CERTARA

Quantify Neuropathic Pain Clinical Outcomes Database

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
format	Excel or web-based platform (optional)
indication	neuropathic pain
trials arms	95/260
patients	29,000
rows of data	10,239
compounds	amitriptyline, desipramine, duloxetine, esreboxetine, fluoxetine, gabapentin, gabapentin er, gabapentin enacarbil, lacosamide, lamotrigine, milnacipran, morphine, nabilone, nortriptyline, oxycodone, pregabalin, sativex, sodium oxybat, topiramate, tramadol, venlafaxine
key efficacy end points	pain intensity, brief pain inventory, short-form mcgill, fiq, global impression of change, sleep (65 endpoints in total)
key safety end points	tolerability percentages (22 endpoints in total)

Features and Benefits

Databases can be delivered as Excel files or through a web-based access platform.

General Features of theDatabase:

- **Comprehensive:** includes information for marketed drugs as well as drugs in development; data source includes journal publications, conference posters, regulatory reviews, etc
- **Ease of tracking**
- **Flexibility:** the database design allows for quick updates as well as expansions to include additional indications/drugs/endpoints/trials
- **Analysis-ready:**
  - Background treatments are categorized
  - Missing covariates are imputed
  - Endpoint data are calculated when applicable
  - Units are normalized
- **Customizability**

Benefits of the Web-based Access Tool:

- **Instant access to up-to-date data**
  - Database will be updated throughout the year, with timestamps for each record which help users to keep track of new updates
  - Web platform acts as a single point of access to all clinical trial databases
- **User-friendly interface**
  - Users can explore and visualize data through a web interface with no requirement for software installation
- **Easy to communicate data and analysis results**
  - Data summary, plotting functions are embedded

Potential Applications – Supporting Model-based Meta-analysis:

Characterize relative (comparative) clinical safety and efficacy profile

- 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

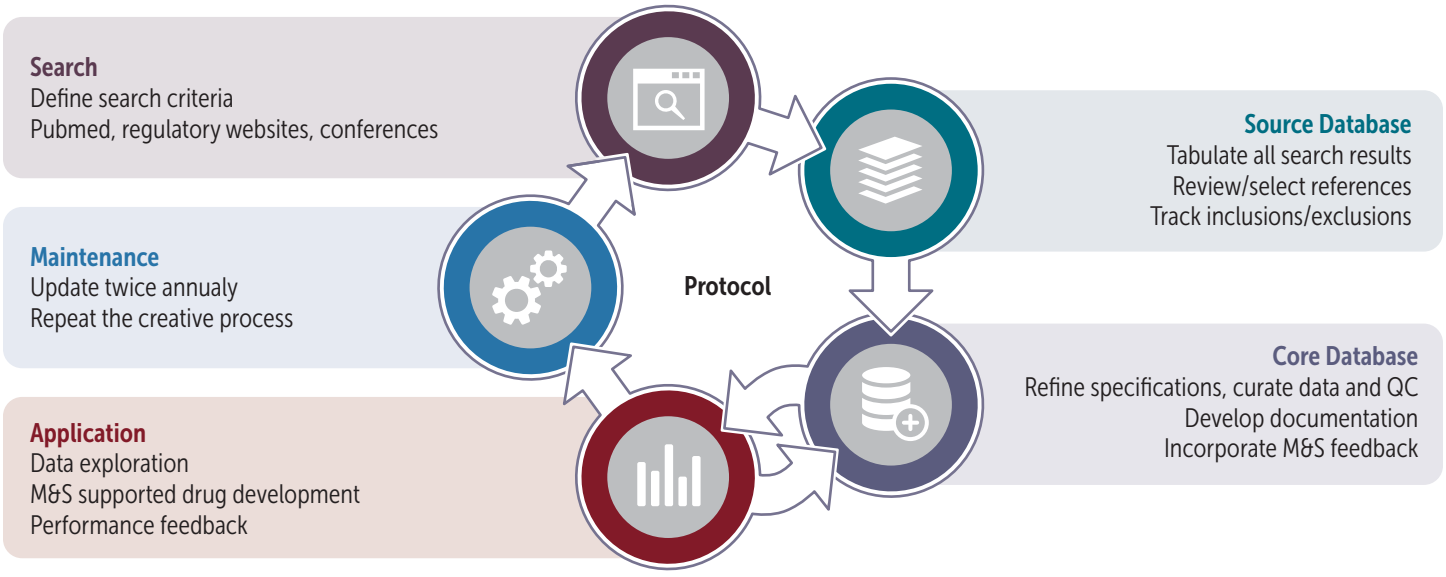
- Scale from different pain measurements
- Explore potential differences or similarities in dose response relationship for a particular drug or drug class across pain indication such as DPN, PHN and fibromyalgia
- Predict drug performance in another pain indication based on consistency of dose response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

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

Organization and Structure

This product consists of two databases, the source database and the clinical outcomes database (core database), developed for neuropathic pain. 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.



Overview of the Neuropathic 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.

288 references were identified and documented in the source database, of which a total of 112 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 112 references selected for inclusion in the database provide information on 95 unique trials and 260 unique arms.

Overview of the Neuropathic Pain Clinical Outcomes Database

The clinical outcomes database contains information from 95 trials, representing 260 unique treatment arms and about 29,000 patients. There are a total of 10,239 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, ie, treatments that were started at time of randomization and not present as background therapy.

Table 2. Number of trials, treatment arms, and patients for each drug

randomized.drug	trials	arms	patients
amitriptyline	5	5	240
amitriptyline + fluoxetine	1	1	31
desipramine	1	1	15
duloxetine	12	21	2,796
duloxetine + gabapentin	1	1	135
esreboxetine	1	1	134
fluoxetine	4	4	97
gabapentin	9	10	914
gabapentin ER	4	7	697
gabapentin enacarbil	4	9	734
gabapentin + morphine	1	1	57
gabapentin + nortriptyline	1	1	40
lacosamide	5	10	1,101
lamotrigine	4	6	442
melatonin	1	1	27
melatonin + fluoxetine	1	2	50
milnacipran	6	9	2,593
morphine	1	1	57
nabilone	1	1	20
nortriptyline	2	2	78
oxycodone	3	3	177
oxycodone + gabapentin	1	1	169
placebo	84	86	9,749
pregabalin	27	50	5,941
pregabalin + oxycodone	1	1	27
retigabine	1	1	125
sativex	1	1	15

sodium oxybate	3	6	874
topiramate	4	8	1,092
tramadol	3	3	282
tramadol + acetaminophen	3	3	397
venlafaxine	2	3	194
TOTAL	**95**	**260**	**29,300**

Table 3. Overview of pain-related endpoints

pain intensity endpoints	trials	arms	patients
average pain	81	224	24,482
50% reduction	48	142	16,513
30% reduction	40	118	15,721
70% reduction	10	32	2,900
night pain	8	27	2,852
pain right now	7	20	4,088
average pain	6	17	4,586
worst pain	6	18	2,207
pain right now	5	16	3,048

bpi endpoints	trials	arms	patients
average pain	27	70	9,436
average interference	24	61	8,683
least pain	17	44	5,429
worst pain	17	44	5,429
general activity	16	42	4,542
pain right now	16	41	4,988
sleep	14	36	3,926
enjoyment of life	12	32	3,552
mood	12	32	3,552
normal work	12	32	3,552
relationships	12	32	3,552
walking ability	12	32	3,552
30% reduction	5	13	1,769
50% reduction	4	11	1,619
pain relief	4	10	919

short-form mcgill endpoints	trials	arms	patients
total	27	81	7,398
VAS pain	25	70	6,383
present pain intensity	22	60	5,140
affective descriptors of pain	16	49	4,550
sensory descriptors of pain	16	49	4,550

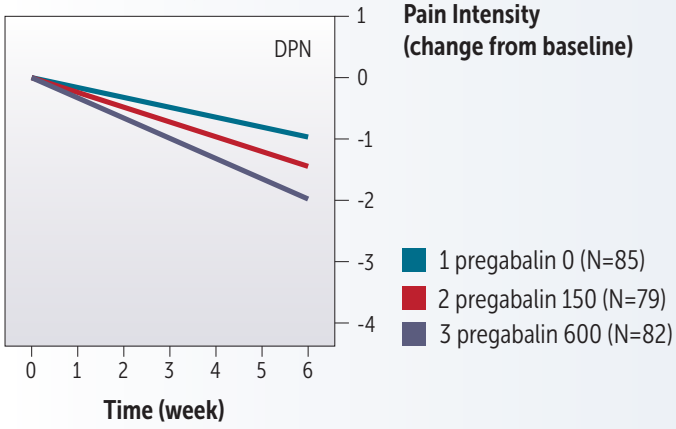
fiq endpoints	trials	arms	patients
total	24	67	10,759
pain	10	27	3,665

Example Plots

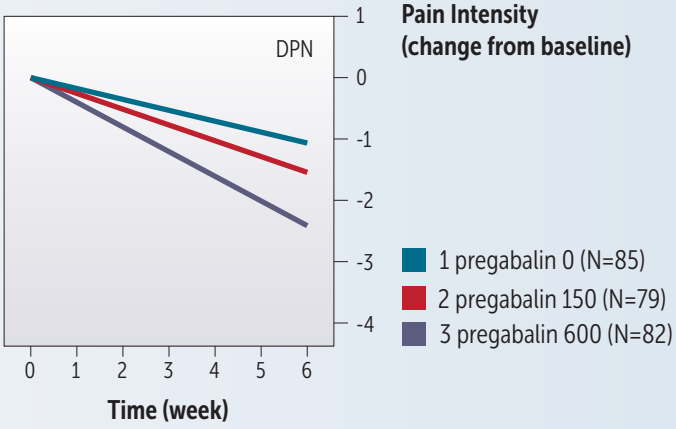
Overview of actual trial data for Pain Intensity endpoints

The following plot shows an example of 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. The average sample size by arm is shown in the legend of each panel, as is the pain indication in the top right corner.

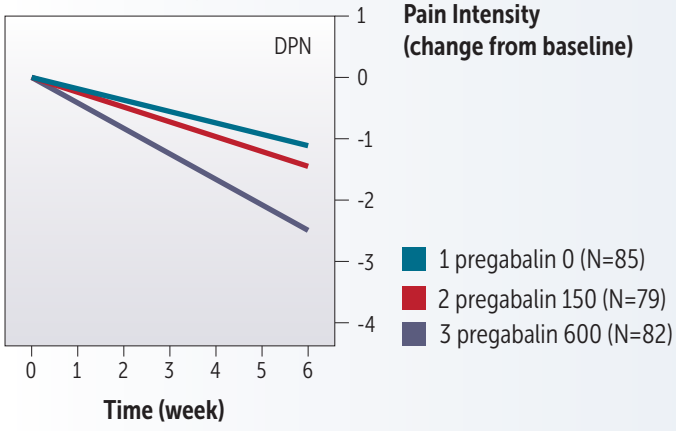
1008-014 pain intensity 0-10 BOCF lsm



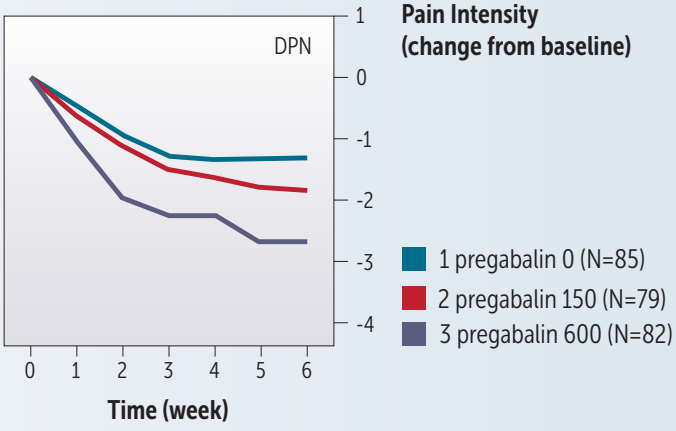
1008-029 pain intensity 0-10 BOCF lsm



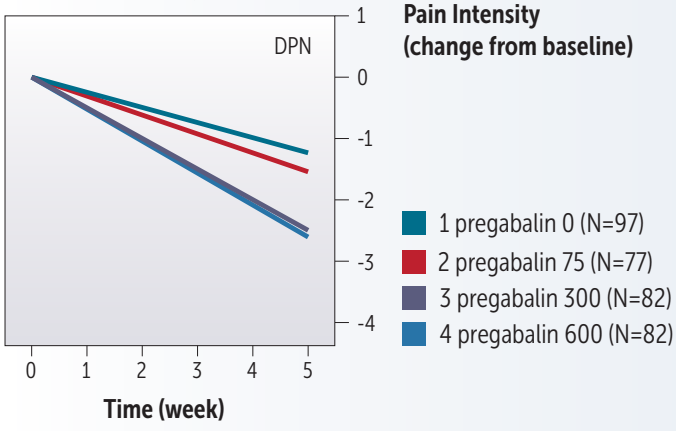
1008-029 pain intensity 0-10 LOCF lsm



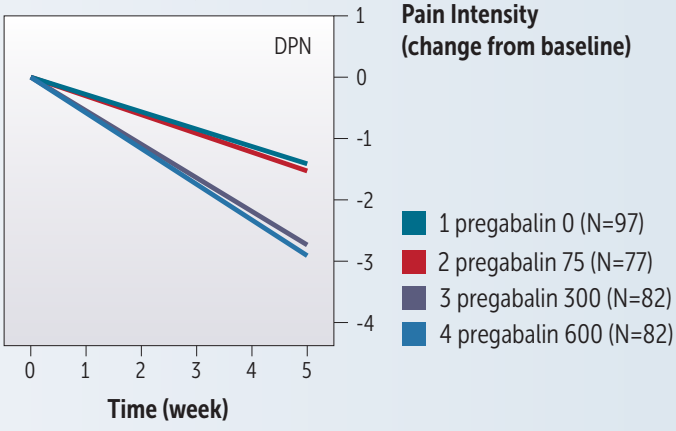
1008-014 pain intensity 0-10 none lsm



1008-014 pain intensity 0-10 BOCF lsm



1008-014 pain intensity 0-10 LOCF lsm



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 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 <=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 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

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

For more information visit www.certara.com or email sales@certara.com.

DS Feb 2017 v1 050117