Tolerability of duloxetine in the elderly and in adults: a protocol and preliminary results of a systematic review and individual participant data meta-analysis of randomized placebo-controlled trials

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Protocol

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Abstract

Background. Duloxetine is an antidepressant which benefits from a wide range of approval in elderly population while its safety of use in elderly population, compared to younger adults, is not clearly assessed. A comparison of tolerability of duloxetine between elderly and younger adults would help to rule on this issue.

Methods and Design. This protocol outlines a systematic review and meta-analysis of individual participant data (IPD) of all double-blind randomized controlled trials comparing the number of serious adverse events among individuals taking duloxetine in comparison to placebo between participants at least 65 years and younger adults in conditions approved by the European Medical Agency (EMA) and the Food Drug Administration (FDA). Secondarily, will be compared the number of any adverse events, clinical efficacy and quality of life between elderly and younger adults under duloxetine, in comparison to placebo. Relevant studies were selected on ClinicalTrials.gov, Clinicaltrialsregister.eu, data sharing platforms, FDA and EMA websites, and from systematic reviews and meta-analyses of duloxetine on PubMed, following Cochrane’s recommendations. Sponsors and authors from eligible studies were invited to share IPD on data sharing platform or directly with our research team. As data cannot be aggregate into a unique database, a two step-approach meta-analysis will be undertaken.

Qualitative results from available data. 77 eligible randomized controlled trials were identified, representing 25303 participants. From online available data, 35 trials were assessed as being at an overall low risk of bias, 31 trials at an unclear risk of bias and 1 at high risk of bias. Evaluation of risk of bias was not feasible for 10 studies.

Conclusion. This study would represent the first meta-analysis investigating the safety of duloxetine in elderly population across all conditions approved by European and American regulatory authorities with an overall low risk of bias.

Registration. PROSPERO: 2019 CRD42019130488.

Background

Rationale

Duloxetine is a medication which has been approved for a wide range of pathologies by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), namely major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain and stress urinary incontinence. These diseases represent a major public health burden for elderly population\(^1\). While several guidelines recommend the use of duloxetine as a first-line medication for these diseases in the elderly\(^2\)-\(^6\), others formally proscribe it\(^7\). As a matter of fact, good practice guidelines of duloxetine use are under debate, notably because of mixed evidence for a favorable risk-benefit balance in older populations\(^5\),\(^8\).

For instance, a mixed treatment meta-analysis, mostly based on indirect evidence, suggests that duloxetine had higher response rates than other antidepressants for major depressive disorder in old-age population (\(\geq 65\) years old), in a context of scarce data in this population\(^9\). In contrast, duloxetine was found to increase the risk
of adverse events. In younger adults, several meta-analyses concluded that duloxetine was associated to a disfavoring risk-benefit balance compared to placebo in osteoarthritis and stress urinary incontinence. Meta-regression analyses from Cipriani et al. (2018) found similar results, observing a significant association between mean age of participants and response to duloxetine (OR = 1.86, CI 95% = 1.66-2.08) with an association between age and number of drop-outs under duloxetine (OR = 1.10, CI 95% = 0.97-1.24), although the latter result did not reach statistical significance.

Concerns about duloxetine use in the elderly have existed since pre-marketing pharmacokinetics studies. Study SAAY brought out a reduced oral clearance of duloxetine of 25% in an elderly class (mean age of 69 years old) compared to a middle-aged class (mean age of 42 years old) of women, under 40mg of duloxetine. Furthermore, AUC measure of exposure was found to be 24% higher in elderly, although not statistically significant in the cohort of 24 participants, but with a half-life elimination reduced by one third in elderly compared to middle-aged individuals. Statistically significant correlation of diminished oral clearance of duloxetine with age was demonstrated, estimated to a reduction of clearance of almost 60% between 23- and 76.8-year-old (Study SAAB). Skinner et al. (2004) estimated that decrease of oral clearance accelerates at around 52 years of age. Similar results have been reproduced in ulterior pooled analyses of phase III trials with comparable effect sizes (procedure EMEA/H/C/572/II/26 reported a 25 percent-decrease of oral clearance between 29- and 69-year-old individuals). Taken together, these early phase I studies demonstrated an increased systemic exposure to duloxetine in elderly population.

However, the clinical interpretation of pharmacokinetics results remains challenging. Many subgroup analyses of pilot trials did not find quantitative differences in tolerability between old and younger adults. One plausible explanation lies in the small sample sizes of elderly participants included in these studies. As mentioned in the FDA CYMBALTA® Label (revised version of 2017), of the 6781 patients in premarketing clinical studies of duloxetine in all conditions, 15.6% were 65 years of age or over. Although it represents about 1058 subjects, no direct comparison of between-age tolerability across diseases is to be found in the literature. Altogether, it seems that the tolerability of duloxetine in elderly needs clarification.

Therefore, we planned to determine whether use of duloxetine in elderly is associated to a higher risk of serious and non-serious adverse events than in younger adults. Lilly (the sponsor of most duloxetine studies) has a commitment to share their clinical trial data as part of a data sharing policy starting in June 2014. We therefore designed an individual participant meta-analysis of randomized controlled trials of any condition with an FDA or EMA approval of use of duloxetine.

### Objectives

Our main objective is to compare the number of serious adverse events (SAE) among individuals taking duloxetine (in comparison to placebo) between participants at least 65 years and younger adults in EMA and FDA approved conditions. Our primary hypothesis is that elderly population is more prone to serious adverse events caused by duloxetine than younger adult population.

Our secondary objectives are to compare the number of any adverse events caused by duloxetine between participants at least 65 years of age and younger adults and to compare both the clinical efficacy of duloxetine
on clinical scales and quality of life between elderly individuals and younger adults, separately for each indication. Furthermore, efficacy and tolerability will be compared between young-old (aged between 65 and 75) and old-old participants (aged 75-year-old or more).

Methods And Design

This systematic review and meta-analysis of individual patient data will be conducted of interventional, prospective, double-blind, randomized, placebo-controlled trials with an independent duloxetine arm. According to a protocol registered on PROSPERO (systematic review registration—2019 CRD42019130488), we have conducted a systematic literature review of relevant trials underwent on participants with an age < and ≥ to 65 years old, in population suffering from a condition having an EMA or FDA approval for duloxetine. In this report we describe all eligible studies and present the outcomes that will be extracted for the individual patient data and the methods that will be used for data synthesis following the PRISMA-P recommendations (Additional file 1). The anticipated end date of study is November 2021.

Eligibility criteria

We used the following eligibility criteria:

- Types of studies: RCTs with both participants ≥ and < to 65 years of age;
- Types of participants: subjects suffering from a disorder with a known approval for duloxetine by the FDA and the EMA, namely: depression, anxiety, diabetic neuropathic pain, fibromyalgia, chronic musculoskeletal pain and stress urinary incontinence;
- Types of interventions: duloxetine whatever the dosage, the administration frequency, the route of administration;
- Type of comparator: placebo;
- Types of outcome measures: report of SAE for each participant under duloxetine and placebo arms and/or non-serious adverse events and/or efficacy and or quality of life;

The research was restricted to trials written in English, whatever their publication status (published/unpublished).

Information sources

Searches were conducted in PubMed (to identify individual studies from published systematic reviews and meta-analyses of duloxetine), ClinicalTrials.gov, Clinicaltrialsregister.eu, data sharing platforms (ClinicalStudyDataRequest.com, YODA and Vivli), FDA drug approval packages and on European public assessment report and withdrawn applications from EMA website. The review was performed on studies available on electronic databases from their date of inception to May 31, 2019.

Search strategy
Trials identification was systematic with different search strategies depending on the source. First, we search PubMed for all systematic reviews and meta-analyses involving duloxetine in an approved indication. Then, individual trials were identified from these systematic reviews and meta-analyses. The search terms were as follows: "(Duloxetine AND Meta-Analysis[ptyp])". In ClinicalTrials.gov, the search was restricted to all interventional studies with adults and older adults, using "duloxetine" as search term. In Clinicaltrialsregister.eu and in data sharing platforms, the search term was “duloxetine” with no filter applied. In FDA website, FDA drug approval packages were downloaded from FDA Approved drug product, entering “duloxetine” as search term. In EMA website, European public assessment reports and withdrawn applications were selected, limited to reports on human with no restriction on the authorization status, using “duloxetine” as search term. The list of included studies, as the list of meta-analyses and of systematic reviews, are reported on additional file 2 and additional file 3, respectively.

**Study records**

*Data management, selection and collection processes*

Selection and coding of the different study characteristics were performed by two independent reviewers (JCR and AJ) in a blinded manner. A third reviewer (FN) arbitrated in case of disagreement. Studies appearing to duplicate authors, treatment comparisons, sample sizes and outcomes were checked one against another to avoid double-counting and integrating data from several reports on the same study and in contact with the studies sponsors. A data extraction sheet based on the Cochrane Handbook for Systematic Reviews of Interventions guidelines was developed. In case of missing data, the sponsor of the study and/or corresponding authors were contacted.

*Collecting IPD*

A data sharing request was sent to all sponsors which trials were spontaneously available on data sharing platforms. For the remaining studies, the request was sent to all correspondent authors and, if possible, a research proposal was addressed to each pharmaceutical sponsor on data sharing platforms (for Eli Lilly, Shionogi, Pfizer and AbbVie trials) or on the sponsor website (for Lundbeck, Takeda and Merck Sharp & Dohme trials). For willing collaborators, the terms of the collaboration will be specified in a data transfer agreement, signed by representatives of the data provider and of the recipients (Clinical Investigation Center, Department of Clinical Pharmacology, Rennes University Hospital, France). Collection of IPD is ongoing.

Participant characteristics requested are baseline age, gender, intervention arm, duloxetine dose, duration of participation in the study, number of serious adverse events from baseline to endpoint, number of non-serious adverse events from baseline to endpoint, study primary outcome and its values at baseline and at endpoint, type of quality of life scale used and its values at baseline and at endpoint. Data will be accepted in any suitable electronic format. Checks on the data will be made to ensure data are correctly coded, that missing data are correctly identified, that extreme values are genuine and to ensure that the data are consistent with published results. Data from all trials will be incorporated into a single database with fields that are consistent across trials.
Data items

For each included study, information was extracted on:

- Characteristics of the study: year, country, number of arms with duloxetine and placebo, funding, disease;
- Characteristic of trial participants: mean age (and its standard deviation), gender, number of patients included in analysis, population of analysis used in the identified report (intention to treat, per protocol, other);
- Type of administration and dose;
- Outcome measures as stated above (including exact definition of outcome/ e.g. MedDRA or other).

Outcomes and prioritization

The main outcome is the number (count) of SAE for each individual patient. In our study, SAE refers exclusively to any undesirable experience associated with the use of a medical product which results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability, or is a congenital anomaly or birth defect. This outcome has the advantages to be simple of interpretation and clinically relevant for safety estimation, containing a severity criterion from its definition.

Additionally, will be assessed as secondary outcomes:

- The number of non-serious adverse events (nsAE). nsAE refers to any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not have severity criteria for SAE nor necessarily have a causal relationship with this treatment. In a randomized placebo-controlled setting, this outcome provides a global estimate of treatment safety, without the severity feature of SAE.
- The efficacy on clinical scale in each indication (i.e. depression, anxiety, pain, urinary incontinence): different scales in the same indication will be standardized by z-scores. This outcome will evaluate the clinical benefit in patients.
- The quality of life scores in each indication: the different scales will be standardized by z-score. In studies where multiple quality of life scales were used, a hierarchy was established by selecting scales which both resume health data in one unique total score and which were the most used among the duloxetine trials. If the only available instrument in a trial did not permit to resume data into one score (e.g. SF36), its general health subscale was retained as indicator of quality of life (detailed in Additional file 4, Table S1). Quality of life scores yield a broad and ecological estimate of the well-being state of the patient.

Risk of bias in individual studies

Two researchers (JCR and AJ) assessed each trial for risk of bias independently, addressing randomization, allocation concealment, blinding of assessors and of study participants, completeness of outcome assessment, selective reporting and other potential sources of bias according to the Cochrane Collaboration tool for assessing risk of bias in its current version, RoB218, at the study level. Discrepancies were resolved by consensus.
Data synthesis

Main analysis

As it appeared that all data were not directly downloadable together but rather provided remotely on separate interfaces, we chose a two-step procedure\textsuperscript{19} to derive incidence rate ratio (for count of binary outcomes) and mean differences (for quantitative outcomes).

The first step consists in comparing the number (count) of SAE between groups of participants arranged by age using a generalized linear mixed model (with a quasi-Poisson link function) in each individual study. Age (binary variable between “young” participants < 65 years old and “old” participants $\geq$ 65 years old) and intervention (binary variable between participants under duloxetine to participant under placebo) will be considered as fixed effects and their interaction will be explored as the main comparison. Incidence rate ratio as well as their variance will be extracted from the interaction between age and intervention.

In the second step, we will pool the extracted incidence rate ratios using a random effect meta-analysis. Similarly, number of non-serious adverse events (count) will be analyzed using a two-step approach based on a generalized linear mixed model (with a quasi-Poisson link function). For both SAE and nsAE, we will use meta-regressions to explore whether these interactions between age and intervention are different across the different conditions (major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain and stress urinary incontinence).

Summary measures for the analyses of efficacy and quality of life: in each condition, clinical scales (i.e. depression, pain, chronic anxiety) and quality of life scales will be analyzed separately using a similar two-step approach relying on results of a linear model. As various scales might be used across studies, we will use z-scores to standardize the different scales and populations.

Missing data will be handled by multiple imputation.

Sensitivity and subgroup analyses

A sensitivity analysis will be performed considering the occurrence of SAE in binary (Yes vs No) with the same two step approach relying on a generalized linear mixed model (with a logistic link function) in each individual study.

A subgroup analysis will be performed applying the same methodology as for adverse events, to explore differences between “young-old” participants (between 65 and 75 years old) and “old-old” participants (>75 years old) in terms of adverse events (serious and non-serious) and of efficacy.

Meta-biases

Missing trials will be explicitly reported with their characteristics and results described. Duplicate publications bias will be limited by the selection and precise identification of published and unpublished trials. If one or more
trials could not be precisely identified by at least an ID number, these trials will be reported in the study results with explained attempts to obtain identification.

Countries where studies took place will be systematically assessed in the description studies table, to account for possible location bias. In addition, we clearly outline in our methods that our analysis select only studies written in English.

**Confidence in cumulative evidence**

We will use GRADE to rate the overall certainty (quality) of evidence that includes the evaluation of risk of bias, inconsistency, indirectness, imprecision and publication factors²⁰.

**Qualitative Results From Online Data**

**Study selection**

Our search identified 448 unique studies that were assessed for eligibility (reported in supplementary file). Of these, 77 studies accounting a total of 25 303 randomized participants fulfilled the eligibility criteria (Figure 1). For searches conducted on PubMed, 48 meta-analyses or reviews were selected from 136 results. Lilly has accepted to share IPD data from 58 studies (Table 1). Lundbeck, Pfizer and Abbott laboratories are still reviewing the data sharing request for 8 studies. No answer was obtained from the Danish Pain Research Center, the University of Nottingham arthritis research UK, the Northwestern University, the New York State Psychiatric Institute and for one study of Boehringer Ingelheim. Data sharing was denied from 6 trials belonging to Shionogi, Merck Sharp & Dohme and Wake Forest University National Institute of Neurological Disorders and Stroke.
| N° | Author         | Sponsor ID    | Sponsor | Contact | Status  | Comments |
|----|----------------|---------------|---------|---------|---------|----------|
| 1  | F1J-MC-HMAH    | Lilly         | Vivli   | Approved|
| 2  | F1J-MC-HMAI    | Lilly         | Vivli   | Approved|
| 3  | Brannan2005    | F1J-US-HMCB  | Lilly   | Vivli   | Approved|
| 4  | Nierenberg2007 | F1J-US-HMCR  | Lilly   | Vivli   | Approved|
| 5  | Perahia2009    | F1J-MC-HMDI  | Lilly   | Vivli   | Approved|
| 6  | F1J-US-HMFA    | Lilly         | Vivli   | Approved|
| 7  | Gaynor2011a    | F1J-US-HMGR  | Lilly   | Vivli   | Approved|
| 8  | Gaynor2011b    | F1J-US-HMGU  | Lilly   | Vivli   | Approved|
| 9  | Mundt2007      | H8I-MC-HQAC  | Lilly   | Vivli   | Approved|
| 10 | Rynn2008       | F1J-MC-HMDT  | Lilly   | Vivli   | Approved|
| 11 | Hartford2007   | F1J-MC-HMDU  | Lilly   | Vivli   | Approved|
| 12 | Davidson2008   | F1J-MC-HMDV  | Lilly   | Vivli   | Approved|
| 13 | Nicolini2009   | F1J-MC-HMDW  | Lilly   | Vivli   | Approved|
| 14 | Koponen2007    | F1J-MC-HMBR  | Lilly   | Vivli   | Approved|
| 15 | Arnold2005     | F1J-MC-HMCA  | Lilly   | Vivli   | Approved|
| 16 | Arnold2012     | F1J-MC-HMGG  | Lilly   | Vivli   | Approved|
| 17 | Arnold2004     | F1J-MC-HMBO  | Lilly   | Vivli   | Approved|
| 18 | Wernicke2006   | F1J-MC-HMAVa | Lilly   | Vivli   | Approved|
| 19 | Raskin2005     | F1J-MC-HMAVb | Lilly   | Vivli   | Approved|
| Page | Reference | F1J-MC-Sequence | Company | Status |
|------|-----------|-----------------|---------|--------|
| 20   | Goldstein2005 | F1J-MC-HMAW | Lilly | Approved |
| 21   | Gao2010 | F1J-MC-HMEQ | Lilly | Approved |
| 22   | Gao2015 | F1J-MC-HMGV | Lilly | Approved |
| 23   | Skljarevski2010a | F1J-MC-HMEN | Lilly | Approved |
| 24   | Skljarevski2009 | F1J-MC-HMEO | Lilly | Approved |
| 25   | Skljarevski2010b | F1J-MC-HMGC | Lilly | Approved |
| 26   | Chappell2009 | F1J-MC-HMEP | Lilly | Approved |
| 27   | Chappell2011 | F1J-MC-HMFG | Lilly | Approved |
| 28   |  | F1J-MC-HMGP | Lilly | Approved |
| 29   | Brecht2007 | F1J-BI-HMDH | Lilly/Boehringer Ingelheim | Approved |
| 30   | Wang2017 | F1J-MC-HMGS | Lilly | Approved |
| 31   |  | F1J-MC-HMAG | Lilly | Approved |
| 32   | Russell2008 | F1J-MC-HMCJ | Lilly | Approved |
| 33   | Arnold2010 | F1J-US-HMGB | Lilly | Approved |
| 34   | Chappell2008 | F1J-MC-HMEF | Lilly | Approved |
| 35   | Frakes2011 | F1J-US-HMGL | Lilly | Approved |
| 36   |  | F1J-MC-SAAL | Lilly | Approved |
| 37   | Zinner1998 | F1J-MC-SAAB | Lilly | Approved |
| 38   |  | F1J-MC-SAAH | Lilly | Approved |
| 39   | Bent2008 | F1J-MC-SBBO | Lilly | Approved |
| 40   |  | F1J-MC-SBAB | Lilly | Approved |
|   | Author          | Study Code | Company | Status   |
|---|----------------|------------|---------|----------|
| 41| Ghoniem2005    | F1J-MC-SBAF| Lilly   | Approved |
| 42| Cardozo2004    | F1J-MC-SBAM| Lilly   | Approved |
| 43| Castro-Diaz2007| F1J-MC-SBBR| Lilly   | Approved |
| 44| Cardozo2010    | F1J-EW-SBCC| Lilly   | Approved |
| 45| Lin2008        | F1J-MC-SBBT| Lilly   | Approved |
| 46| Mah2006        | F1J-MC-SBBU| Lilly   | Approved |
| 47| Dmochowski2003 | F1J-MC-SBAV| Lilly   | Approved |
| 48| Van Kerrebroeck2004 | F1J-MC-SBAT | Lilly | Approved |
| 49|                | F1J-MC-SAAA | Lilly   | Approved |
| 50| Millard2004    | F1J-MC-SBAX| Lilly   | Approved |
| 51|                | F1J-MC-SBBL | Lilly   | Approved |
| 52| Kinchen2005    | F1J-MC-SBBA| Lilly   | Approved |
| 53|                | F1J-MC-HMATa| Lilly   | Approved |
| 54| Goldstein2004  | F1J-MC-HMATb| Lilly   | Approved |
| 55| Detke2004      | F1J-MC-HMAYa| Lilly   | Approved |
| 56| Perahia2006    | F1J-MC-HMAYb| Lilly   | Approved |
| 57| Detke2002a     | F1J-MC-HMBHa| Lilly   | Approved |
| 58| Detke2002b     | F1J-MC-HMBHb| Lilly   | Approved |
| 59| Tourian2009    | 3151A1-335 | Pfizer  | Approved |
| 60|                | M06-850    | Abbott Laboratories | Vivli | Approved |
| Page | Author(s)            | Drug ID   | Sponsor       | Platform                | Status   |
|------|----------------------|-----------|---------------|-------------------------|----------|
| 61   | Baldwin2012          | 11984A    | Lundbeck      | Lundbeck platform       | Approved |
| 62   | Boulenger2014        | 13267A    | Lundbeck      | Lundbeck platform       | Approved |
| 63   | Mahablesh warkar2013 | LuAA21004_304 | Takeda       | Lundbeck platform       | Approved |
| 64   | Mahablesh warkar2015a | LuAA21004_315 | Takeda       | Lundbeck platform       | Approved |
| 65   | Mahablesh warkar2015b | Lu_AA21004_202 | Takeda       | Lundbeck platform       | Approved |
| 66   | Sofat2017            | 11.0126   | St George's, University of London, Rosetrees Trust | Pr Harrison Dr Sofat | Approved |
| 67   | Dulo2006             | Danish Pain Research Center | Danish Pain Research Center | No answer | 3 attempts to contact dr Eriksson (two wrong mails) |
|      |                      |           |               |                         | 3 attempts to contact the DPRC |
|      |                      |           |               |                         | 3 attempts to contact the secretary of the DPRC |
| 68   | Reckziegel2007       | 13124     | University of Nottingham arthritis research UK | Contact authors: Pr D. Auer Pr Reckziegel | No answer |
|      |                      |           |               |                         | 3 attempts to contact each author by mail |
| 69   |                      | 1208.10   | Boehringer Ingelheim | No answer | |
| 70   | Tétrault2016         | STU000395 56 | Lilly/ Northwestern University | Contact author: Pr Apkarian | No answer |
| 71   | Hellerstein2012      | #4967/6363R | Lilly/ New York State Psychiatric Institute | Contact author: Pr D. Hellerstein | No answer |
| 72   |                      | IRB00003943 | Wake Forest University | Contact author: | Denial |
Table 2 presents the characteristics of eligible studies and their participants. Trials were conducted in 45 countries on five continents (South Africa, Argentina, Brazil, Canada, Mexico, Puerto-Rico, USA, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, Russia, Spain, Ukraine, China, Hong Kong, India, Israel, Japan, Korea, Malaysia, The Philippines, Taiwan, Turkey and Australia) – even though just one country was represented for Africa (South Africa, with less than <2% of African subjects in those trials). Data on countries were not available online for Detke2004 (HMAW) which took place in 3 countries, F1J-MC-HMAI which comprised 13 studies, and HMAYa where the number of countries was not reported. Trials enrolled participants of both sexes. Duloxetine dosage was determined in 76/77 trials: dosage ranged from 5 to 120 mg/day. All studies administered oral duloxetine to participants in the intervention arm. Exposition to intervention ranged from 4 to 52 weeks. Twenty-four trials explored duloxetine in major depressive disorder, 18 trials used duloxetine in urinary incontinence, 9 in osteoarthritis pain, 9 in diabetic neuropathic pain, 8 in fibromyalgia, 5 in general anxiety disorder and 4 in chronic low back pain. 71/76 studies were multicenter. All studies were in parallel design. 62/77 studies belong to the same sponsor or associated.
Table 2
Characteristics of eligible studies

| Study N| Sponsor ID | Country | Sponsor | Medical Condition | N° center | IT T or PP | Design | Duration of treatment (weeks) | Number of arms | Drugs | Mean Age (sd) | % Female | Dose Primary Outcome Quality of life score |
|--------|------------|---------|---------|-------------------|-----------|------------|--------|-------------------------------|----------------|--------|---------------|----------|---------------------------------------------|
| Skljera vs Sklja re 2010 a | F1 J- M | Internationally | CL BP | Multi center | IT T | Parallel | 13 | 2 | PB 12 | 1 | 51 | .1 | 5 | 3.46 |
| DLX | 11 | 5 | 51 | .8 | 61 | 12 | 0 | BP | EQ | 5D |
| Skljera vs Sklja re 2009 O | T M | Locally | CL BP | Multi center | IT T | Parallel | 11 | 4 | PB 17 | 7 | 53 | .9 | 7 | 1.52 |
| DLX | 59 | 52 | .9 | 61 | .0 | 20 | BP | EQ | 5D |
| DLX | 11 | 6 | 53 | .3 | 57 | .8 | 60 | |
| DLX | 11 | 2 | 54 | .9 | 58 | 12 | 0 | |
| Skljare vs Kim | F1 | J-MC-HM-GC | Internationa1 | Lil | CL | Multi | T | Parallel | PB | 3 | 63 | 0-0 | BP | EQ |
|-------|----|------------|---------------|-----|----|-------|---|----------|----|---|----|----|----|----|
|       | J-M | C-HM-GC   |               |     |    |       |   |          |    |   | 1  | 1  |    | 5D |
| 2010b |     |           |               |     |    |       |   |          |    |   | 1  | 1  |    |    |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |

| Konno | F1 | J-JE-HM-GY | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
|-------|----|------------|-------|----------|----|-------|---|----------|----|---|----|----|----|----|
|       | J-E | H-M-G-Y   | Japan | Shionogi | CL | Multi | T | Parallel | PB | 6 | 57 | 0-0 | BP | EQ |
| 2016  |     |           |       | Lil |     |       |   |          |    |   | 1  | 1  |    | 5D |
| Year | Month | Code | DL | X | V1 |  V2 |  V3 |  V4 | V5 |  V6 |  V7 |
|------|-------|------|----|---|----|----|----|----|----|----|----|
| 2006 | 4     | AV   | DL | X |    |    |    |    |    |    |    |
|      | 2     |      |    |   |    |    |    |    |    |    |    |
|      | 1     |      |    |   |    |    |    |    |    |    |    |
|      | 1     |      |    |   | 61 | 45 | 12 | 0  |    |    |    |
| 2005 | 1     |      |    |   | 59 | 54 | 0  | 0  |    |    |    |
|      | 0     |      |    |   | 58 | 58 | 60 |    |    |    |    |
|      | 0     |      |    |   | 58 | 58 |    | 12 |    |    |    |
|      | 1     |      |    |   | 59 | 48 | 0  | 0  |    |    |    |
|      | 0     |      |    |   | 60 | 48 |    | 12 |    |    |    |
|      | 0     |      |    |   | 60 | 34 | 20 |    |    |    |    |
|      | 1     |      |    |   | 59 | 30 | 60 |    |    |    |    |
|      | 0     |      |    |   | 60 | 39 | 12 |    |    |    |    |
|      | 0     |      |    |   |    |    |    |    |    |    |    |
| Country     | Date | Year of Study | Abbreviation | Study Design | Intervention Type | Participants | Age of Intervention | BP Intervention | Team | Average Pain Item of BP Intervention |
|-------------|------|---------------|--------------|--------------|-------------------|--------------|---------------------|----------------|------|-------------------------------------|
| China       | 2010 | F1            | Chinese      | DNP          | Multi-center      | Parallel     | 12                  | 2              | PB   | 10.84                              |
|             |      |               |              |              |                   |              |                     |                |      |                                     |
|             |      |               |              |              |                   |              |                     |                |      | (1.0, 84)                           |
|             |      |               |              |              |                   |              |                     |                |      |                                     |
| China       | 2015 | F1            | Chinese      | DNP          | Multi-center      | Parallel     | 11                  | 2              | PB   | 10.91                              |
|             |      |               |              |              |                   |              |                     |                |      |                                     |
|             |      |               |              |              |                   |              |                     |                |      | (9.52)                             |
|             |      |               |              |              |                   |              |                     |                |      |                                     |
| Japan       | 2011 | F1            | Japanese     | DNP          | Multi-center      | Parallel     | 12                  | 2              | PB   | 10.95                              |
|             |      |               |              |              |                   |              |                     |                |      |                                     |
|             |      |               |              |              |                   |              |                     |                |      | (9.42)                             |
|             |      |               |              |              |                   |              |                     |                |      |                                     |
| USA         | 2000 | F1            | American     | DNP          | Multi-center      | Parallel     | 6                   | 2              | PB   | 10.93                              |
|             |      |               |              |              |                   |              |                     |                |      |                                     |
|             |      |               |              |              |                   |              |                     |                |      | (9.39)                             |
|             |      |               |              |              |                   |              |                     |                |      |                                     |

Note: The table provides a snapshot of data related to various studies, including details such as country, date, and observed BP values.
| Arno Id | F1 J- USA | Lily M | Multi G | IT T | Par lel | 12 3 | PB 12 0 | 49 10 0- | Av er QL D | S |
|---------|----------|-------|--------|-----|--------|------|--------|----------|-------------|---|
| 2005    | J- MM C- H | M     | G      | center |        |      | 1      | 9 (1 1. 83) |             |   |
|         | F1 J- USA | Lily M | Multi G | IT T | Par lel | 12 3 | PB 12 0 | 49 10 0- | Av er QL D | S |
|         | J- MM C- H | M     | G      | center |        |      | 1      | 9 (1 1. 83) |             |   |

| DL X   | 11 11 6 | 8 2 8 | 48 10 0 | 60       |         |
|---------|---------|-------|---------|----------|---------|
| AV age pain item of the BP I |

| DL X   | 15 15 5 | 5 2 8 | 50 96 0- | 0       |         |
|---------|---------|-------|---------|----------|---------|
|         | J- MM C- H | M     | G      | center |        |      | 1      | 9 (1 1. 83) |             |   |

| R us se l | F1 J- USA | Lily M | Multi G | IT T | Par lel | 14 4 | PB 14 4 | 50 95 0- | Av er QL D | S |
|-----------|----------|-------|--------|-----|--------|------|--------|----------|-------------|---|
| 2008      | J- MM C- H | M     | G      | center |        |      | 1      | 9 (1 1. 83) |             |   |

| DL X   | 79 15 0 | 5 2 8 | 51 97 0 | 60       |         |
|---------|---------|-------|---------|----------|---------|
|         | F1 J- USA | Lily M | Multi G | IT T | Par lel | 14 4 | PB 14 4 | 50 95 0- | Av er QL D | S |
|         | J- MM C- H | M     | G      | center |        |      | 1      | 9 (1 1. 83) |             |   |

| DL X   | 15 15 0 | 5 2 8 | 51 97 0 | 60       |         |
|---------|---------|-------|---------|----------|---------|
|         | J- MM C- H | M     | G      | center |        |      | 1      | 9 (1 1. 83) |             |   |
| AR | F1 | U | Lil | Multi | IT | Parallel | PB | 10 | 0-0 | FI | BS | SD |
|----|----|---|-----|-------|----|----------|----|----|-----|----|----|----|
| 20 | JU | SA | M | G | MG | center | 26 | 1  | 0-0 | FI | BS | SD |
| 10 | | | | | | | 7 | 3 | 0-0 | FI | BS | SD |
| 26 | | | | | | | 3 | 4 | 0-0 | FI | BS | SD |
| 19 | | | | | | | 1  | 1 | 7 | FI | BS | SD |
| 15 | | | | | | | 5 | 2 | 0-0 | FI | BS | SD |

| AR | F1 | U | Lil | Multi | IT | Parallel | PB | 10 | 0-0 | FI | BS | SD |
|----|----|---|-----|-------|----|----------|----|----|-----|----|----|----|
| 20 | JU | SA | M | G | MG | center | 10 | 3 | 0-0 | FI | BS | SD |
| 04 | | | | | | | | | | | |

| CH | F1 | Int | Lil | Multi | IT | Parallel | PB | 16 | 0-0 | Av | S | D |
|----|----|-----|-----|-------|----|----------|----|----|-----|----|----|----|
| 20 | JM | M | I | M | MG | center | 27 | 8 | 4 | 7 | 1 | 36 |
| 08 | | | | | | | 16 | 2 | - | | |

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| Name          | F1    | U     | Lily | G     | Multi | IT | Parallel | PB  | 15 | 6 | 0-0 | 9 | 6 | 12 | 0 | BP  |
|---------------|-------|-------|------|-------|-------|----|----------|-----|-----|---|-----|---|---|----|---|-----|
| Ryann         | 2008  | J-M   | S    | A     | Multi | 6 | 2       | 40  | .9  | 8 | 6   | 40 | 0-0 | 12 | 0 | H    |
|               |       | M     | C-H  | D     | Center|    |          | (1  | 4.  | 19 |     | (1 |   |     |   |     |
|               |       |       |      |       |       |    |          |     |     |   |     |     |   |     |   |     |
|               |       |       |      |       |       |    |          | 42  | .3  | 2  | 1   | 42 | 0-0 | 12 | 0 |     |
|               |       |       |      |       |       |    |          | (1  | 3.  | 93 |     | (1 |   |     |   |     |
| Harford       | 2007  | J-M   | S    | A     | Multi | 6 | 2       | 41  | .8  | 5  | 4   | 41 | 0-0 | 12 | 0 | H    |
|               |       | M     | C-H  | D     | Center|    |          | (1  | 4.  | 23 |     | (1 |   |     |   |     |
|               |       |       |      |       |       |    |          |     |     |   |     |     |   |     |   |     |
|               |       |       |      |       |       |    |          | 40  | .3  | 2  | 1   | 40 | 0-0 | 12 | 0 |     |
|               |       |       |      |       |       |    |          | (1  | 3.  | 58 |     | (1 |   |     |   |     |
| Davenport     | 2008  | J-M   | S    | A     | Multi | 7 | 2       | 45  | .6  | 8  | 4   | 45 | 0-0 | 12 | 0 | MI   |
|               |       | M     | C-H  | D     | Center|    |          | (1  | 4.  | 05 |     | (1 |   |     |   |     |
|               |       |       |      |       |       |    |          |     |     |   |     |     |   |     |   |     |
|               |       |       |      |       |       |    |          | 58  | .6  | 9  | 12  | 58 | 0-0 | 12 | 0 |     |
|               |       |       |      |       |       |    |          | (1  | 3.  | 58 |     | (1 |   |     |   |     |

Note: The table contains data on various centers with details such as name, F1, U, Lily, G, Multi, IT, Parallel, PB, and other values.
| DL X | 21 | 44 | 61 | 60 | Improvement scale |
|------|----|----|----|----|-------------------|
|      | 3  | .9 | 1  | 12 |                   |
|      | 8  | (1 | 3  | 62 |                   |
| Ni   | J- | M |   |    |                   |
| co   | M |   |    |    |                   |
| lin | M | H |   |    |                   |
| i   | D | W |   |    |                   |
| et  |   |   |    |    |                   |
| al  |   |   |    |    |                   |
| 20  | 09|   |    |    |                   |
| DL X | 84 | 44 | 48 | 20 |                   |
|      | 5  | .7 | .8 | 1  |                   |
|      | 7  | (1 | 1  |    |                   |
|      | 3  |    | 45 |    |                   |
| DL X | 15 | 42 | 56 | 60 |                   |
|      | 8  | .5 | .9 | 6  |                   |
|      | 2  | (1 | 2  | 58 |                   |
|      | 45 |    |    |    |                   |
| K   | J- | M |   |    |                   |
| op | M | C- |   |    |                   |
| en | M | H |   |    |                   |
| 20 | 07| B |   |    |                   |
| DL X | 16 | 43 | 64 | 60 |                   |
|      | 8  | .1 | .2 | 9  |                   |
|      | 1  | (1 | 2  | 92 |                   |
|      | 2  |    |    |    |                   |
| DL X | 17 | 44 | 72 | 12 |                   |
|      | 0  | .1 | .3 | 5  |                   |
|      | 0  | (4 | 3  | 87 |                   |
| 12  | 08| E | M |    |                   |
| 0   | .1| B | D |    |                   |
|     |    | M | D |    |                   |
|     |    |   | multi |    |                   |
|     | 7  | 2 |    |    |                   |
| PB  | 16| 5 |    |    |                   |
|     | 0  | 0 |    |    |                   |
|     | 0  |    |    |    |                   |
|     |    | 0  |    |    |                   |
|     |    | 0  |    |    |                   |
|     |    | 0  |    |    |                   |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| F1 | J-M | C-H | M | A | H |   |
| One | M | Multi | IT | Par |   |   |
| country | D | center | T |allel |   |   |
| DL | 16 | 2 | 10 | 2 |   |   |
| PB | 88 | 37 | 55 | 0 |   |   |
| DL | 89 | 59 | 20 |   |   |   |
|   | X | 20 |   |   |   |   |
| F1 | J-M | C-H | M | Al |   |   |
| Interna | M | Multi | IT | Par |   |   |
| tional | D | center | T |allel |   |   |
| DL | 13 | 43 | 66 | 5 |   |   |
|   | X | 0 | 4 |   |   |   |
| F1 | J-M | C-H | M | Ata |   |   |
| USA | M | Multi | IT | Par |   |   |
|   | D | center | T |allel |   |   |
| DL | 91 | 43 | 68 | 40 |   |   |

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| DLX | D   | F1 | M | A | Ly | M | D | Multi | IT | T   | Par | lel | 8 | 3 | PB | 93 | 43 | .6 | 7 | (1 | 2 | 16 | 7 | 2 | .3 | 12 | 0 |
|-----|-----|----|---|---|----|---|---|-------|----|----|-----|-----|----|---|----|----|----|----|---|----|----|----|---|----|---|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|----|----|---|----|---
| Pe  | ra | Lil | M | Multi | IT | Pa | 7 | 3 | PB | 99 | 44 | 65 | 0- | H | S |
|-----|----|-----|---|-------|----|----|---|---|----|----|----|----|---|   |   |
| M   | A  | D   |   | center| T  | ral|   |   |    | 6  | 7  | 0  | M | D |   |
| H   | 0  | 05  |   |       |    |    |   |   |    | (1 | 2  | 70 |   |   |   |

| DL  | 93 | 46 | 66 | 80 | 7  |
|-----|----|----|----|----|----|
| X   | .4 | .7 | (1 | 2  | 70 |
|     | (1 | 0  | 75 |    |    |

| DL  | 10 | 45 | 74 | 12 | 0  |
|-----|----|----|----|----|----|
| X   | .3 | .8 | (1 | 0  | 75 |
|     | (1 | 0  | 75 |    |    |

| D   | F1 | U  | Lil | M | Multi | IT | Pa | 11 | 2 | PB | 12 | 42 | 68 | 0- | H | QL |
|-----|----|----|-----|---|-------|----|----|----|---|----|----|----|----|---|   |   |
| et  | J- | S  | M   | D | center| T  | ral|   |   |    | 4  | 3  | 0  | M | D |   |
| ke | M  |   | C   | D |       |    |    |   |   |    | (1 | 2  | 58 |   |   |   |
| 20  | H  |   | M   | D |       |    |    |   |   |    | (1 | 2  | 58 |   |   |   |
| 02  | B  |   | H   | D |       |    |    |   |   |    | (1 | 3  | 74 |   |   |   |
| a   | a  |   | b   | D |       |    |    |   |   |    | (1 | 3  | 74 |   |   |   |

| DL  | 12 | 42 | 65 | 60 | 0  |
|-----|----|----|----|----|---|
| X   | .4 | .0 | .6 | .0 |   |
|     | (1 | 3  | 74 |    |   |

| D   | F1 | U  | Lil | M | Multi | IT | Pa | 11 | 2 | PB | 13 | 41 | 71 | 0- | H | QL |
|-----|----|----|-----|---|-------|----|----|----|---|----|----|----|----|---|   |   |
| et  | J- | S  | M   | D | center| T  | ral|   |   |    | .0 | .2 | 0  | M | D |   |
| ke | M  |   | C   | D |       |    |    |   |   |    | (1 | 4  | 66 |   |   |   |
| 20  | H  |   | M   | D |       |    |    |   |   |    |   | (4 | 66 |   |   |   |
| 02  | B  |   | H   | D |       |    |    |   |   |    |   | (4 | 66 |   |   |   |
| b   | a  |   | b   | D |       |    |    |   |   |    |   | (4 | 66 |   |   |   |

| DL  | 12 | 40 | 66 | 60 | 0  |
|-----|----|----|----|----|---|
| X   | .8 | .4 | .6 | .0 |   |
|     | (1 | 2  | 56 |    |   |
|     | (1 | 2  | 56 |    |   |

| Br  | F1 | U  | Lil | M | Multi | IT | Pa | 9  | 2 | PB | 14 | 40 | 62 | 0- | Av |
|-----|----|----|-----|---|-------|----|----|----|---|----|----|----|----|   |
| an  | J- | S  | M   | D | center| T  | ral|   |   |    | .3 | .4 | 0  | e |   |
| n   | U  |   | S   | D |       |    |    |   |   |    | (1 | 3  | 5) |   |   |   |
| 20  | H  |   | M   | D |       |    |    |   |   |    | (1 | 3  | 5) |   |   |   |
| 05  | M  |   |     | D |       |    |    |   |   |    | (1 | 3  | 5) |   |   |   |

| DL  | 14 | 40 | 68 | 60 |   |
|-----|----|----|----|----|---|
|     | 40 | .4 | .0 |   |   |
|     | (1 | 3  | 5) |   |   |
|     | (1 | 3  | 5) |   |   |
| Niemeier   | F1 J-U | U S A | Lil | M D | Multi center | IT T | Parallel   | 8  | 2   | 13 | 7 | 42 | 67 | 0-0 | M S | D | S    |
|------------|--------|-------|-----|-----|--------------|------|------------|----|-----|----|---|----|----|-----|-----|---|-----|
| 2007       |        |       |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |       |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |       |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |

| Pelham     | F1 J-M | Int         | Lil | M D | Multi center | IT T | Parallel   | 52 | 2   | 14 | 2 | 48 | 74 | 0-0 | S m e | D | S    |
|------------|--------|-------------|-----|-----|--------------|------|------------|----|-----|----|---|----|----|-----|-----|---|-----|
| 2009       |        | Internatio Na l |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |              |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |              |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |

| Gaynor     | F1 J-U | Int         | Lil | M D | Multi center | IT T | Parallel   | 7  | 2   | 26 | 6 | 45 | 69 | 0-0 | M S | D | S    |
|------------|--------|-------------|-----|-----|--------------|------|------------|----|-----|----|---|----|----|-----|-----|---|-----|
| 2011       |        | Internatio Na l |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |              |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |              |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |

| Gaynor     | F1 J-U | Int         | Lil | M D | Multi center | IT T | Parallel   | 7  | 2   | 26 | 6 | 44 | 66 | 0-0 | M S | D | S    |
|------------|--------|-------------|-----|-----|--------------|------|------------|----|-----|----|---|----|----|-----|-----|---|-----|
| 2011       |        | Internatio Na l |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |              |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |              |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |

|            |        |              |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |              |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
|            |        |              |     |     |              |      |            |    |     |    |   |    |    |     |     |   |     |
| Name          | H | U | S | L | M | D | M | D | Multi | IT | Par | lel | PB | 0-0 |
|---------------|---|---|---|---|---|---|---|---|-------|----|-----|-----|----|-----|
| Munich        | 20 | 07 |     |     |     |     |     |     |     |     |     |     | 35 |     |
| Brackenheim   | 20 | 07 |     |     |     |     |     |     |     |     |     |     | 17 | 60  |
| Hellstein      | 20 | 12 |     |     |     |     |     |     |     |     |     |     | 32 |     |
| Baldwin       | 20 | 12 |     |     |     |     |     |     |     |     |     |     | 15 | 60  |

Average pain item on BP

X 1 .1 .1
5 (1.2.47)

Daily Telephone Assessment

DL X 17 60

DL X 16 .48 .75 .9

DL X 32 .41 .54 .30

DL X 5 .45 .67 .60
| B | 13 | Int | Lu | M | Multi | IT | Pa | PB | 8 | 2 | 45 | 69 | 0-0 | M | S | A | D | D | S |
|---|----|-----|----|---|-------|----|----|----|---|---|----|----|---|---|---|---|---|---|
| ou | 26 | er | nd | D | center | Par | lel | 3 | .6 | (1 | 4 | .4 | 0 | | | | | | |
| le | 7A | na | be | ck | | | | | | | | | | | | | | | |
| 20 | 14 | | | | | | | | | | | | | | | | | | |

| To | 31 | U | Pfi | M | Multi | IT | Pa | PB | 8 | 2 | 39 | 58 | 0-0 | H | A | M | D | 1 | 7 |
|---|----|---|----|---|-------|----|----|----|---|---|----|----|---|---|---|---|---|---|
| uri | 51 | S | ze | r | center | Par | lel | 4 | .2 | (1 | 2 | .4 | 0 | | | | | | |
| an | | A | | | | | | | | | | | | | | | | | |
| 20 | 33 | 09 | 5 | | | | | | | | | | | | | | | | |

| M | Lu | Int | Ta | M | Multi | IT | Pa | PB | 8 | 2 | 45 | 61 | 0-0 | D | S | D | S |
|---|----|-----|ke | D | center | Par | lel | 0 | .3 | (1 | 2 | .07 | | | | | | |
| ah | A | er | da | D | | | | | | | | | | | | | | | |
| ab | A2 | na | | | | | | | | | | | | | | | | | |
| le | 10 | tio | | | | | | | | | | | | | | | | | |
| sh | 04 | na | | | | | | | | | | | | | | | | | |
| w | 2 | l | | | | | | | | | | | | | | | | | |
| ar | 02 | | | | | | | | | | | | | | | | | | |
| 20 | 15 | 1a | | | | | | | | | | | | | | | | | |

| M | Lu | U | Ta | M | Multi | IT | Pa | PB | 7 | 2 | 42 | 60 | 0-0 | H | A | M | D | 2 | 4 |
|---|----|---|ke | D | center | Par | lel | 6 | .8 | (1 | 3 | .76 | | | | | | |
| ah | A | S | da | D | | | | | | | | | | | | | | | |
| ab | A2 | | | | | | | | | | | | | | | | | | |
| le | 10 | | | | | | | | | | | | | | | | | | |
| sh | 04 | | | | | | | | | | | | | | | | | | |
| w | _3 | | | | | | | | | | | | | | | | | | |
| ar | 04 | | | | | | | | | | | | | | | | | | |
| 20 | 13 | | | | | | | | | | | | | | | | | | |

| M | Lu | U | Ta | M | Multi | IT | Pa | PB | 7 | 2 | 42 | 72 | 0-0 | M | S | A | D | 2 | 4 |
|---|----|---|ke | D | center | Par | lel | 4 | .0 | (1 | 2 | .55 | | | | | | |
| ah | A | S | da | D | | | | | | | | | | | | | | | |
| ab | A2 | | | | | | | | | | | | | | | | | | |
| le | 10 | | | | | | | | | | | | | | | | | | |
| sh | 04 | | | | | | | | | | | | | | | | | | |
| w | _3 | | | | | | | | | | | | | | | | | | |
| ar | 15 | | | | | | | | | | | | | | | | | | |
| Country | Company | Region | Facility | Type | Site | Patients | P1 | P2 | P3 | P4 |
|---------|---------|--------|----------|------|------|----------|----|----|----|----|
| U.S.    | F1      | Single | Parallel |     |     | 10       |    |    |    |    |
| U.S.    | F1      | Multi  | Parallel |     |     | 8        |    |    |    |    |
| U.S.    | F1      | Multi  | Parallel |     |     | 13       |    |    |    |    |
| U.S.    | F1      | Multi  | Parallel |     |     | 12       |    |    |    |    |
| U.S.    | F1      | Multi  | Parallel |     |     | 12       |    |    |    |    |
| U.S.    | F1      | Multi  | Parallel |     |     | 12       |    |    |    |    |

**Notes:**
- P1, P2, P3, P4 represent different pain intensity levels.
- The data is presented in a tabular format, with columns for country, company, region, facility type, site, number of patients, and pain intensity levels.
| F1 | Int   | Lil  | OAP | Multi   | IT | Pa         | PB | 8.75 | 12  | eBP |
|----|-------|------|-----|---------|----|------------|----|------|-----|-----|
| J- | natio | ly   |     | center  | T  | Parallel   | 7  |      |     |     |
| M  | na    |      |     |         |    |            |    |      |     |     |
| H  |       |      |     |         |    |            |    |      |     |     |
| M  |       |      |     |         |    |            |    |      |     |     |
| G  |       |      |     |         |    |            |    |      |     |     |

| W  | Ch     | Lil  | OAP | Multi   | IT | Pa         | PB | 5.12 | 71  | 0-  | 0   |
|----|--------|------|-----|---------|----|------------|----|------|-----|-----|-----|
| an | na     | ly   |     | center  | T  | Parallel   | 7  |      |     |     |     |
| g  |        |      |     |         |    |            |    |      |     |     |     |
| 20 |        |      |     |         |    |            |    |      |     |     |     |
| 17 |        |      |     |         |    |            |    |      |     |     |     |

| T  | S      | U    | OAP | Multi   | IT | Pa         | PB | 5.8  | 74  | 0-  | 0   |
|----|--------|------|-----|---------|----|------------|----|------|-----|-----|-----|
| tre|        |      |     | center  | T  | Parallel   | 7  |      |     |     |     |
| au|        |      |     |         |    |            |    |      |     |     |     |
| lt|        |      |     |         |    |            |    |      |     |     |     |
| 20 |        |      |     |         |    |            |    |      |     |     |     |
| 16 |        |      |     |         |    |            |    |      |     |     |     |

| S  | U      | OAP | Multi   | IT | Pa         | PB | 0-  | 0   |
|----|--------|-----|---------|----|------------|----|-----|-----|
| of |        |     | center  | T  | Parallel   |    |     |     |
| at|        |     |         |    |            |    |     |     |
| 20 |        |     |         |    |            |    |     |     |
| 17 |        |     |         |    |            |    |     |     |

| DL | X      |     |     |     |     |     |     |     |     |     |
|----|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 21 |        |     |     |     |     |     |     |     |     |     |
| 17 |        |     |     |     |     |     |     |     |     |     |
| 21 |        |     |     |     |     |     |     |     |     |     |
| Study | Country/Region | Participants | Type of Study | Number of Sites | Intervention | Data Collection | Results | Comments |
|-------|----------------|--------------|---------------|----------------|--------------|----------------|---------|----------|
| Zinner, 1998 | UK, Germany | Single center | Parallel | 3 | PB | DL | 84 | 0.0-0.4 | Decreaser of baseline stress and weight |
| Uchi, 2018 | Japan | Multi-center | Parallel | 12 | PB | DL | 60 | 0.0-0.4 | Average pain item of the BPQ |
| Reckziegel, 2017 | UK, Germany | Single center | ITT | 4 | PB | DL | 60 | 0.0-0.4 | Brain functional connectivity |
| | | | | | | | | |
| F1 | Japan | Multi-center | ITT | 12 | PB | DL | 80 | 0.0-0.4 | Average pain item of the BPQ |
| | | | | | | | | |
| F1 | Japan | Multi-center | crossover | 8 | PB | DL | 30 | 0.0-40 | Average pain item of the BPQ |
| | | | | | | | | |
| Activity Index | DL | X | .4 | tivity Index | DL | X | .4 |
|---------------|----|---|----|-------------|----|---|----|
|               | 8  | 2 |    |             | 10 | 0 | 0  |
|               |    |   |    |             | 8 | 2 |    |
|               | PB | 28| 54 |             | IE | 10| 80 |
|               |    | 40|    |             | EQ | 80| 0  |
|               |    |   |    |             |    |   |    |
|               | 52 | 53| 10 |             | IE | 60| 0  |
|               |    |   |    |             | EQ | 60| 0  |
|               |    |   |    |             |    |   |    |
|               | DL | 55| 54 |             | IE | 12| 0  |
|               |    | 0 |    |             |    |   |    |
|               |    |   |    |             |    |   |    |
|               | DL | 13| 53| 10          | IE | 20| 0  |
|               |    |   |    |             |    |   |    |
|               |    |   |    |             |    |   |    |
|               | DL | 12| 52| 10          | IE | 40|    |
|               |    |   |    |             |    |   |    |
|               |    |   |    |             |    |   |    |
|               | DL | 13| 53| 10          |    |   |    |
|               |    |   |    |             |    |   |    |
|               |    |   |    |             |    |   |    |
|               | DL | 12| 52| 10          |    |   |    |
|               |    |   |    |             |    |   |    |
|               |    |   |    |             |    |   |    |
|               | DL | 13| 53| 10          |    |   |    |
|               |    |   |    |             |    |   |    |
|               |    |   |    |             |    |   |    |
| Country | F1 | J-E | W-S | B | C | Intern | Lil | Ul | Multi | IT | Parallel | PB | 13 | 55 | 10 | 0 | 0- | IE | F | K | H | Q |
|---------|----|-----|-----|---|---|--------|-----|----|-------|----|-----------|----|----|----|----|---|----|----|---|---|---|---|
| Car | 20 | do | zo | 10 | | 6 | 2 | PB | 13 | 55 | 10 | 0 | 0- | IE | F | K | H | Q |
| 20 | 10 | | | | | 6 | 2 | 13 | 55 | 10 | 0 | 0- | IE | F | K | H | Q |
| Lin | 20 | | | | | 8 | 2 | PB | 61 | 56 | 10 | 0 | 0- | IE | F | I- | Q | OL |
| 20 | 08 | | | | | 8 | 2 | 61 | 56 | 10 | 0 | 0- | IE | F | I- | Q | OL |
| Mah | 20 | | | | | 8 | 2 | PB | 60 | 48 | 10 | 0 | 0- | IE | F | I- | Q | OL |
| 20 | 06 | | | | | 8 | 2 | 60 | 48 | 10 | 0 | 0- | IE | F | I- | Q | OL |
| Dom | 12 | | | | | 12 | 2 | PB | 33 | 53 | 10 | 0 | 0- | IE | F | I- | Q | OL |
| 12 | 2 | | | | | 12 | 2 | 33 | 53 | 10 | 0 | 0- | IE | F | I- | Q | OL |
| Date  | F1 J-MC-S | Int. | Lil. | UL-S | Multi | IT | T  | Parallel | PB | 52 | 10 | 0 | IE | I-Q OL | I-Q OL |
|-------|-----------|------|------|------|-------|----|----|----------|----|-----|-----|---|----|--------|--------|
| 2003  | 4         | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
|       | 4         | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
| 2004  | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
|       | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
| 2005  | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
|       | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |

---

| Date  | F1 J-MC-S | Int. | Lil. | UL-S | Multi | IT | T  | Parallel | PB | 52 | 10 | 0 | IE | I-Q OL | I-Q OL |
|-------|-----------|------|------|------|-------|----|----|----------|----|-----|-----|---|----|--------|--------|
| 2003  | 4         | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
|       | 4         | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
| 2004  | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
|       | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
| 2005  | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
|       | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |

---

| Date  | F1 J-MC-S | Int. | Lil. | UL-S | Multi | IT | T  | Parallel | PB | 52 | 10 | 0 | IE | I-Q OL | I-Q OL |
|-------|-----------|------|------|------|-------|----|----|----------|----|-----|-----|---|----|--------|--------|
| 2003  | 4         | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
|       | 4         | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
| 2004  | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
|       | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
| 2005  | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
|       | 10        | 0    |      |      |       |    |    |          |    |     |     |   |    |        |        |
Risk of bias within studies

Figure 2 provides details of the risk of bias assessment from data available online. 35 trials were assessed as being at an overall low risk of bias. Thirty-one trials were assessed as being at unclear risk of bias and 1 at high risk of bias. In this latter study (Perahia2009, HMDI), participants were randomized to duloxetine or placebo after a 32-week exposition to duloxetine, at risk of selecting subjects with a better tolerability to duloxetine.

Conclusion

To our knowledge, this study would represent the first meta-analysis investigating the safety and utility of duloxetine in elderly population across all conditions approved by European and American regulatory authorities.

Reported results are solely based on online available data. While these suggest an overall low risk of bias across eligible studies, sponsors are yet to be contacted to fully describe characteristic of patients and studies, as to appraise the effective risk of bias of each study. Afterward, a comparison between our current results and results obtained after personal communication with the sponsor can provide an interesting indicator of sponsors’ transparency on trials with duloxetine. While 58 studies have been approved for sharing data, these studies all belong to the same sponsor, owner of the duloxetine. The other sponsors are still evaluating our proposal, have not answered to our proposal or have denied to share their data. In addition, IPD data can only
be processed in independent platforms forbidding the direct aggregation of data from other data sharing platforms. These hurdles highlight current issues in realizing one-step IPD meta-analysis when multiple sources are concerned, for both industrial and academic sponsors.

The scope of our meta-analysis is intended to benefit to a wide range of medical specialties as an help for the prescribers and as a better care for elderly population. Furthermore, our study exemplifies current possibilities and limits of sharing of individual data in meta-research.

**Abbreviations**

CI: Confidence Interval

EMA: European Medical Agency

FDA: Food Drug Administration

IPD: Individual participant data

nsAE: Non-serious adverse event

OR: Odds-Ratio

RCT: Randomized controlled trial

SAE: Serious adverse event

SF36: 36-Item Short Form Survey

**Declarations**

**Patient’s and Public Involvement**

Patients were not involved in the development of the research question and study design.

**Availability of data and materials**

The dataset analyzed during the current study is not publicly available due to the terms of the data sharing agreements signed with Vivli but are available from the Vivli data sharing platform on reasonable request. For one study, the data are available from the corresponding author on reasonable request.

**Competing interests**

All authors have no conflict of interests to declare.

**Author’s contributions**
JCR participated in the development of the study protocol and writing of the manuscript and is responsible for data extraction and eligibility review. CR participated in the study protocol analysis plan and will be responsible for final analyses. AJ is responsible for data and eligibility review. FN developed the study design and protocol analysis plan and supervises the realization of the study. GR participated in the development of the study protocol and supervises the realization of the study.

All authors read and approved the final manuscript.

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Figures
Figure 1. PRISMA flow diagram of included studies

Figure 1

PRISMA flow diagram of included studies
Figure 2. Methodological quality summary: review authors’ judgements about each methodological quality item for each included study

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- Additionalfile1.docx
- Additionalfile2.docx
- Additionalfile4.docx
- Additionalfile3.docx