This study H0P-MC-BP05 (NCT05630196) is a sub-study of Master Protocol H0P-MC-CPMP (NCT05986292)

H0P-MC-BP05: Statistical Analysis Plan Version 2

Randomized, Placebo-Controlled, Phase 2 Clinical Trial to Evaluate LY3857210 for the Treatment of Chronic Low Back Pain

NCT05630196

Approval Date: 27-Jun-2023

1. Statistical Analysis Plan: H0P-MC-BP05: Intervention-Specific Appendix (ISA) for LY3857210

LY3857210 for the Treatment of Chronic Low Back Pain

This is a randomized, placebo-controlled, Phase 2 clinical trial to evaluate LY3857210 for the treatment of chronic low back pain.

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Protocol H0P-MC-BP05
Phase 2

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3. Abbreviations and Definitions

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
API	average pain intensity
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMA	Bayesian model averaging
BP05	H0P-MC-BP05
cLDA	constrained longitudinal data analysis
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CPMP	H0P-MC-CPMP
CTR	Clinical Trial Registry
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
FDA	United States Food and Drug Administration
FMQ	FDA Medical Query
GCP	good clinical practice
GFR	glomerular filtration rate

Term	Definition
ISA	intervention-specific appendix
LDA	longitudinal data analysis
LLT	lowest level term
LY	LY3857210
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
NRS	numeric rating scale
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PD	pharmacodynamic
PDEP	preliminary data entry period
PK	pharmacokinetic
CCI	[redacted]
PT	preferred term
PTEAE	Post-treatment-emergent adverse event
QTcF	Fridericia's corrected QT interval
RMDQ	Roland-Morris Disability Questionnaire
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ToE	totality of evidence
ULN	upper limit of normal
VAS	visual analog scale

4. Revision History

SAP Version 1 was approved on 20 January 2023 prior to unblinding data for Study H0P-MC-BP05 (BP05).

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- Section 7.12.3: change SMQ to FMQ, which is FDA new standard.

CCI

- Section 7.18: added seizures in the totality of evidence of safety.

5. Study Objectives

5.1. Primary Objective

The primary objective of this ISA is stated in the H0P-MC-CPMP (a) protocol. See Section 7.10.1 for more details on the primary analysis method. For Study BP05, endpoint is defined as 8 weeks post initial treatment administration at Visit 7. Unless otherwise specified, the time point for secondary endpoint measurements is the same as the primary endpoint.

5.2. Secondary Objectives

Secondary objectives applicable to all ISAs are listed in the Study CPMP SAP Version 5.

Additional secondary endpoints specific to Study BP05 are listed in Table BP05.5.1.

Table BP05.5.1. Additional Secondary Endpoints Specific to Study H0P-MC-BP05

Objective	Endpoint Measure
Other Secondary	
Physical Functioning Efficacy of LY3857210 versus placebo	• Mean change from baseline to endpoint in RMDQ total score • Proportion of participants with reduction from baseline of at least 3.5 points in RMDQ total score at each time point • Proportion of participants with reduction from baseline greater than or equal to 30%, 50%, and 70% in RMDQ total score at each time point • Time to first treatment response with at least 30%, 50%, and 70% reduction from baseline in RMDQ total score

Abbreviation: RMDQ = Roland-Morris Disability Questionnaire.

5.3. Exploratory Objectives

Exploratory objectives and endpoints specific to Study BP05 are shown in Table BP05.5.2.

6. Study Design

6.1. Summary of Study Design

The CPMP protocol provides a summary of the overall study design for the chronic pain master protocol. ISA-specific study design is provided in the BP05 protocol.

6.2. Determination of Sample Size

Up to approximately 125 participants will be randomized in a CCI to LY3857210 and placebo, respectively. It is expected that approximately 80% of participants, will complete the double-blind treatment period of the study. CCI

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CCI If there is no treatment difference between placebo and LY3857210, the probability of passing the primary objective specified above (that is, false positive rate) is approximately 0.04. The simulation for the power calculation and sample size determination was carried out using the R package simfast v1.3.0.9000.

6.3. Method of Assignment to Treatment

The method of treatment assignment is described in the CPMP SAP Version 5.

7. A Priori Statistical Methods

7.1. General Considerations

The estimand for the primary clinical question of interest has been described in the CPMP SAP Version 5.

Unless otherwise specified, efficacy and safety analyses will be conducted for the 8-week double-blind period and separately for the entire 10-week study period.

Other general considerations for analyses are described in the CPMP SAP Version 5.

7.2. Adjustments for Covariates

The general adjustment strategy has been described in the CPMP SAP Version 5.

Randomization into Study BP05 is stratified by the presence of neuropathic pain as defined by the painDETECT score. Stratification factors included in the models for the primary, secondary, and some exploratory outcomes are show in Table BP05.7.1.

Table BP05.7.1. Stratification Factor Included in Models for Primary, Secondary, and Exploratory Outcomes

Neuropathic pain	painDETECT score
Positive presence	≥19
Unclear or negative	<19

The painDETECT total score is derived from patient responses to 9 questions on the painDETECT questionnaire. Seven questions ask about the gradation of pain, scored from 0 to 5 (never = 0, hardly noticed = 1, slightly = 2; moderately = 3, strongly = 4, very strongly = 5). One question asks about the pain course pattern, scored from −1 to 2, depending on which pain course pattern diagram is selected. Another question asks about radiating pain, answered as yes or no and scored as 2 or 0, respectively. The final score is between −1 and 38, and a score of 19 or higher suggests that pain is likely to have a neuropathic component (Freynhagen et al. 2006).

7.3. Handling of Dropouts or Missing Data

The missing data strategy has been described in the CPMP SAP Version 5.

7.4. Multiple Comparisons/Multiplicity

There is no plan to formally adjust for multiplicity.

7.5. Use of an “Efficacy Subset” of Participants

There are no plans to use a modified efficacy subset.

7.6. Participant Disposition

The summary of participant disposition has been described in the CPMP SAP Version 5.

7.7. Participant Characteristics

The summary of participant characteristics has been described in the CPMP SAP Version 5.

ISA-specific considerations are described below:

- painDETECT ≥19 (that is, positive for neuropathic pain)
- RMDQ total score at baseline.

7.8. Treatment Compliance

Treatment percentage of compliance will be calculated as:

$$\frac{Total\ pills\ taken * 100}{Total\ pills\ expected}\%$$

with total pills taken calculated by total pills dispensed minus total pills returned. A patient is considered to be compliant for a given period if this percentage is between 80% and 120%. Treatment compliance will be assessed at Visits 5 and 7 (and early discontinuation visit, if applicable); at Visits 4 and 6, the investigational product will not be returned to the site. Treatment compliance will be reported for the 8 weeks of the treatment period (Visit 3 to 7). The percentage of patients who are compliant with study drug will be summarized by treatment group. For patients who discontinue early, time after the penultimate visit will be excluded for calculation of treatment compliance. For example, if patient discontinued early at Visit 6, treatment compliance will be derived only from data collected through Visit 5. Comparisons between treatment group for treatment compliance will be performed using a Fisher's Exact test. Listings for treatment compliance of individual patients by treatment period will also be provided.

Depending on the level of observed treatment compliance, and where appropriate, sensitivity analyses of primary endpoints may be conducted by excluding patients with poor treatment compliance.

7.9. Concomitant Therapy and eCOA Compliance

The summary and reporting of concomitant therapy and eCOA compliance has been described in the CPMP SAP Version 5. As described in Section 6.2, painDETECT will additionally be included as a covariate for modelling rescue medication.

Concomitant therapy will be reported separately for the 8 weeks of the double-blind period and for the entire 10-week study period.

7.10. Efficacy Analyses

7.10.1. Primary Outcome and Methodology

The analysis of the primary outcome has been described in the CPMP SAP Version 5, and it constrains baseline means to be equal between arms. CCI [redacted]

CCI As noted in Section 5, endpoint for the primary analysis is defined as 8 weeks post initial treatment administration.

Calculation of the weekly/bi-weekly time intervals used for analysis of weekly/biweekly mean scores from the eCOA device will follow the algorithm described in the CPMP SAP Version 5, Section 6.12.1, except that the end of the final interval will be determined based on the last VAS collection date, or the last scheduled visit start date if VAS results are missing for the last scheduled visit.

7.10.2. Additional Analyses of the Primary Outcome

Descriptive statistics of primary outcome variables by demographics, disposition, disease characteristics, and treatment administration may be summarized by ISA, in order to examine the population homogeneity assumption between ISAs.

7.10.3. Secondary Efficacy Analyses

Secondary efficacy analyses common to all ISAs within CPMP have been described in the CPMP SAP Version 5. Unless otherwise specified, the time point for secondary endpoint measurements is the same as that for the primary endpoint. Study BP05 will also consider the following secondary analyses.

The RMDQ is a simple, sensitive, and reliable method to measure disability in patients with back pain. The RMDQ consists of 24 statements relating to the person's perceptions of back pain and associated disability based on:

- physical ability/activity
- sleep/rest
- psychosocial
- household management
- eating, and
- pain frequency.

Participants are asked if they feel the statement is descriptive of their own circumstance on that day. The total score is obtained by counting the number of ‘‘Yes’’ responses, ranging from 0 = no disability to 24 = maximal disability.

A Bayesian longitudinal MMRM analysis will be performed to evaluate the change from baseline to each postbaseline visit in the RMDQ total score. The model will utilize the cLDA so that a common mean is estimated at baseline. More details on this approach are provided in the CPMP SAP Version 5.

Information included in the model is shown in Table BP05.7.2.

Table BP05.7.2. Information Included in Bayesian Longitudinal MMRM to Evaluate the Change from Baseline to Each Postbaseline Visit in the RMDQ Total Score

Categorical effects	• The interaction of treatment and timepoint (constrained to estimate a common mean at baseline across treatments) • Average baseline pain severity category (baseline NRS <7, baseline NRS ≥7) • Presence of neuropathic pain (painDETECT ≥19, painDETECT <19) • Pooled investigative site
Continuous covariates	• None

Abbreviation: NRS = numeric rating scale.

Other Secondary Analysis

The proportion of participants in each treatment group meeting prespecified binary efficacy outcomes will be calculated for each postbaseline time point and will be used to compare treatment groups. The prespecified binary efficacy outcomes include the proportion of participants:

- with a reduction greater than or equal to 30%, 50%, and 70% from baseline as measured by the RMDQ score, and
- with at least a 3.5-point reduction from baseline in the RMDQ score.

A Bayesian pseudo-likelihood–based categorical repeated measures model will be used to estimate the proportion of participants in each treatment group meeting the prespecified threshold for each postbaseline time interval up to Week 8. These estimates will be used to compare treatment groups. More details on this approach are provided in the CPMP SAP Version 5.

The model will include the categorical and continuous covariates described for the secondary analysis of RMDQ total score.

In addition, time to first treatment response from baseline based on the prespecified binary thresholds above will be assessed. Analyses will be conducted according to the time to event analyses specified in the CPMP SAP Version 5.

7.11. Pharmacokinetic/Pharmacodynamic Methods

The plasma concentrations for LY3857210 will be reported graphically and summarized descriptively across the study visits.

Exploratory model-based analyses may be conducted to assess the relationship of LY3857210 plasma concentrations to efficacy and/or safety outcomes.

Additional analyses may be conducted, as needed.

Data from this study may be pooled with data from other studies.

7.12. Safety Analyses

The general analysis of safety has been described in the Study CPMP SAP Version 5. However, additional ISA-specific safety considerations are described in the sections below.

7.12.1. Extent of Exposure

Duration of exposure (defined as time since first dose of study treatment to last dose of study treatment in days) to study drug will be summarized by treatment group using descriptive statistics; the summary will also include the total exposure in patient years.

Duration of exposure (days):

> Date of last dose during the double-blind treatment period – Date of first dose for the treatment period + 1.

Total exposure in patient years will be calculated as follows:

> Summary of duration (days) of exposures for all participants in the treatment group / 365.25.

7.12.2. Adverse Events

The general analysis of AEs has been described in the CPMP SAP Version 5.

This ISA will report TEAEs separately for the entire 8-week double-blind period, the 2-week post-treatment period, and the entire 10-week study. For TEAEs in the double-blind period, the baseline will be prior to first dose date.

A PTEAE is defined as an event that first occurs or worsens in severity after double-blind treatment phase (after Visit 7) and on or before study discontinuation. This ISA will report PTEAEs for the post-treatment period, as they are important for assessing withdrawal or abuse liability potential. The MedDRA LLT will be used in the post-treatment-emergent computation. The maximum severity for each LLT during the double-blind treatment period (Visits 3 through 7) will be used as a reference.

The baseline of PTEAE is from the first dosing date to Visit 7. The post-treatment phase will be included as postbaseline for this analysis. While unusual, it is possible to have a missing severity for events. CCI
CCI
CCI and PTEAEs will be determined by comparing with treatment period.

PTEAEs will be summarized by PT and by PT within SOC in participants who received LY3857210.

7.12.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

TEAEs by PT will be reported.

The general summary of AEs is described in the CPMP SAP Version 5. Other AEs include

- Abuse liability and withdrawal potential following the most recent Lilly Guidance for Assessment of Abuse Potential during Clinical Development.
- Seizures FMQ both narrow and broad terms will be analyzed.

7.12.4. Neurological Exam

In this ISA, neurological exam results will be reported for the entire 10-week study period. Study BP05 will consider the following analyses for the Neurological Exam, which evaluates 6 items and will be summarized by normal/abnormal percentage by item. In addition, we will summarize shift tables for each item in the Neurological Exam.

7.12.5. Clinical Laboratory Evaluation

The general analysis of laboratory parameters is described in the CPMP SAP Version 5.

In this ISA, laboratory results will be reported for the entire 10-week study period. Study BP05 will also consider the following analyses of lab analytes used to assess renal function. The planned summaries for these analytes are the same as those that have been described in the Study

CPMP SAP Version 5; however, the reporting of these analytes will be separate from the general analysis of laboratory parameters.

- Renal data analyses:
  - Serum creatinine (change from baseline in mg/dL)
  - eGFR; Chronic Kidney Disease Epidemiology Collaboration algorithm using serum creatinine) Algorithm: Provided by central laboratory
  - For eGFR calculation, we will summarize shift tables of eGFR changes for baseline versus postbaseline by minimum, maximum, and last observed eGFR result:
    - Category 1: Normal or increase in GFR (≥90 mL/min/1.73m^2)
    - Category 2: Mild reduction in GFR (60 to 89 mL/min/1.73m^2)
    - Category 3a: Moderate (a) reduction in GFR (45 to 59 mL/min/1.73m^2)
    - Category 3b: Moderate (b) reduction in GFR (30 to 44 mL/min/1.73m^2)
    - Category 4: Severe reduction in GFR (15 to 29 mL/min/1.73m^2)
    - Category 5: Kidney failure (GFR <15 mL/min/1.73m^2 or dialysis).

Abnormal eGFR is specified below and will be summarized in the laboratory summary tables.

- Abnormal low: < 90 mL/min/1.73m^2
- Abnormal high: As specified by central laboratory.

7.12.6. Vital Signs and Other Physical Findings

The analysis of vital sign parameters is described in the CPMP SAP Version 5.

Vital signs will be reported separately for the 8-week treatment period and the entire 10-week study period.

7.12.7. Electrocardiograms

The analysis of ECG parameters is described in the CPMP SAP Version 5. ECG will be reported separately for the 8-week treatment period and the entire 10-week study period.

7.12.8. Suicidal Ideation or Behavior

Reporting of suicidal ideation/behavior through the Columbia Suicide-Severity Rating Scale has been described in the CPMP SAP Version 5. Suicidal ideation/behavior will be reported separately for the 8-week treatment period and the entire 10-week study period.

7.13. Subgroup Analyses

General subgroup analyses are described in the CPMP SAP Version 5.

Subgroup analyses considered for the primary outcome are shown in Table BP05.7.3.

Table BP05.7.3. Subgroup Analyses for Primary Outcome

Subgroup Variable	Categories
Neuropathic pain	Categories: Positive presence (painDETECT total score ≥19) Unclear or negative (painDETECT total score <19)

The subgroup analyses will be conducted using similar modeling approaches as the primary analysis. Additional factors in the model are described in the CPMP SAP Version 5. The treatment difference at the endpoint will be reported within each level of the subgroup factor along with 95% credible intervals. Frequentist MMRM may be performed as a sensitivity analysis using the modeling approach described in the CPMP SAP Version 5.

7.14. Protocol Deviations

Participants with study important protocol deviations will be summarized by type of deviation and listed by treatment and investigative site.

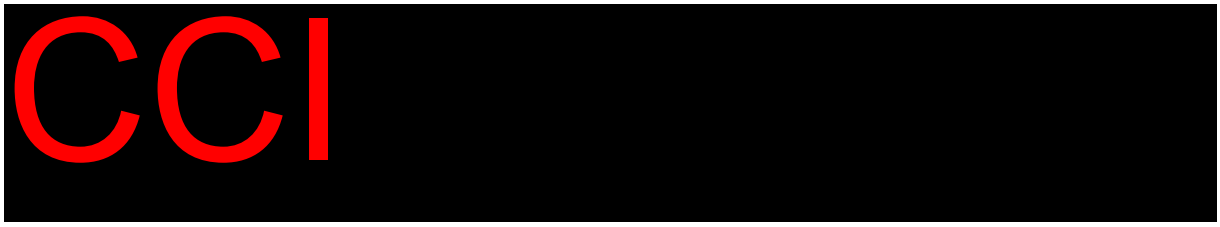
Important protocol deviations for the study are described in the CPMP and Study BP05 Trial Issue Management Plans.

7.15. Interim Analyses and Data Monitoring

Safety review will be conducted under the auspices of an Assessment Committee according to the specifications set forth in the protocol. These analyses will be at the CPMP level and will consider data from all ongoing ISAs. Details are provided in the CPMP SAP Version 5. No interim analyses are planned for Study BP05. Unplanned interim analyses may be conducted for reasons including futility analyses, early efficacy analyses, safety analyses, or other analyses, if deemed needed for key business decisions and planning.

7.16. Planned Exploratory Analyses

The following analyses may be conducted for exploratory purposes:



7.17. Totality of Evidence for Efficacy

The totality of evidence analysis approach for efficacy data has been briefly described in the CPMP SAP Version 5. A multivariate Bayesian model will be fit within each ISA to assess efficacy ToE across domains. To inform the aggregation of model-based estimates for domain scores, important weights for each scale within a domain are described in Table BP05.7.4.

7.18. Totality of Evidence for Safety

The totality of evidence analysis approach for safety data has been briefly described in the CPMP SAP Version 5. The key safety events to be considered for Study BP05 are listed below by domain:

General Adverse Event Information

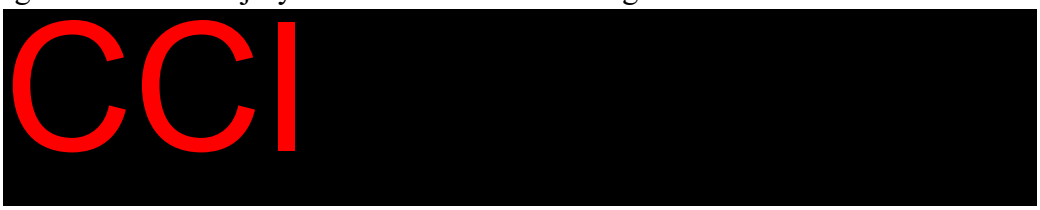
- Serious AEs including death related to study treatment
- Study discontinuation due to AE
- Treatment discontinuation due to AE.

Cardiovascular

- QTcF prolongation: >60 msec increase or QTcF >500 msec
- Serious cardiac disorders AE.

Liver function

- Drug-induced liver injury: at least 1 of the following 2 conditions:



Metabolic function

- Serious hypoglycemia AE
- Serious hyperglycemia AE
- Treatment-emergent hemoglobin A1c: Shift from low/normal at baseline to high at least once.

Renal function

- Treatment-emergent abnormal eGFR: Shifts
  - Mild at baseline to moderate/severe
  - Moderate at baseline to severe.

Neurologic function

- Treatment-emergent abnormal shift on the overall neurologic assessment
- Serious neurologic events
- Seizures FMQ both narrow and broad terms.

7.19. Annual Report Analyses

Analyses will be produced as needed for the purposes of providing periodic safety reviews to regulatory agencies (for example, Development Safety Update Reports). Data from this ISA will be combined with data from other clinical studies that investigated LY3857210. In all analyses, a combined LY arm will be created which includes participants assigned to any dose of LY3857210 in the included studies, including LY-combination regimens.

The following data will be summarized by treatment group.

- enrollment (ongoing and completed)
- demographics (race, ethnicity, and gender)
- exposure
    - cumulative number of subjects exposed to LY3857210
    - cumulative number of subjects exposed to LY3857210 by age
    - cumulative number of subjects exposed to LY3857210 by sex
    - cumulative number of subjects exposed to LY3857210 by race
- cumulative summary of serious AEs.

The following listings will be provided.

- list of serious AEs during the reporting period
- list of subjects who died
- cumulative list of subjects who discontinued due to an AE (discontinued from treatment or study), and
- list of subjects who discontinued due to an AE during the reporting period.

Additional analyses may be added or omitted at the time of report submission as needed.

7.20. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the CTR requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset that will be converted to an XML file. Both “Serious” AEs and “Other” AEs are summarized by treatment group and by MedDRA PT.

- A serious AE is an AE that is considered “Serious” whether or not it is a treatment emergent.

- An AE is considered in the "Other" category if it is both a TEAE and is not serious. For each "Serious" AE and "Other" AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, "Other" AEs that occur in fewer than 5% of participants in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the Clinical Study Report and manuscripts.

8. Unblinding Plan

The general unblinding plan is described in the CPMP SAP Version 5 and in the CPMP Blinding and Unblinding Plan Version 2. Unblinding considerations specific to Study BP05 are provided below.

PK/PD Analysis Planning

A limited number of prespecified individuals who are not part of the blinded study team and do not have direct site contact, data entry, or data validation responsibilities, may receive access to unblinded data, prior to an interim or final database lock, to initiate the PK and/or PK/PD model development processes. This will be described in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

9. References

Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22(10):1911-1920. https://doi.org/10.1185/030079906x132488

Silva L, Zanella G. Robust leave-one-out cross-validation for high-dimensional Bayesian models. 2022. https://doi.org/10.48550/arXiv.2209.09190