lamotrigine/pregabalin/topiramate/tramadol acetaminophen
<b>50% reduction</b>	28	85	9376	/amitriptyline/duloxetine/gabapentin/lamotrigine/nortriptyline/pregabalin/topiramate/tramadol acetaminophen/venlafaxine
<b>70% reduction</b>	7	21	1932	/duloxetine/pregabalin
<b>average pain</b>	49	132	13085	/amitriptyline/amitriptyline fluoxetine/desipramine/duloxetine/fluoxetine/gabapentin/gabapentin morphine /lacosamide/ lamotrigine/ morphine/ nortriptyline/ oxycodone/ oxycodone gabapentin/pregabalin/topiramate/tramadol/tramadol acetaminophen/venlafaxine
<b>worst pain</b>	4	12	1462	/duloxetine/topiramate
<b>Brief Pain Inventory</b>				
<b>30% reduction</b>	3	9	1024	/duloxetine/gabapentin
<b>50% reduction</b>	2	7	874	/duloxetine
<b>average interference</b>	11	28	3618	/duloxetine/gabapentin/oxycodone/pregabalin/tramadol acetaminophen
<b>average pain</b>	11	29	3697	/duloxetine/gabapentin/oxycodone/pregabalin/tramadol acetaminophen
<b>enjoyment of life</b>	5	15	1423	/duloxetine/gabapentin/gabapentin morphine/morphine/oxycodone
<b>general activity</b>	6	19	1880	/duloxetine/gabapentin/gabapentin morphine/morphine/oxycodone
<b>least pain</b>	8	22	2855	/duloxetine/oxycodone/tramadol acetaminophen
<b>mood</b>	5	15	1423	/duloxetine/gabapentin/gabapentin morphine/morphine/oxycodone
<b>normal work</b>	5	15	1423	/duloxetine/gabapentin/gabapentin morphine/morphine/oxycodone
<b>pain right now</b>	7	19	2414	/duloxetine/oxycodone/tramadol acetaminophen
<b>relationships</b>	5	15	1423	/duloxetine/gabapentin/gabapentin morphine/morphine/oxycodone

<b>sleep</b>	5	15	1423	/duloxetine/gabapentin/gabapentin morphine/morphine/oxycodone
<b>walking ability</b>	5	15	1423	/duloxetine/gabapentin/gabapentin morphine/morphine/oxycodone
<b>worst pain</b>	8	22	2855	/duloxetine/oxycodone/tramadol acetaminophen
<b>Short-Form McGill</b>				
<b>VAS pain</b>	18	51	4685	/amitriptyline/gabapentin/gabapentin morphine/lacosamide/morphine/nortriptyline/pregabalin
<b>affective descriptors of pain</b>	8	24	2417	/gabapentin/gabapentin morphine/morphine/pregabalin/tramadol acetaminophen
<b>present pain intensity</b>	15	41	3674	/amitriptyline/gabapentin/gabapentin morphine/lacosamide/morphine/pregabalin/ tramadol acetaminophen/venlafaxine
<b>sensory descriptors of pain</b>	8	24	2417	/gabapentin/gabapentin morphine/morphine/pregabalin/tramadol acetaminophen
<b>total</b>	20	58	5294	/duloxetine/fluoxetine/gabapentin/gabapentin morphine/lamotrigine/morphine/nortriptyline/pregabalin/ tramadol acetaminophen/venlafaxine
<b>FIQ</b>				
<b>pain</b>	3	6	582	/duloxetine/fluoxetine/tramadol acetaminophen
<b>total</b>	9	27	3223	/amitriptyline/amitriptyline fluoxetine/duloxetine/fluoxetine/gabapentin/pregabalin/ tramadol acetaminophen

## 6. Example Plots

### 6.1. Overview of actual trial data for Pain Intensity endpoints

The following pdf documents show the time course of pain intensity mean change from baseline measured by the daily diary (VAS or 11-category Likert score) or other instruments such as the brief pain inventory (BPI), short form McGill (SFMAC), and fibromyalgia impact questionnaire (FIQ). The graphs show the time course for each treatment arm and each trial that has information on these endpoints. Often multiple imputation methods are used to evaluate the change in pain score. A different graph is shown for the different imputation methods such as LOCF, BOCF, or no imputation. The title for each graph shows the trial name, the instrument used to measure the pain, the

range of the pain scale (i.e. 100 mm VAS or 0-10 Likert score), the imputation method and the summary statistic (least squares mean or raw mean). If no trial name is available, the first author and year of publication are used. The average sample size by arm is shown in the legend of each panel, as is the pain indication in the top left corner. The symbol size is proportional to the precision of the observation; the larger the symbol, the more precise the observation.



pain.pdf

## 7. Outcome fields

### Efficacy Endpoints

The following efficacy endpoints were collected. They are organized by endpoint category

- Pain intensity measured in a daily diary on an 11 point categorical (Likert) scale, a 5 point categorical scale, or a 100 mm visual analog scale (pain intensity). In certain occasions the pain score was only reported at the visits. Within the pain intensity endpoint category there are several endpoints:
  - average pain
  - 30% reduction from baseline of average pain
  - 50% reduction from baseline of average pain
  - 70% reduction from baseline of average pain
  - worst pain
  - night pain
  - pain right now
- Pain relief measured in a daily diary on an 11 point categorical (Likert) scale, a 5 point categorical (Likert) scale, or a 100 mm visual analog scale (pain relief).
  - average pain relief
- Brief pain inventory (BPI, Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23:129–38.):
  - average pain measured on a score from 0-10 (this is comparable to average pain measured under the pain intensity category)
  - 30% reduction from baseline of average pain
  - 50% reduction from baseline of average pain
  - worst pain
  - pain right now
  - least pain
  - general activity
  - mood
  - walking ability
  - normal work
  - relationships
  - sleep
  - enjoyment of life
  - average interference
  - pain relief

- Fibromyalgia Impact Questionnaire (FIQ, Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. *J Rheumatol* 1991;18(5): 728–33.) :
  - total score (measured on a 0-80 or a 0-100 scale)
  - pain score (score range 0–10). This is comparable to average pain measured under the pain intensity category
- Short-Form McGill Pain Questionnaire (SFMAC, Melzack R. The short-form McGill Pain Questionnaire. *Pain* 1987;30:191–7):
  - past week pain intensity (VAS pain). This is comparable to average pain measured under the pain intensity category
  - present pain intensity
  - past week intensity of sensory descriptors of pain
  - past week intensity of affective descriptors of pain
  - past week intensity of sensory and affective descriptors of pain (total score)
- The 36-Item Short-form Health Survey (SF36, Ware JEJ. SF-36 Health Survey: Manual and Interpretation Guide, Boston, MA: The Health Institute, New England Medical Center, 1993.)
  - mental component summary
  - physical component summary
  - physical functioning
  - social functioning
  - bodily pain
  - general health perceptions
  - vitality
  - mental health
  - role emotional
  - role physical
- Sleep (sleep)
  - sleep interference score
  - several other measures of sleep that are reported sporadically.
- Patient global impression of change, measured as 7 categories (PCIG)
  - mean score
  - improved (score <=3)
  - unchanged (score=4)
  - worse (score>4)
  - very much improved (score=1)
  - much improved (score=2)
  - minimally improved (score=3)
  - minimally worse (score=5)
  - much worse (score=6)
  - very much worse (score=7)
  - Sometimes certain categories are grouped. For example very much improved and much improved (score <=2)

- Clinical global impression of change, measured as 7 categories (CCIG)
  - mean score
  - improved (score  $\leq 3$ )
  - unchanged (score=4)
  - worse (score $>4$ )
  - very much improved (score=1)
  - much improved (score=2)
  - minimally improved (score=3)
  - minimally worse (score=5)
  - much worse (score=6)
  - very much worse (score=7)
  - Sometimes certain categories are grouped. For example very much improved and much improved (score  $\leq 2$ )
- Clinical global impression of severity, measured as 7 categories (CGI severity)
  - mean score

### **Safety and tolerability endpoints**

The following safety and tolerability information were extracted:

- Dropout (treatment discontinuation) (dropout). This refers to all patients that did not complete the study.
- Dropout related to adverse events (dropout AE)
- Dropout related to lack of efficacy (dropout Efficacy)
- Any adverse events (AE any)
- Serious adverse event (AE serious)
- AE resulting in dose interruption, stop, or reduction (AE dose stop)
- Dizziness
- Somnolence
- Sedation
- Constipation
- Weight gain
- Dry mouth
- Headache
- Nausea
- Vomiting
- Difficulty with concentration/attention
- Fatigue

- Loss of appetite
- Blurred vision
- Visual disturbance
- Confusion
- Abnormal Thinking