Sistema Socio Sanitario
Regione Lombardia
ATS Brescia

Agenzia di Tutela della Salute di Brescia
Sede Legale: viale Duca degli Abruzzi, 15 – 25124 Brescia
Tel. 030.38381 Fax 030.3838233 - www.ats-brescia.it - informa@ats-brescia.it
Posta certificata: protocollo@pec.ats-brescia.it
Codice Fiscale e Partita IVA: 03775430980

DECRETO n. 106 del 24/02/2017

Cl.: 1.1.02

OGGETTO: Approvazione bozza di convenzione con la Società Oxon Epidemilogy Limited per lo Studio "Dolore neuropatico localizzato (Localised Neuropatic Pain, LNP) gestito nel contesto delle cure primarie in Francia, Irlanda, Italia, Spagna e Regno Unito: uno studio trasversale di prevalenza, caratteristiche cliniche e di trattamento, e stato di salute autoriferito da pazienti" promosso da Grunenthal GmbH.

Il DIRETTORE GENERALE - Dr. Carmelo Scarcella
nominato con D.G.R. X/4615 del 19.12.2015

Acquisiti i ***pareri*** del
DIRETTORE SOCIOSANITARIO Dr.ssa Annamaria Indelicato
e del
DIRETTORE AMMINISTRATIVO Dott.ssa Teresa Foini

Sistema Socio Sanitario
Regione Lombardia
ATS Brescia

IL DIRETTORE GENERALE

Richiamati:
- il Decreto del Ministero della Salute del 10.05.2001 "Sperimentazione Clinica controllata in Medicina Generale e in Pediatria di Libera Scelta" con cui sono state regolamentate le attività di sperimentazione clinica dei medicinali di fase III e fase IV effettuate dai Medici di Medicina Generale e dai Pediatri di Libera Scelta;
- il Decreto del Direttore Generale Sanità della Regione Lombardia n. 27931 del 21.11.2001 ad oggetto "Linee Guida Regionali applicative del Decreto del Ministero della Sanità 10 Maggio 2001 in materia di sperimentazione clinica in medicina di base ed in pediatria di libera scelta";
- il Decreto D.G. n. 286 del 12 luglio 2016 con cui è stata istituita la "Commissione per la Sperimentazione Clinica Controllata in Medicina Generale e Pediatria di Libera Scelta" dell'ATS di Brescia;

Premesso che la Società Oxon Epidemiology Limited, in data 18.11.2016 (atti ATS prot. n. 0103293/16), per conto di Grunenthal GmgH, ha inoltrato richiesta per l'effettuazione dello Studio "Dolore neuropatico localizzato (Localised Neuropatic Pain, LNP) gestito nel contesto delle cure primarie in Francia, Irlanda, Italia, Spagna e Regno Unito: uno studio trasversale di prevalenza, caratteristiche cliniche e di trattamento, e stato di salute autoriferito da pazienti" con il coinvolgimento di n. 1 Medico di Medicina Generale dell'ATS di Brescia;
Preso atto che il Comitato Etico Provinciale, in data 15.11.2016, ha espresso parere favorevole allo Studio proposto (Atti ATS prot. n. 0000230/17), che coinvolge n. 1 Medico di Medicina Generale;
Considerato che la Commissione per la Sperimentazione Clinica Controllata in Medicina Generale e Pediatria di Libera Scelta, nella seduta del 07.12.2016:
- ha preso atto della compatibilità degli obiettivi dello Studio in questione con la migliore assistenza possibile ai pazienti non inclusi nello Studio stesso;
- ha rilevato che lo Studio non reca pregiudizio ai compiti previsti dagli accordi, compresi quelli regionali e i suggerimenti di cui alle recenti Linee Guida;
- ha valutato lo schema di convenzione, che regola, tra l'altro, gli aspetti economico/finanziari e definisce i requisiti che devono essere posseduti dai Medici Sperimentatori;
- ha valutato favorevolmente lo Studio, come da nota ATS prot. n. 0109941 del 13.12.2016, previa comunicazione dei criteri adottati per l'individuazione dell'unico Medico di Medicina Generale partecipante allo Studio;

Preso atto che la Commissione per la Sperimentazione Clinica Controllata in Medicina Generale e Pediatria di Libera Scelta ha recepito la nota di chiarimenti relativa ai criteri di individuazione dell'unico Medico di Medicina Generale partecipante allo Studio, pervenuta in data 25.01.2017 (Atti ATS prot. n. 0007733 del 25.01.2017);
Ritenuto, pertanto, di approvare la bozza di convenzione con la Società Oxon Epidemiology Limited per lo Studio "Dolore neuropatico localizzato (Localised Neuropatic Pain, LNP) gestito nel contesto delle cure primarie in Francia, Irlanda, Italia, Spagna e Regno Unito: uno studio trasversale di prevalenza, caratteristiche cliniche e di trattamento, e stato di salute autoriferito da pazienti" promosso da Grunenthal GmgH di cui all'Allegato "A" (composto da n. 37 pagine) al presente provvedimento e parte integrante dello stesso;
Evidenziato che la Società Oxon Epidemiology Limited si impegna a corrispondere ad ATS un importo pari ad € 25,00 + IVA per lo screening di ciascun paziente (n. 100 pazienti) con Dolore Neuropatico Localizzato e ad € 80,00 + IVA per ogni paziente arruolato dallo Sperimentatore e per la compilazione delle CRF;

Vista la proposta presentata dal Direttore Sanitario, Dr. Fabrizio Speziani, qui anche Responsabile del procedimento, che attesta la regolarità tecnica del presente provvedimento;
Vista l'attestazione del Direttore del Servizio Risorse Economico-Finanziarie, Dott.ssa Lara Corini, in ordine alla regolarità contabile;
Dato atto che il parere del Direttore Sanitario è assorbito nella funzione esercitata dal medesimo in qualità di proponente;
Acquisiti i pareri del Direttore Sociosanitario, Dr.ssa Annamaria Indelicato e del Direttore Amministrativo, Dott.ssa Teresa Foini che attesta, altresì, la legittimità del presente atto;

D E C R E T A

a) di approvare la bozza di convenzione con la Società Oxon Epidemiology Limited per lo Studio "Dolore neuropatico localizzato (Localised Neuropatic Pain, LNP) gestito nel contesto delle cure primarie in Francia, Irlanda, Italia, Spagna e Regno Unito: uno studio trasversale di prevalenza, caratteristiche cliniche e di trattamento, e stato di salute autoriferito da pazienti", promosso da Grunenthal GmgH, di cui all'Allegato "A" (composto da n. 37 pagine) al presente provvedimento e parte integrante dello stesso;
b) di precisare che la convenzione verrà sottoscritta dal Direttore Sanitario, Dr. Fabrizio Speziani, delegato con Decreto D.G. n. 286 del 12.07.2016;
c) di prendere atto che in data 13.12.2016 il Promotore ha versato la somma di € 1.500,00 (esclusa IVA), quale corrispettivo dovuto per l'esame della domanda;
d) di registrare i ricavi discendenti dal presente provvedimento al Conto "Sperimentazione farmaci comm." cod. 77.7.221 Bilancio Sanitario anni 2016, 2017 e 2018 quantificati come segue:
   - € 1.500,00 (esclusa IVA) per l'esame della domanda;
   - € 1.000,00 (esclusa IVA) per la stipula della convenzione;
   - € 25,00 + IVA per lo screening di ciascun paziente (n. 100 pazienti) con Dolore Neuropatico Localizzato ed € 80,00 + IVA per ogni paziente arruolato dallo Sperimentatore e per la compilazione delle CRF, corrisposti da Oxon Epidemiology Limited al termine della sperimentazione, previa emissione di idonea fattura, per la remunerazione del Medico Sperimentatore;
   - un importo corrispondente al 20% dell'eccedenza se il compenso totale per lo Sperimentatore supera € 20.000,00 (esclusa IVA), entro 60 dalla fine dello Studio;
e) di precisare che i costi derivanti dal presente provvedimento relativamente al corrispettivo spettante al Medico Sperimentatore (quantificato in € 25,00 + IVA per lo screening di ciascun paziente (n. 100 pazienti) con Dolore Neuropatico Localizzato ed € 80,00 + IVA per ogni paziente arruolato dallo Sperimentatore e per la compilazione delle CRF saranno registrati nella contabilità dell'Agenzia – Bilancio Sanitario al conto "assistenza medico generica comm." cod. 43.3.105 – programma di spesa n. 14011 - e riconosciuti al Medico Sperimentatore solo ad incasso avvenuto da parte di ATS e previa presentazione di fattura da parte del Medico stesso all'ATS;
f) di trasmettere copia del presente provvedimento all'Agenzia Italiana del Farmaco (Ufficio Sperimentazione Clinica) e alla Direzione Generale Welfare (U.O. Programmazione Rete Territoriale – Struttura Cure Primarie) a cura della Direzione Sanitaria;
g) di precisare che gli oneri relativi all'imposta di bollo saranno assolti dall'ATS secondo le modalità di cui al D.M. del 17.06.2014, art. 6;

h) di demandare alla Direzione Sanitaria la comunicazione al Servizio Risorse Economico-Finanziarie entro il 31 gennaio di ciascun anno, dell'imposta di bollo dovuta per i conseguenti adempimenti;
i) di dare atto che il presente provvedimento è sottoposto al controllo del Collegio Sindacale, in conformità ai contenuti dell'art. 3-ter del D.Lgs. n. 502/1992 e ss.mm.ii. e dell'art. 12, comma 14, della L.R. n. 33/2009;
j) di disporre, a cura della U.O. Affari Generali, la pubblicazione all'Albo on-line – sezione Pubblicità legale - ai sensi dell'art. 17, comma 6, della L.R. n. 33/2009, e dell'art. 32 della L. n. 69/2009, ed in conformità al D.Lgs. n. 196/2003 e secondo le modalità stabilite dalle relative specifiche tecniche.

Firmato digitalmente dal Direttore Generale
Dr. Carmelo Scarcella

CONVENZIONE PER L’EFFETTUAZIONE DELLO STUDIO DENOMINATO
“Dolore neuropatico localizzato (Localised Neuropatic Pain, LNP) gestito nel contesto delle cure primarie in Francia, Irlanda, Italia, Spagna e Regno Unito: uno studio trasversale di prevalenza, caratteristiche cliniche e di trattamento, e stato di salute autoriferito da pazienti”

TRA

l'AGENZIA per la TUTELA della SALUTE di BRESCIA (di seguito denominata "AGENZIA"), con Sede Legale in Brescia, Viale Duca degli Abruzzi n. 15, Codice Fiscale e Partita IVA n. 03775430980, di cui il Rappresentante Legale è il Direttore Generale, Dr. Carmelo Scarcella, rappresentata per la firma del presente atto dal Direttore Sanitario, Dr. Fabrizio Speziani, delegato con Decreto D.G. n. 286 del 12 luglio 2016,

E

La Società OXON EPIDEMIOLOGY LIMITED con sede legale in C/Doctor Fleming 51, 28036 Madrid Codice Fiscale e Partita IVA 931917613 rappresentata dal Dr.Nawab Qizilbash, domiciliato c/o OXON EPIDEMIOLOGY LIMITED in quanto legalmente abilitato dalla medesima a rappresentare all’esterno la volontà a impegnarsi, anche patrimonialmente per essa (d’ora innanzi denominata “PROMOTORE”),

PREMESSO

- che è intenzione del PROMOTORE effettuare, ai sensi del D.M. 10 maggio 2001 (pubblicato sulla G.U. n.139 del 18 giugno 2001) e della Circolare Ministeriale n.6 del 2 settembre 2002, lo Studio Osservazionale denominato “Dolore neuropatico localizzato (Localised Neuropatic Pain, LNP) gestito nel contesto delle cure primarie in Francia, Irlanda, Italia, Spagna e Regno Unito: uno studio trasversale di prevalenza, caratteristiche cliniche e di trattamento, e stato di salute autoriferito da pazienti (d'ora innanzi denominato "STUDIO"), avente lo scopo di descrivere le caratteristiche cliniche e di trattamento dei pazienti LNP individuati tra i pazienti con dolore cronico in cure primarie in cinque paesi europei, specificamente Francia (FR), Irlanda (IE), Italia (IT), Spagna (SP) e Regno Unito (UK);
- che il PROMOTORE è un’Azienda basata sulla ricerca di nuovi principi attivi farmaceutici e la loro successiva messa a punto per il migliore trattamento e la cura delle malattie, in particolare nel campo del Dolore Neuropatico Localizzato, è quindi suo interesse migliorare le conoscenze scientifiche su queste patologie;
- che il PROMOTORE ha ideato e messo a punto uno Studio Osservazionale dal titolo “Dolore neuropatico localizzato (Localised Neuropatic Pain, LNP) gestito nel contesto delle cure primarie in Francia, Irlanda, Italia, Spagna e Regno Unito: uno studio trasversale di prevalenza, caratteristiche cliniche e di trattamento, e stato di salute autoriferito da pazienti”, secondo i criteri di inclusione indicati nel Protocollo, allegato alla presente convenzione;
- che all’ATS di Brescia afferisce n. 1 Medico di Medicina Generale, individuato da apposito elenco conservato agli atti istruttori della Commissione per la Sperimentazione Clinica Controllata in Medicina Generale e Pediatria di Libera Scelta, che ha dato la propria adesione a partecipare allo Studio;
- che lo STUDIO non prevede indagini diagnostiche o interventi terapeutici aggiuntivi, rispetto alla pratica ambulatoriale abituale;
- che il Protocollo è stato sottoposto al Comitato Etico Provinciale, che ha preso atto dello Studio in questione in data 15/11/2016 (Atti ATS prot. n. 0000230/17);
- che la Commissione per la Sperimentazione Clinica Controllata in Medicina Generale e

Pediatria di Libera Scelta dell’ATS di Brescia:

1. ha valutato che lo STUDIO è coerente e non interferisce con le priorità di assistenza, formazione e ricerca dell’ATS;
2. ha verificato che quanto richiesto dallo STUDIO garantisce comunque la miglior assistenza possibile ai pazienti non inclusi nello STUDIO stesso e non reca pregiudizio ai compiti previsti dagli accordi convenzionali, ivi compresi quelli regionali;
3. ha valutato che le procedure incluse nel protocollo dello STUDIO non costituiscono un aggravio assistenziale particolare e corrispondono a quanto previsto per una normale “buona assistenza”;
4. ha preso atto che lo STUDIO prevede l'utilizzo del farmaco da sperimentare nel rispetto delle indicazioni d’uso Autorizzate all’Immissione in Commercio in Italia;
5. ha valutato che per l’espletamento dello STUDIO sono individuati i seguenti specifici requisiti professionali e strutturali da parte del Medico di Medicina Generale coinvolto (in seguito denominato Sperimentatore):
   - iscrizione nell’apposito Registro Sperimentatori dell’ATS di Brescia;
   - puntuale trasmissione all'ATS dei reports informativi previsti nell'ambito del Governo Clinico;
   - iscrizione alla Mailing-list del Dipartimento Cure Primarie;
   - dichiarazione di situazioni che non configurino conflitto di interessi;
   - dichiarazione di conformità delle procedure diagnostiche e valutative alla pratica clinica corrente;
6. ha definito che lo Sperimentatore può dedicare allo studio al massimo 50 minuti per paziente, comunque non superiore a un totale di 20 ore;
7. ha preso atto che è Sperimentatore il Medico di Medicina Generale in possesso dei requisiti richiesti, individuato nell’apposito elenco conservato agli atti.

SI CONVIENE E SI STIPULA QUANTO SEGUE

ART. 1 – Premesse.
Le premesse formano parte integrante della presente convenzione.

ART. 2 – Oggetto della convenzione.
Il PROMOTORE affida all'AGENZIA l’incarico di eseguire lo STUDIO, in conformità al PROTOCOLLO, con la massima diligenza e professionalità; l’AGENZIA si avvarrà di n.1 Sperimentatore, che tratterà, in via previsionale, 20 pazienti.
Il Centro Sperimentale dovrà condurre lo STUDIO secondo le modalità ed i termini descritti nel protocollo intitolato “Dolore neuropatico localizzato (Localised Neuropatic Pain, LNP) gestito nel contesto delle cure primarie in Francia, Irlanda, Italia, Spagna e Regno Unito: uno studio trasversale di prevalenza, caratteristiche cliniche e di trattamento, e stato di salute autoriferito da pazienti identificato con codice OXON 05715 di seguito definito PROTOCOLLO.
Durante e al termine dell’incarico, lo SPERIMENTATORE dovrà inviare al PROMOTORE tutte le schede raccolta dati (CRF) debitamente compilate, in formato elettronico o cartaceo.
Durante l’incarico, lo SPERIMENTATORE dovrà segnalare le reazioni avverse analogamente a quanto previsto dalle norme in vigore per le segnalazioni spontanee post-marketing.
Le parti convengono che lo STUDIO sarà condotto autonomamente dall’AGENZIA e per essa dallo SPERIMENTATORE, sotto la propria piena ed esclusiva responsabilità, per quanto attiene gli eventuali trattamenti di dati personali dei pazienti o soggetti coinvolti nello STUDIO, in piena conformità all’informativa ai cittadini ed alle disposizioni ex art. 76 e segg. del D.Lgs. n.196 del 30/06/2003 – Codice in Materia di Protezione Dati Personali, in particolare sul trattamento dei dati nell’ambito del Progetto CRS – SISS, promosso dalla regione Lombardia, per avvalersi delle più avanzate tecniche di sicurezza.

ART. 3 – Responsabili dello STUDIO
Il Responsabile Scientifico dello STUDIO, per il PROMOTORE, è la Dr.ssa Annalisa Rubino.

Il Coordinatore Scientifico individuato è la Dr.ssa Annalisa Rubino in qualità di Formatore.

ART. 4 – Conduzione dello STUDIO.
Lo STUDIO dovrà essere condotto in conformità alle vigenti disposizioni emanate nella Circolare del Ministero della Salute n. 6 del 2 settembre 2002, denominata "Attività dei Comitati Etici istituiti ai sensi del Decreto ministeriale 18 marzo 1998" ed eseguito secondo le clausole ed i metodi descritti nel PROTOCOLLO, in ottemperanza a quanto disposto dal Comitato Etico Provinciale.
Lo STUDIO dovrà essere effettuato nel rispetto della normativa vigente in materia di tutela della privacy relativamente al trattamento dei dati personali, con particolare riguardo a quello dei dati sensibili.
Si precisa che in nessun caso verranno forniti al PROMOTORE dati personali, ma solo ed esclusivamente informazioni e dati anonimi di carattere statistico e/o in forma aggregata.
Il PROMOTORE dichiara e garantisce che non è prevista polizza assicurativa in quanto trattasi di Studio Osservazionale;
L’AGENZIA dichiara e garantisce che:

- lo Sperimentatore coinvolto nello STUDIO è autorizzato a condurre la sperimentazione;
- lo Sperimentatore è autorizzato a partecipare all’iniziativa formativa propedeutica allo STUDIO, organizzata dal PROMOTORE.

ART. 5 – Consenso informato.
Lo SPERIMENTATORE, prima di iniziare lo STUDIO, deve acquisire il consenso scritto informato del paziente secondo lo schema allegato al PROTOCOLLO.

ART. 6 – Numero di pazienti da arruolare nello STUDIO.
Lo SPERIMENTATORE partecipante potrà includere nello STUDIO n. 20 pazienti.

ART. 7 – Durata.
La presente convenzione decorrerà dalla data di sottoscrizione della stessa fino alla compiuta realizzazione dell’Incarico, che avverrà entro e non oltre il termine ultimo di 14 mesi dalla partenza dello studio.
Qualora lo STUDIO non si concluda entro il termine stabilito, le Parti, previa richiesta scritta del PROMOTORE, a mezzo lettera raccomandata A.R. all'AGENZIA, ovvero tramite PEC, con un preavviso di almeno 90 giorni, possono prorogare la convenzione sino al termine necessario per la conclusione dello STUDIO.
Nel caso in cui lo STUDIO, non conclusosi, non venga prorogato, il PROMOTORE corrisponderà all’Agenzia i compensi effettivamente maturati fino a quel momento.

ART. 8 – Formazione propedeutica allo STUDIO.
Il PROMOTORE si impegna ad attivare, a proprie spese, una specifica iniziativa formativa rivolta allo Sperimentatore, in accordo con l’AGENZIA e comunicandone la data di inizio.

ART. 9 – Corrispettivo di pagamento all’AGENZIA.
Il PROMOTORE si impegna a corrispondere all’AGENZIA:
a) Euro 1.000,00 (IVA esclusa) da versare alla stipula della Convenzione;
b) Euro 25,00 + IVA per lo screening di ciascun paziente (nr 100 pazienti) con Dolore Neuropatico Localizzato
c) Euro 80,00 + IVA per paziente arruolato e per la compilazione delle CRF
da corrispondere allo SPERIMENTATORE entro 60 giorni dalla fine dello STUDIO;
d) un importo corrispondente al 20% dell’eccedenza se il compenso totale per lo Sperimentatore supera i 20.000,00 Euro (IVA esclusa), entro 60 giorni dalla fine dello STUDIO.
L’importo di cui ai punti b) e c) verrà corrisposto a fine studio mediante bonifico bancario, previo invio di fattura da parte dell’AGENZIA, con l’indicazione dello SPERIMENTATORE e dei

pazienti arruolati dallo stesso, intestata ed inviata a:
OXON Epidemiology Ltd
200 Northcote Road, London E17 7DH UK
P.IVA 931917613
C.F. 931917613

ART. 10 – Riconoscimento economico al Centro Sperimentale.
Al termine dello STUDIO, l’AGENZIA garantisce il riconoscimento economico previsto allo SPERIMENTATORE che ha eseguito l’incarico di cui all’art.2.

ART. 11 – Responsabilità Civile e Assicurazione.
Il PROMOTORE solleva l’AGENZIA da ogni responsabilità per danni diretti e/o indiretti conseguenti allo Studio e dichiara che l’assicurazione per tale STUDIO è ricompresa nell’ambito della copertura assicurativa prevista per l’ordinaria attività clinica generale svolta dal Medico Sperimentatore.

ART. 12 – Risoluzione della convenzione/Interruzione dello Studio.
In tutti i casi di grave inadempimento, anche di una sola clausola, della convenzione da parte dei Contraenti e/o dei contenuti dello STUDIO da parte del PROMOTORE, si applicheranno le norme del codice civile in materia di risoluzione per inadempimento.
L’AGENZIA si riserva il diritto di interrompere lo STUDIO prima del termine previsto qualora, secondo il giudizio della Commissione e nell’esercizio dei propri compiti di sorveglianza (DM 10/05/2001, Allegato 1, art. 3.1.6) si ravvisino problematiche che pregiudichino la normale “buona assistenza”.
Il PROMOTORE si riserva il diritto di interrompere lo STUDIO prima del termine previsto qualora, secondo i criteri di valutazione concordati con il Responsabile Scientifico dello STUDIO stesso, l’arruolamento dei soggetti non soddisfi criteri qualitativi e/o quantitativi, oppure la registrazione dei dati rilevati sia inaccurata e/o incompleta, con irrimediabile perdita dei dati di interesse.
Il PROMOTORE si riserva inoltre il diritto di interrompere lo STUDIO prima del termine previsto, qualora motivi legati a decisioni interne non ne consentano, oggettivamente, la prosecuzione.
Qualora lo STUDIO venga anticipatamente interrotto per il verificarsi di una delle cause di risoluzione della convenzione, il PROMOTORE corrisponderà all'AGENZIA i compensi effettivamente maturati fino a quel momento.
La notizia dell'interruzione verrà data alla controparte entro 30 giorni tramite Raccomandata A.R., ovvero tramite PEC, e sarà comunicata anche al Responsabile Scientifico dello STUDIO e – per Suo tramite – allo Sperimentatore.

ART. 13 – Segretezza.
L’AGENZIA s’impegna a mantenere segrete le notizie e le informazioni fornite dal PROMOTORE per l'esecuzione dello STUDIO e a non rivelarle a chicchessia, se non previo consenso scritto del PROMOTORE stesso, impegnandosi altresì a non usare le stesse ad altro scopo che esuli quello inerente lo STUDIO.
L’AGENZIA s’impegna altresì ad estendere tale obbligo allo Sperimentatore e a qualunque altra persona che, per qualsiasi motivo, dovesse venire a conoscenza di tali notizie ed informazioni.

ART. 14 – Proprietà dei risultati dello Studio.
Si precisa che, con il presente contratto, lo Sperimentatore trasmette i dati dello Studio al PROMOTORE che ne acquisisce tutti i diritti esclusivi.
Viene riservata al PROMOTORE la piena proprietà di tutte le informazioni, anche se non brevettabili, nonché dei brevetti e di ogni altro diritto di privativa industriale risultanti dallo STUDIO, fatti salvi i diritti alla paternità di autore, ai sensi delle vigenti leggi.
Nel caso in cui dallo STUDIO scaturissero informazioni brevettabili, il PROMOTORE avrà la

facoltà, ma non l’obbligo, di chiedere, a nome proprio o di una consociata, la brevettazione dei risultati, in Italia e all’estero, sopportandone le relative spese.

ART. 15 – Pubblicazione dei risultati dello Studio.
A STUDIO concluso, il PROMOTORE s’impegna a comunicare all’AGENZIA i risultati dello stesso, attraverso la stesura di un rapporto finale, completo dell’autorizzazione alla pubblicazione dei dati.
L’AGENZIA avrà il diritto di utilizzare i dati derivanti dalla stessa a fini didattici, in comunicazioni a congressi e per pubblicazioni scientifiche.
Eventuale diniego da parte del PROMOTORE dovrà essere validamente motivato.
L’AGENZIA dovrà citare il PROMOTORE nella pubblicazione.

ART. 16 – Rapporti con il Medico Sperimentatore.
Le prestazioni oggetto della presente Convenzione non possono comunque configurare un rapporto subordinato fra il PROMOTORE e il Medico di Medicina Generale Sperimentatore afferente, in regime di convenzione, all’AGENZIA.

ART. 17 – Referente amministrativo.
E' identificato, in nome e per conto del PROMOTORE, quale referente per gli aspetti amministrativi dello STUDIO in questione il Dr. Lorenzo Passarini.

ART. 18 – Modifiche alla convenzione.
Eventuali modifiche della presente convenzione potranno essere effettuate, previo accordo tra le Parti contraenti, solo tramite la stesura di apposite modifiche scritte.

ART. 19 – Registrazione e imposta di bollo.
La seguente scrittura privata è soggetta all’imposta di bollo fin dall’origine, ai sensi del D.P.R. 26 ottobre 1972, n. 642 – Allegato A – Tariffa parte I – articolo 2, che risulta a carico del contraente.
Il PROMOTORE si impegna pertanto a corrispondere all’AGENZIA – entro il termine di 90 giorni dalla data di sottoscrizione del presente accordo – un importo pari all’imposta complessiva dovuta.
Il presente atto è soggetto a registrazione solo in caso d'uso, ai sensi dell'art. 5, 2° comma, D.P.R. n. 131/86. Le spese di registrazione sono a carico della parte richiedente.

ART. 20 – Privacy.
Con riferimento al disposto del Decreto Legislativo n.196/2003, concernente la tutela dei dati personali, le parti si danno reciprocamente atto di essere a conoscenza del fatto che i dati relativi al proprio Ente verranno dall'altra parte conservati ed utilizzati al fine di adempiere agli obblighi contenuti in questo contratto. Pertanto, con la firma di questo contratto, le parti intendono anche esprimere esplicitamente il proprio consenso ai trattamenti sopra descritti e nei limiti delle finalità sopraccitate.
Le parti prendono altresì atto dei diritti a loro riconosciuti sulla tutela dei dati personali ed in particolare del diritto di richiedere l’aggiornamento, la rettifica o la cancellazione degli stessi, in caso di loro uso difforme da quanto previsto dalla Legge.

ART. 21 – Foro competente.
Per qualsiasi controversia derivante dall’applicazione ed interpretazione della presente convenzione, sarà competente in via esclusiva il Foro di Brescia, con espressa esclusione di qualsiasi altro Foro, generale e facoltativo.

Letto, approvato e sottoscritto in forma digitale.

Per l’ATS di BRESCIA
Per delega del Direttore Generale
(Decreto DG n. 286 del 12 luglio 2016)
Il Direttore Sanitario
Dr. Fabrizio Speziani

Per la Società OXON EPIDEMIOLOGY LIMITED
Il Legale Rappresentante
Dr. Nawab Qizilbash

Allegato: Protocollo di Studio composto da n. 31 pagine.

Observational Study

Localised Neuropathic Pain (LNP) managed in the primary care setting in France, Ireland, Italy, Spain, and the United Kingdom: A cross-sectional study of prevalence, clinical characteristics, treatment patterns and patient's reported outcomes

Protocol number	OXON-05715
Protocol version identifier	1.5
Date of last version of protocol	02/06/2016
Research question and objectives	The objectives of the study are: • To describe clinical characteristics and patterns of treatment of Localised Neuropathic Pain (LNP) patients; • To evaluate patient's health status (self-administered EQ-5D questionnaire and the CPSI scale); • To estimate the prevalence of LNP among patients treated in the primary care in each of the study countries.
Countries of study	France (FR), Ireland (IE), Italy (IT), Spain (SP), United Kingdom (UK)
Author	**Annalisa Rubino** Director of Risk Management Epidemiology OXON Epidemiology 200 Northcote Road, London E17 7DH, UK Telephone: +44 (0)7764577484 Email: annalisa.rubino@oxonepi.com

Study Sponsor

Study Sponsor	**Grünenthal GmbH** **52099 Aachen, Germany** **phone: +49 241 5 69 2532** **fax: +49 241 5 69 1830**
Grünenthal contact person	**Karin Kleutgens (Dipl. Biol.)** Associate Director – Retail Products & Field Engagement Medical Affairs Europe and North America Grünenthal GmbH 52099 Aachen, Germany phone: +49 241 5 69 2532 fax: +49 241 5 69 1830 mobile: +49 160 97825267 *Email:* Karin.Kleutgens@grunenthal.com

STUDY TEAM

Name	Company	Function	Contact details
Karin Kleutgens	Grünenthal	Associate Director – Retail Products & Field Engagement Medical Affairs Europe and North America	Grünenthal GmbH 52099 Aachen, Germany phone: +49 241 5 69 2532 fax: +49 241 5 69 1830 mobile: +49 160 97825267 Email: Karin.Kleutgens@grunenthal.com
Annalisa Rubino	OXON Epidemiology	*Project Director* – Director of Risk Management Epidemiology	1 Euston Square, 40 Melton Street, London, NW1 2FD, UK Tel: +44 (0)7764577484 Email: annalisa.rubino@oxonepi.com
Lorenzo Dominguez	OXON Epidemiology	Project Manager	C/ Dr Fleming 51, 28036 Madrid (Spain) Tel: +34 91 345 9395 Email: lorenzo.dominguez@oxonepi.com
Ivan Alcolea	OXON Epidemiology	Project Associate	Tel: +34 91 345 9395 Email: ivan.alcolea@oxonepi.com
Marta Mariño	OXON Epidemiology	PV Director	Tel: +34 606 128 708 Fax: +34 91 359 2447 Email: marta.marino@oxonepi.com
Raul Sanchez	OXON Epidemiology	Data Management Director	Tel: +34 91 345 9395 Email: raul.sanchez@oxonepi.com
Ignacio Mendez	OXON Epidemiology	Director of Data Analytics	Tel: +34 91 345 9395 Email: ignacio.mendez@oxonepi.com
Esther Artime	OXON Epidemiology	Research Associate in Risk Management and Medical Writer	Tel: +34 91 345 9395 Email: esther.artime@oxonepi.com

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AE	Adverse Events
AR	Adverse Reaction
CIOMS	Council for International Organizations of Medical Sciences
CPSI	Chronic Pain Sleep Inventory
CRF	Case Report Form
CRO	Clinical Research Organisation
DMP	Data Management Plan
DPN	Diabetic Peripheral Neuropathy
EC	Ethics Committees
eCRF	electronic Case Report Form
eDC	electronic Data Capture
EQ-5D	EuroQol five Dimensions
GP	General Practitioner
ICF	Informed Consent Form
ICSR	Individual Case Safety Reporting
LBP	Low Back Pain
LNP	Localised Neuropathic Pain
NHS	National Healthcare System
PHN	Post-herpetic Neuralgia
PIS	Patient Information Sheet
PV	Pharmacovigilance
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation

3. RESPONSIBLE PARTIES

The execution of this protocol is the responsibility of the following parties:

Study Conduct	OXON Epidemiology will conduct the study on behalf of Grünenthal GmbH. OXON Epidemiology (OXON), a contract research organisation delegated to serve as the study coordinating centre, will be the Grünenthal representative for this study. OXON is responsible for overall conduct, deliverables and timelines for the study and communication with Grünenthal.
Study Sponsor	Grünenthal GmbH is the sponsor and will cover the legal aspects of the study such as indemnity and insurance.

4. ABSTRACT

Title: Localised Neuropathic Pain (LNP) managed in the primary care setting in France, Ireland, Italy, Spain, and the United Kingdom: A cross-sectional study of prevalence, clinical characteristics and treatment patterns, patient's reported outcomes.

Version: 1.5 (02/06/2016)

Rationale and Background

- Neuropathic pain represents a major burden in primary care and it can be challenging to manage. Patient's self-reported health status and pain-related sleep disturbance may provide valuable insights when assessing the responses to treatment for chronic pain;
- Neuropathic pain is often localised and therefore amenable to topical therapeutic interventions; however Localised Neuropathic Pain (LNP), as defined in the literature, is not yet commonly understood, nor mentioned in treatment guidelines, which could impact the choice of appropriate therapy;
- Topical treatment can offer a better management of the pain, in that topical medications can bypass those adverse events associated with systemic therapy that often limit dosage titration and optimal pain management;
- This study aims to fill knowledge gap on clinical characteristics, treatment patterns, patient's reported health status and prevalence of LNP patients managed in primary care in each of the study countries.

Study objectives

The primary objective of the study is:

To describe clinical characteristics and patterns of treatment of LNP patients identified among chronic pain patients in primary care in five European countries, namely France (FR), Ireland (IE), Italy (IT), Spain (SP) and the United Kingdom (UK).

The secondary objectives of the study are:

- To evaluate patient's health status (self-administered EQ-5D questionnaire/Chronic Pain Sleep Inventory, CPSI);
- To estimate the prevalence of LNP among patients managed in the primary care in each of the study countries.

Study design

Observational cross-sectional study of patients presenting signs and symptoms of LNP in the primary care setting of 5 EU countries: FR, IT, IE, SP, UK.

Population

The study population is the primary care population of chronic pain patients presenting signs and symptoms of LNP, as defined by Mick et al, 2014 (1).

Inclusion Criteria

- Patient presents signs and symptoms of LNP
- Patient is able to understand and complete the consent form and patient questionnaires
- Patient is 18 years or older at the time of screening
- Patient signed the Informed Consent

Exclusion Criteria

- Patient is currently participating in another study (interventional or non-interventional)
- Patient has been already included in the study

Study Setting

The study aims to select at least 50 General Practitioners (GPs; i.e. 10 in each study country), depending of the number of eligible patients at each sites. Information on the adult patient population in the clinic of all GPs who accept to participate to the study will be retrieved. This information will consist on the number of patients of 18 years old or more by gender and age groups. This information from every GP will be filed into a GP Population Study Table. The GPs will be required to identify in their database all patients ≥ 18 years old with a record of chronic pain by selected medical codes and to invite them to book an appointment. Anonymized information on patient's age, gender and diagnostic codes qualifying them as chronic pain patients will be registered into a Study Logbook. During the booked visit the GP will screen patients by means of the study screening tool and will identify patients presenting signs and symptoms of LNP. A selection of the relevant codes to record chronic pain will be conducted in the medical dictionary in use in primary care in each study country (e.g. ICD9, ICD10 etc.). The screening tool has been described in the literature and consists of the evaluation of the chronic pain history coupled, the evaluation of distribution of symptoms and sensory signs, and the examination of the location and size of the painful area (1).

Eligible patients will be invited to participate to the study. Patients who sign an informed consent will be enrolled as study patients. The result of the screening for each screened patient (positive identification of LNP [Yes/No/Unavailable for screening]), along with the participation in the study and the reason for not participating, where applicable, will be noted into the corresponding record of the Study Logbook. The GP (or dedicated person at the site) will provide clinical and treatment data of study patients by means of an electronic Case Report Form (eCRF). Patient characteristics including demographic, lifestyle, medical history, clinical characteristics of pain, and previous and current treatment characteristics will be collected. Additionally, patients will be requested to fill in the EQ-5D and the CPSI questionnaires. Information from GPs and questionnaires as filled in by the patients will be later merged with the eCRF in a single data source.

The opportunistic enrolment of patients who present themselves at a study site, irrespective of the invitation to book an appointment, will be also undertaken whenever feasible. No follow up of patients is planned.

Participating GPs will receive training on the overall scope and procedures of the study. In order to facilitate the identification of LNP study patients and to warrant some consistency across study sites and countries, participating GPs will receive expert training on the optimal use of the LNP screening tool.

Variables

A study Case Report Form (CRF) will collect data about LNP study patients. These include but are not limited to the following:

- Demographic (e.g. age, gender)
- Lifestyle characteristics (Body Mass Index, smoking status, alcohol abuse)
- Clinical characteristics of pain: Duration of LNP, Localization, Current pain intensity
- Aetiology: PHN, painful DPN, post-surgery NP, neuropathic LBP, mastectomy or other cancer NP
- Co-morbidities: diabetes, depression, CV, cancer, inflammation
- Current and previous treatment of neuropathic pain
- Treatment with anti-inflammatory products

Additionally, study patients will be required to self-report about their health status by means of the EQ-5D and CPSI questionnaires.

Data sources

A web-based electronic Data Capture (eDC) system will be used to collect CRF data and patient's responses to EQ-5D and CPSI questionnaires and to create the study database for analysis.

The study will have three data sources:

- The eDC which will be used to address the study primary objective and for the description of the patient's health status (EQ-5D and CPSI scores);
- The Study Logbook which will be used as a secondary data source for the assessment of the study conduct, representativeness of included patients, generalizability of study results and to estimate the prevalence of LNP among chronic pain patients;
- The GP Population Study Table which will be used as an external data source to estimate the prevalence of LNP among the general population.

Study size

The study population will include a total of 1000 patients with LNP (e.g. 200 patients in each study country).

Data analysis

The primary endpoints for this cross-sectional study are the following:

- Clinical characteristics of LNP patients;
- Patterns of treatments of LNP patients.

In addition, the study will quantify:

- Patient's self-reported health status (EQ-5D and CPSI scores).
- Prevalence of patients presenting sign and symptoms of LNP among patients managed in primary care. Estimates will result from the number of patients positive to the screening for LNP over the total number of patients screened, where the patients screened are those with a record of chronic pain registered in the Study Logbook.

Analyses will be mainly descriptive in nature. Categorical data will be summarized by counts and percentages. Continuous data will be summarized using number, mean, standard deviation (SD), median, quartiles, minimum and maximum and in the case of non-normally distributed data, median, range and interquartile range. All statistical tests used for comparisons to assess differences or associations will be 2-sided and conducted at the 0.05 alpha level. P-values will be presented to three decimal places.

A detailed statistical analysis plan (SAP) will be developed and approved before final database lock and will include methods of analysis and presentation and table shells. All analyses will be performed using SAS 9.4 (or higher) statistical software (SAS, Cary, North Carolina, USA).

Milestones

The ethics approvals in each of the study countries are planned to be completed within four months from completion of this protocol. Data collection will start six months after project start and will be completed within five months. The final study report is expected to be available 14 months after project start.

It is anticipated that the preparation of a manuscript for publication in a peer reviewed journal will start in parallel with the development of the final study report.

5. AMENDMENTS AND UPDATES

None

Number	Date	Section	Amendment/update	Reason
1	[Date]	[Text]	[Text]	[Text]
2	[Date]	[Text]	[Text]	[Text]
3	[Date]	[Text]	[Text]	[Text]
4	[Date]	[Text]	[Text]	[Text]
5	[Date]	[Text]	[Text]	[Text]

6. MILESTONES

The timelines below are subject to receiving timely approvals from national competent authorities and ethics committees.

Milestone	Planned date
Project Start	March 2016
Protocol Agreement with Sponsor	April 2016
Ethics and R&D approvals	4 months (May – August 2016)
Start of data collection	Sept 2016
End of data collection	Jan 2017
Final study report	May 2017
Submission of Publication	June 2017

7. RATIONALE AND BACKGROUND

7.1. Background

Chronic pain is a debilitating condition and can pose a major burden on the affected individuals and the society overall. The prevalence of chronic pain especially of neuropathic origin (i.e. neuropathic pain) has been shown to be 7-8 % of the general population in selected EU countries, although the frequency of chronic pain has been reported to increase in the adult population and it is more prevalent among the elderlies (2–4). Neuropathic pain (NP) is often misdiagnosed or underdiagnosed and patients can experience a trail of treatment errors, with personal and social negative impact.

Neuropathic Pain originates from a lesion or disease of the somatosensory system. The NP aetiology can involve viral infections (e.g. herpes zoster, HIV), metabolic disorders (e.g. diabetes), inflammation, cancer, post-surgical and -traumatic sequelae, as well as events affecting the central nervous system (e.g. stroke, spinal cord lesions). Patients who suffer from NP often experience constant burning pain, intermittent stabbing, lancinating pains and allodynia (2), (3). Clinical signs and symptoms are similar across different NP conditions and several grading scales and other diagnostic tools (e.g. Neuropathic Pain Scale) have been developed to assess the complex domains of NP.

Neuropathic pain can be restricted to a consistent and circumscribed area. Localisation (and size) are important characterising features of NP and The International Association for the Study of Pain (IASP) proposed to define Localised Neuropathic Pain (LNP) as "a type of neuropathic pain that is characterised by consistent and circumscribed area(s) of maximum pain" (4). Post-Herpetic Neuralgia (PHN), painful Diabetic Poly-Neuropathy (DPN) and neuropathic Low-Back pain (LBP) are often characterised by localised pain. Although LNP is not yet commonly understood, nor mentioned in treatment guidelines, a well-recognised classification of LNP could support the identification of patients who could benefit from topical treatment.

A screening tool based on the IASP grading principles for NP has been tested within the primary care setting in Spain. The study has shown that the tool, which focus on the evaluation of the NP history coupled with the distribution of symptoms and sensory signs, is easy to use for a prompt initial identification of NP and LNP in primary care (1). The LNP screening tool consists of four questions about the history, the anatomy, the sensory examination, and the size of the painful area. The first question relates to the anamnesis to verify if the patient's history could give reason for a nerve lesion or disease which may result in experiencing neuropathic pain symptoms (e.g. previous infection with herpes zoster); The second question aims at evaluating the pain distribution in order to assess the neuroanatomic plausibility (e.g. can the chronic pain be linked with a possible nerve damage); The subsequent sensory examination of the clinical signs tests the signs stimulated by touch, prick, vibration, cold, heat or pressure, using a device from daily practice (e.g. a pencil). Finally, if the three questions afore mentioned make NP probable, the location and size of the painful area is evaluated, namely if the chronic pain area is circumscribed and localized i.e. smaller than an A4 paper. In summary, if the medical history, the anatomy and the signs of pain make NP plausible and the painful area is circumscribed the patient probably suffers from LNP and topical medications may represent an appropriate choice of effective pain management.

The experience of chronic pain is recognised to impact severely the quality of life of affected patients (5). Furthermore, it is recognised that chronic pain patients experience significant sleep problems, mainly described as primary sleep disorders, including difficulties falling asleep, awakening by pain during the night or in the morning (6–9). Self-reported health status and pain-related sleep disturbance may provide valuable insights when assessing the responses to treatment for chronic pain, including LNP. However, quality of life as well as sleep difficulties among patients who experience LNP has not yet been fully described in literature.

The EuroQol five dimensions questionnaire (EQ-5D) is a standardized instrument for measuring generic health status and has been extensively used in pain research. It includes two components, health state description and evaluation. In the description part, patients are required to report on five dimensions (5D) of their health status, namely mobility (walking ability), self-care (the ability to wash or dress by oneself), usual activities (performance in work, study, housework, etc.), pain/discomfort (how much pain or discomfort they experience), and anxiety/depression (how anxious or depressed they are). Patients self-rate their level of severity for each dimension using a five-level scale. In the evaluation part, patients evaluate their overall health status using the visual analogue scale.

The Chronic Pain Sleep Inventory (CPSI) has been developed among others and validated as a study instrument to evaluate quality of sleep in patient experiencing chronic pain. The CPSI incorporates 5 items -- trouble falling asleep, needing sleep medication, awakenings due to pain in the night and morning, and overall quality of sleep. A CPSI validation study supports the scoring of a reliable single index from 3 of the 5 CPSI items that all attribute sleep problems to pain (8).

7.2. Rationale

Current systemic treatment options for NP include Anticonvulsants (Gabapentin, Pregabalin) and Tricyclic antidepressants (Amitriptyline, Desipramine, Nortriptyline) as first line treatment. Secondary or tertiary line treatments are SNRIs (Venlafaxine, Duloxetine) and Opioids (Methadone, Morphine and Tramadol). Although systemic treatments have been proved to be effective in relieving pain and ameliorating the patient's quality of life their tolerability is often limited by side effects. The occurrence of therapeutic side effects can impact severely dose titration effort leading to sub-optimal treatment of pain and overall compromised patient care.

Topical application of analgesics (without local anaesthetic effects) can offer a valid therapeutic alternative, providing LNP is recognised. To date only sparse data is available in literature about the features of LNP, its therapeutic management and its frequency in the primary care population in Europe.

This study will attempt to fill such a knowledge gap in the primary care population of five EU countries, namely France, Ireland, Italy, Spain and the United Kingdom. Data on the frequency of LNP and the clinical profile of patients showing signs and symptoms of LNP, their current treatment patterns, and patient's reported health status, including quality of sleep, can help to identify unmet medical needs in such a problematic therapeutic area.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Questions

This study aims to address the following research questions:

- What is the clinical profile and pattern of treatment of LNP patients in the primary care setting across EU
- What is LNP patient's self-reported quality of life, including quality of sleep
- How frequent is LNP among patients managed in primary care across EU

8.2. Objectives

8.2.1. Primary objectives

To address the study research questions, the primary objective of the project is:

- To describe clinical characteristics and patterns of treatment of LNP patients identified among chronic pain patients in primary care in five European countries, namely France (FR), Ireland (IE), Italy (IT), Spain (SP) and the United Kingdom (UK).

8.2.2. Secondary objectives

The secondary objectives of the study are:

- To evaluate patient's reported health status (self-administered EQ-5D questionnaire/Chronic Pain Sleep Inventory, CPSI);

- To estimate the prevalence of LNP among patients managed in the primary care in the study countries (see details in section 9.4.1.2.

9. RESEARCH METHODS

9.1. Study design

To meet the study objectives, an observational cross-sectional study will be conducted within the primary care setting of each study country.

9.2. Setting

The study aims to select a minimum of 50 General Practitioners (GPs; i.e. 10 in each study country).

The number of participating GPs will be finalized during the study, based on the results of patient enrollment effort to ensure that the target population is included in the study (see 9.3 below). The selection of study sites will also be adapted to specific circumstances and characteristics of the healthcare system of study country. Where possible GPs participating in established research networks will be approached. Such a network has been identified for instance in Italy (SIMG) and in Ireland (Irish College of General Practitioners). In the UK, study GPs will be initially approached through the National Institute for Health Research Clinical Research Network (NIHR CRN). This research infrastructure network is funded by the Department of Health and could facilitate the identification and recruitment of suitable GP sites to support study activity in the primary care setting. The NIHR CRN would be able to work with local GP practices to ensure recruitment of eligible patients from a wide patient population with representative demographic profile, ethnic identity, and socio-economic status. Additionally, the study will be registered with the NIHR Clinical Research Network, for its inclusion on the CRN study portfolio in order to facilitate GPs participation and commitment. It is anticipated that GPs who are familiar with the requirements of medical research can provide higher data quality and full commitment to the conduct of the study. Ready available databases will also be used for approaching GPs if needed.

For all GPs who accept to participate in the study, the number of registered patients ≥ 18 years old, by gender and age groups (18-20; 21-30; 31-40; 41-50; 51-60; 61-70; 71-80; >80), will be retrieved. This information will be filed into a GP Population Study Table. Registration with a GP is a requirement of the health care system in all study countries, but France. In this country the GP Population will consist of the total number of patients who attended each participating GP clinic at least once during the study period. This starts 6 months before start of data collection and finishes at the end of data collection at each site.

The study GPs will be required to invite patients ≥ 18 years old with a record of chronic pain to attend their clinic. Chronic pain patients will be identified by selected medical coding recorded in the patient medical record within the 6 months (180 days) preceding the start of data collection at each study site. Anonymized information on patient's age, gender and diagnostic medical codes qualifying them as chronic pain patients will be registered into a Study Logbook. A comprehensive listing of the medical codes relevant to this purpose will be prepared from each of the Medical Dictionaries in use in the five study countries (e.g. ICD 9, ICD, 10, READ) and will be included to the site initiation package.

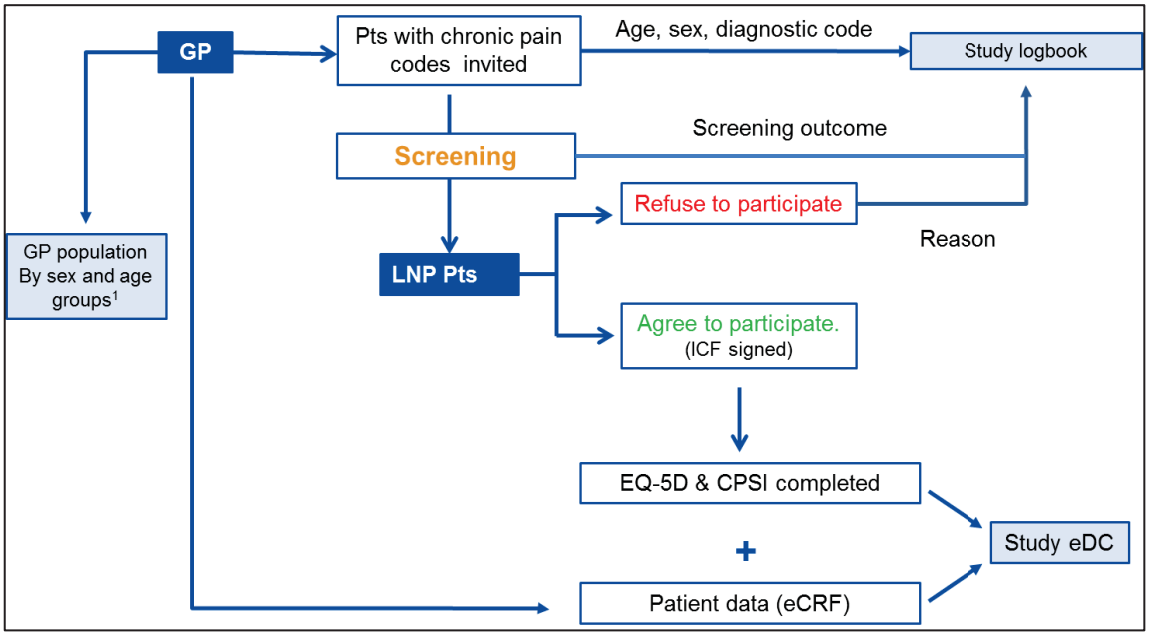
During the patient's visit the GP will be required to screen patients in order to identify LNP patients. In the absence of common diagnostic procedures and of specific medical coding for LNP, the LNP patients to be enrolled in this study will be identified by screening patients with a medical record of chronic pain with the study screening tool. Such a screening tool has been previously applied in the primary care setting (1; see also Annex 1) and requires the application of four screening questions and of a diagnosis algorithm, as detailed in Section 7.1. To facilitate the examination and to warrant some consistency across study sites and countries, participating GPs will receive expert training on the optimal use of the screening tool chosen for this study.

For each screened patient the result of screening (positive identification of LNP [Yes/No/Unavailable for screening]) will be recorded into the corresponding record of the Study Logbook.

Chronic pain patients who present signs and symptoms of LNP as for the study screening tool, and who meet all eligibility criteria for the study will be invited to participate and will be provided with an inform consent form. Only patients who provide written informed consent will be included in the study. Participation in the study (Yes/No) and the reason for not participating will be recorded for each patient in the Study Logbook. Patients who provide written informed consent will be required to self-report on the health status through the EQ-5D and CPSI questionnaires. Patient characteristics including demographic, lifestyle, medical history, clinical characteristics of pain, and previous and past treatment characteristics will be collected by the GP in an electronic Case Report Form (eCRF). Information from EQ-5D and CPSI and from the eCRF will be later merged in a single data source (EDC). The study process flow is summarized in the Figure 1 below.

Study procedures with respect to patient identification and enrolment will be adapted to the primary care setting and existing networks of each study country. Where and when feasible or appropriate, opportunistic patient recruitment will be also considered: Throughout the five months enrolment period, adult patients with a 6 month history of chronic pain who present themselves to the GP clinic, irrespective of a previous invitation to attend, could be screened for LNP and if eligible could be invited to participate to the study. A record of the patients presenting themselves with chronic pain will be maintained in the Study Logbook. The study enrolment period of five months can ensure a chance to all potential chronic pain patients to attend the clinic as for routine practice and needs. Such an approach will minimize any potential for selection bias towards patients who require less frequent medical attention.

Figure 1. Study Process flow

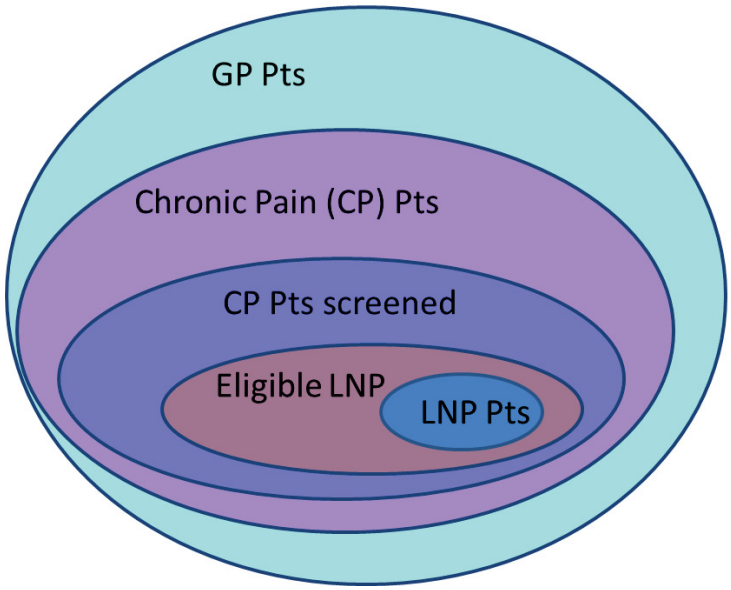


[1] GP Population Study Table

9.3. Study population

The study population will include 1000 LNP patients identified within chronic pain patients managed in primary care in the study countries (e.g. 200 patients in each study country). Based on data from the literature (1,10), it is estimated that this study population will result from the screening of approximately 5400 chronic pain patients, as summarized in Figure 2.

Figure 2. Selection of the Study Population[1]



Study GPs

50

GP expected Pts	1,500	75,000
Chronic Pain Pts	*8 %	6,000
CP Pts screened	90 %	5,400
LNP eligible Pts	**20%	1,080
LNP study Pts	90%	972

Adapted from *Bouhassira et, 2008 (11); **Mick et al, 2014 (1); [1] Percentages always refer to the previous line.

Patients will be selected according to study procedures and individual eligibility criteria detailed below (Section 9.3.1).

9.3.1. Eligibility criteria

Patients must meet all of the following criteria to be eligible:

Inclusion criteria

- Patient presents signs and symptoms of LNP;
- Patient is able to understand and complete the consent form and patient questionnaires;
- Patient is 18 year or older at the time of screening;
- Patient signed the Informed Consent.

Exclusion criteria

- Patient is currently participating in another study (interventional or non-interventional);
- Patient has been already included in this study.

9.4. Variables

For each of the study patients the following variable will be collected and analyzed:

- Demographic (e.g. age, gender)
- Lifestyle characteristics (Body Mass Index, smoking status, alcohol abuse)
- Clinical characteristics of pain: Duration of LNP, Localization, Current pain intensity
- Aetiology: PHN, painful DPN, post-surgery NP, neuropathic LBP, mastectomy or other cancer NP
- Co-morbidities: diabetes, depression, CV, cancer, inflammation
- Current and previous treatment of neuropathic pain
- Treatment with anti-inflammatory products

9.4.1. Study Measures

9.4.1.1. *Primary Endpoint*

- The primary endpoints for the study will be the important clinical and treatment characteristics at the time of the visit, including but not limited to:Clinical characteristics:
    - Duration of LNP: Obtained from the difference of the date of the visit minus the date of first diagnosis of chronic pain collected from the medical record. The variable will be treated as continuous for its description, but further categorization is anticipated for the study of subgroups. The definition of the number of categories and the cut-off points will be based on the observed distribution. However, it is expected to have a maximum of three categories representing short, medium and long duration.
    - Location: Obtained by an anatomical pain localization figure provided in the eCRF and collected by the GP at the time of screening. The figure provides a total of 27 non-mutually exclusive localizations (13 in the front and 14 in the back). Further recoding into a small number of categories corresponding to greater anatomic areas is anticipated.
    - Intensity of pain: Assessed by the GP after asking the patient during the screening visit on the intensity of pain in a 11-point Numeric Rating Scale (0 = No pain; 10 = Worst imaginable pain). The variable will be described as a continuous variable. A further categorization into mild (1-3 points), moderate (4-6 points) and severe pain (7-10 points) for the analysis of subgroups is anticipated.

- Aetiology of LNP: Obtained at the time of the visit by the GP from the clinical records as multi-response variables for patients that have ever experience in the past one of the following conditions:
    - Post-Herpetic Neuropathy (PHN)
    - Painful Diabetic Poly-neuropathy (DPN)
    - Neuropathic Low Back Pain (LBP)
    - Post-surgery NP
    - Mastectomy or other cancer surgery NP

- Co-morbidities in the 6 months preceding the screening: Obtained at the time of the visit by the GP from the clinical records as multi-response variables for patients that have a record of one of the following conditions in the 6 months previous to the date of the visit.
    - Diabetes
    - Cardiovascular diseases
    - Cerebrovascular diseases
    - Depression
    - Cancer
    - Arthritis (osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis)
    - Fibromyalgia
    - Ankylosing spondylitis
    - Other inflammatory disorder
    - Other comorbidity

- Therapy for chronic pain in the 6 months preceding the screening. Obtained at the time of the visit by the GP from the clinical records as multi-response variables for patients that have a record of the following treatments (or other) in the 6 months previous to the date of the visit:
    - Anticonvulsants (Gabapentin, Pregabalin)
    - Tricyclic antidepressants (Amitriptyline, Desipramine, Nortriptyline)
    - SNRIs (Venlafaxine, Duloxetine)
    - Opioids for mild to moderate pain (Hydrocodone, Tramadol, Codeine)
    - Opioids for moderate to severe pain (Morphine, Oxycodone, Hydromorphone, Meperidine, Methadone, Fentanyl)
    - 5% Lidocaine plaster
    - 8% Capsaicin plaster
    - Non-steroid anti-inflammatory drugs (e.g Ibuprofen, diclofenac, etc)
    - Corticosteroids

  In addition, GPs will collect information on the presence of treatment switching (change from a previous pain treatment to another) in the last 6 months; and if the patient have been on combination therapy (two or more medicines used together to treat pain). For those patients with a record of combination therapy, GPs will also report:
    - The number of different combinations prescribed in the last 6 months
    - The number of medicines of any combination in the last 6 months (as a multi-response variable)
    - If any of the combinations in the last 6 months included topical medication
    - Medications used in combination with lidocaine plaster (as a multi-response variable)

- Current therapy for chronic pain: A multi-response variable for patients who have a record of the pain treatments listed above at the time of the visit by the GP. If applicable, current treatment description will contain the description of any combination by the number of medicines included, and the use of topical medicines in the combination. In addition, the time since the initiation of the therapy, measured as the subtraction of the date of initiation of current treatment from the date of the visit, will be estimated.

9.4.1.2. *Secondary Endpoints*

- EQ-5D score (Patient's self-reported health status)
- CPSI scores (Patient's self-reported quality of sleep)
- Prevalence of LNP among patients managed in primary care at each study country will be estimated from the number of patients positive to the screening for LNP over the total number of patients registered with each study GP, as recorded in the GP Population Study Table. Additionally LNP prevalence among patients with chronic pain will be estimated from the information contained in the Study Logbook, which contains the number of patients with chronic pain identified at each site and the number of them with a positive screening of LNP.

9.5. Data sources

Data from patients who agreed to participate in the study will be collected by means of a bespoke electronic Case Report Form (eCRF) developed for this study, and that GPs will be required to complete with clinical and therapy data of the study patients.

In addition, patients will be asked to fill in the paper EQ-5D and the CPSI questionnaires that they will be provided at the end of the visit. The data collected with the patient instruments will be transferred in the patient electronic file (eCRF) by dedicated staff at the GP clinic.

A web-based electronic data capture (eDC) system will be used to collect GPs and patient input and to create the study database for analytical purposes. Along with the eDC the study will have 2 additional data sources:

- The Study Logbook, which will be used as a secondary data source for the assessment of the study conduct, representativeness of included patients, generalizability of study results and to estimate the prevalence of LNP among chronic pain patients;
- The GP Population Study Table which will be used as an external data source to estimate the prevalence of LNP among the general population.

9.6. Study size

Based on the estimates provided in

Table 1 below, sample size is planned to ensure that the study will target a total of 1000 LNP patients, with approximately 200 patients in each of the countries (FR, IE, IT, SP, and UK). Such a sample size allows acceptable estimates precision for the categorical primary study outcome(s).

Anticipated precision estimates for continuous variable (e.g. BMI, pain intensity) are summarised in Table 2.

Table 1. Precision of study of 200-1000 LNP patients (categorical variables)

Confidence Level	Sample Size (N)	Target Width	Actual Width	Proportion (P)	Lower Limit	Upper Limit	Width if P = 0.5
0.950	200		0.088	0.100	0.062	0.150	0.143
0.950	200		0.115	0.200	0.147	0.262	0.143
0.950	200		0.131	0.300	0.237	0.369	0.143
0.950	200		0.140	0.400	0.332	0.471	0.143
0.950	200		0.143	0.500	0.429	0.571	0.143
0.950	1000		0.038	0.100	0.082	0.120	0.063
0.950	1000		0.051	0.200	0.176	0.226	0.063
0.950	1000		0.058	0.300	0.272	0.329	0.063
0.950	1000		0.062	0.400	0.369	0.431	0.063
0.950	1000		0.063	0.500	0.469	0.531	0.063

Table 2. Precision of study of 200-1000 LNP patients for the examples of the primary end-point pain intensity(continuous variables[1])

Confidence Level	Sample Size	Precision (distance from the mean)	Standard deviation
0.95	200	0.146	1.05[1]
0.95	1000	0.065	1.05[1]
0.95	200	0.05	0.36[2]
0.95	1000	0.022	0.36[2]

[1] A Standard deviation of 1.05 was selected as it corresponds to published standard deviation for the minimum clinically significant difference of 1.41 in the Patient-Assigned 11-Point numeric pain scale scores for pain in Kendrick and Strout 2004 (12) .

[2] A Standard deviation of 0.36 was selected as it corresponds to published standard deviation for the EQ-5D index score in patients with chronic pain with neuropathic characteristics in Torrance et al 2014 (13)

9.7. Data management

A data management plan (DMP) will be written to guide all aspects of data handling. It will include all data forms and annotations, database specifications and format, data validation plan and database structure for the final transfer of files into SAS for statistical analysis. The eCRF will undergo testing before it is released to study participants.

The eCRF will not collect any personal information about patients. The identification of patients will be controlled by a unique identification code formed by one sequential number for sites plus a sequential number starting from 1 to identify individually any patient within the same site. This way to identify patients ensures that from the eCRF data it is not possible to trace down personal information and patient's identity.

9.8. Data analysis

Statistical analyses will be mainly descriptive in nature as there is no hypothesis testing. A detailed statistical analysis plan (SAP) will be developed before final database lock and will include methods of analysis and presentation and table shells. All analyses will be performed using SAS 9.4 (or higher) statistical software (SAS, Cary, North Carolina, USA).

9.8.1. Definition of analysis sets

Study populations

General population of the study: All patients ≥18 years registered at the GPs participating in the study. This population, summarized in the GP Population Study Table, will be the basis for the analysis of the prevalence of LNP among the general population.

Chronic pain population of the study: All subjects in the general population of the study with a record of chronic pain. This population will be the basis for the analysis of the prevalence of LNP among chronic pain patients.

LNP population: All LNP patients attended in primary care by the GPs participating into the study in each of the study countries.

Screened population

All patients in the general population with a record of chronic pain in the 6 months preceding the start of screening and data collection at each study site and any opportunistic patient with symptoms compatible with chronic pain attended during the recruitment phase by the participating GPs, who undergo a screening process for LNP with the study screening tool. The screened population, registered in the Study Logbook, will be the basis for the analysis of the representativeness of included patients and for the estimation of the prevalence of LNP among chronic pain patients.

Eligible populations

All patients identified as LNP patients with the study screening tool, who meet fully the eligibility criteria independently of providing a signed informed consent to participate to the study.

Enrolled populations

All patients who are eligible for the study and provide a signed informed consent for their participation.

Full Analysis Set (FAS)

All enrolled patients with valid information for the assessment of at least one of the primary endpoints (clinical characteristics and treatment patterns). The FAS, which is included in the eCRF database, will be the basis for the analysis of the primary and secondary endpoints (e.g. EQ-5D and CPSI scores) excluding prevalence estimates. As the study is descriptive, and the primary endpoints are characteristics of the patients and their treatments, all correctly included patients will likely be part of the FAS, which will be also used to assess patient's reported health status.

9.8.2. General statistical considerations

In brief, categorical data will be summarized by counts and percentages. Continuous data will be summarized using number, mean, standard deviation (SD), median, quartiles, minimum and maximum and in the case of non-normally distributed data, median, range and interquartile range. Corresponding 95% confidence intervals will be reported as appropriate. The assessment of normality of the distribution of continuous variables will be made through the Shapiro-Wilks test

Comparisons will be made for the assessment of differences or associations. Appropriate univariate tests for study of associations will be selected depending on the nature of the comparison:

- Independent samples: t-test, for dichotomous (e.g. with lidocaine topical treatment by duration of LNP or by NRS of pain intensity), or ANOVA, for categorical variables (e.g. number of medicines in current treatment combination by duration of LNP or by NRS of pain intensity), will be used for normally-distributed continuous variables; Mann-Whitney U or Kruskal-Wallis respectively for non-normally distributed continuous variables, and chi-square test or Fisher's exact test for categorical variables (e.g. patients with lidocaine topical treatment by smoking habit)
- Related samples: Pearson correlation for two continuous variables (e.g. pain intensity and CPSI overall sub-score), and Intra-class correlation coefficient for more than two continuous variables (e.g. all sub-scores of the CPSI); and Spearman correlation for two ordinal variables will be used to assess consistency between different variables collected in the eCRF and the self -reported health status. If the categorization of these variables is considered, the comparison between two related dichotomous variables will be done with Cohen's Kappa and McNemar test, and Cochran's Q test will be used for more than two dichotomous variables.

All statistical tests will be 2-sided and conducted at the 0.05 alpha level. P-values will be presented to three decimal places.

The statistical analysis will include a summary of the study conduct, an assessment of sample representativeness, a descriptive analysis and the analysis of the objectives.

No adjustment will be made for multiple comparisons or for multiple analyses.

9.8.2.1. Assessment of representativeness

Study representativeness is important to ensure that the LNP prevalence estimates can be generalized to the respective study countries. The universal access to healthcare services and in particular to primary care in all study countries could allow to approximate the population attending GP clinics to the general population of the respective countries.

Within study sites patient selection bias will be minimized with the eligibility assessment of all and consecutive patients with chronic pain attending the GP clinic. Nonetheless, the self-selection of patients may introduce some selection bias. For instance, more elderly/frail LNP patients or those who experience more severe pain might be less amenable to participation. To better inform the generalisability of the study results a GP Population Study Tables and a Study Logbook will be maintained. Patients approached at the GP sites for enrollment, whose demographic profile information has been collected in the Study Logbook, will be divided into:

- Eligible patients who agree to participate in the study
- Eligible patients who refuse to participate in the study

Potential sample bias will be assessed by comparing available demographic information of those who participate with those who do not participate.

Furthermore, demographic information of patients with chronic pain who are not eligible for the study, will be recorded in the Study Logbook, and will be compared with information from the eligible population to assess for representativeness and generalisability of the results.

9.8.2.2. *Descriptive analyses*

Patient's demographic characteristics as well as other characteristics not included in the study objectives will be described globally and for each country: Country, age group, gender, weight, height (Body Mass Index), lifestyle characteristics (smoking status, alcohol abuse), use of sleeping aid medication.

9.8.2.3. *Primary analyses*

The primary analysis will consist on a description of the LNP study population, from the FAS, overall and for each country. Summary descriptive statistics will include:

- Clinical characteristics of LNP
- Aetiology of LNP
- Co-morbidities
- Treatment of chronic/neuropathic pain

Following the overall description, summary description of patients will be provided according to the main patient (e.g. age group, gender), and clinical characteristics (e.g. duration, location, intensity) and treatment patterns (e.g. anticonvulsants, SNRIs) identified when the number of patients in each characteristic allows. Patient profiles depending on these characteristics will be studied with multivariate analytical approaches. A full specification of these analyses will be provided in the SAP.

9.8.2.4. *Secondary analyses*

Secondary analysis will include a description patient's responses to EQ-5D and CPSI questionnaires:

- EQ-5D by separate domain, visual analogic scale on Health Related Quality of Life and scoring tariff using UK population weights
- CPSI by separate items

Following the overall description, summary description of ED-5D and CPSI scores will be provided according to the main patient (e.g. age group, gender) or clinical characteristics (e.g. duration, location, intensity) and treatment patterns (e.g. anticonvulsants, SNRIs) identified when the number of patients in each characteristic allows. Patient profile depending on these characteristics will be studied with multivariate analytical approaches. A full specification of these analyses will be provided in the SAP.

In addition, and using the data collected in the Study Logbook and in the GP Population Study Table, prevalence of LNP will be obtained and reported. The prevalence values will be expressed as percentages and will include:

- Prevalence of LNP among general population: It will be calculated as the number of eligible LNP patients identified in the screening and recorded in the Study Logbook, divided by the sum of all patients registered with the participating GPs in the study, obtained from the GP Population Study Table. This prevalence will be reported globally and by country
- Prevalence of LNP among patients with chronic pain: Globally and by country. It will be calculated as the number of eligible LNP patients identified in the screening and recorded in the Study Logbook, divided by the sum of all patients identified as patients with chronic pain included in the Study Logbook

9.8.2.5. Missing data

Missing data in the CRF, EQ-5D questionnaire, and CPSI will be dealt according to published guidelines for each of the tools. For the description of each of the items in the scales, the number of patients with missing responses will be provided.

Missing data may affect the subjects who can be included in the analyses, and this will be detailed in the SAP.

9.9. Quality control

Standard operating procedures will be applied to ensure quality to all aspects of the study conduct and data management and statistical analysis.

In addition, data generated by this study must be available for inspection upon request by representatives of national and/or local health authorities, sponsor monitors, representatives, and collaborators, as appropriate. The investigator must notify OXON promptly of any inspections scheduled by regulatory/ethical authorities, and promptly forward copies of inspection reports to OXON.

9.10. Limitations of the research methods

Some general limitations of the study include the following:

- Random selection of study sites cannot be achieved in the study countries. Nonetheless, within each site, patient enrolment procedures have been designed to prevent selection bias. Furthermore, the patient population profile of the study sites will be compared to available national demographic and medical statistics in order to better understand the generalizability of the study results at least at national level in each of the study countries.
- Only patients able to understand and complete the ICF will be included in the study.
- Participants who refuse to participate might limit the patient representativeness of the study results. This will be examined by comparing participating and non-participating patients on some key variables.
- Lack of consensus on the definition of LNP might lead to the enrolment of a non-homogenous population across study sites and countries. Effort will be made to train the participating GPs on the use of a publically available tool that can facilitate the identification of LNP patients consistently across study sites.
- The size of the study populations will allow an acceptable level of precision for the study primary endpoints; however, such a level of precision may be diluted in stratified analyses.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Ethics Committee

This type of study requires review and approval by ethics committee (EC). Thus, the study will be conducted under the auspices of independent EC (and any local EC/R&D if applicable) in all study countries as defined in local regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

OXON will ensure that an appropriately constituted EC that complies with the requirements of the applicable country-specific regulations will be responsible for the approval of the study. Prior to initiation of the study, the study protocol, patient information sheet and informed consent form, and any other specifically required documentation related to the study, will be submitted to the relevant EC for its review and approval.

10.2. Patient informed consent

In accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki, patients should provide written consent before enrollment into the study. Investigators must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representatives, are clearly and fully informed about the purpose of the study, potential risks, the patient's rights and responsibilities when participating in this study. If local regulations do not require an ICF to be signed by the patient, the site staff should document key elements of the informed consent process in the patient's medical record.

Informed consent for the study will be sought. By signing the ICF, the patient consents to participate in the study.

10.3. Data protection and confidentiality

The confidentiality of records that could identify patients within the study database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

For the purposes of protecting a patient's identity, a unique code will be assigned to each patient, such as a sequential number per site plus a sequential number per patient within the same site (for example, 01/01). Only the investigator (GP) and the site staff have access to the link between patient's assigned code and the patient's identity. However, in case of an audit or inspection, subject to local laws and regulations, government officials, IRB/EC representatives and sponsor representatives may access this information at the study site. Data that could directly identify the patient will not be collected in the "study database".

10.4. Archiving of study documents

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact OXON prior to destroying any records associated with the study. A copy of the database will be provided to the Sponsor together with the study documentation included in the final study report.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

This study is not designed to collect information on Adverse Events (AEs) or PV data associated with the use of any specific medicinal product. However, it is possible that, during the conduct of the study participating patients/GPs may spontaneously provide information that meets the criteria for an Adverse Reaction (ADR)*/PV data** related to any of the Grünenthal's medicinal products.

If during the course of the study any personnel become aware of any ADR or any PV Data regarding any Grünenthal product, it shall be reported to OXON PV immediately by completing the Safety Information Reporting Form and forwarding it to drugsafety@oxonepi.com.

OXON PV will review and process the ADRs and/or PV Data received and report it by email to Grünenthal PV within 1 working day of becoming aware of the event.

A comprehensive PV plan, a stand-alone document specific for the study, will be developed to provide additional information regarding the PV procedures to be followed and requirements of PV data collection for agreement and subscription of the study sponsor in order to assure compliance with their procedures.

Grünenthal will be responsible for submitting any required Individual Case Safety Reporting (ICSR) to the relevant National Competent Authorities (NCAs) according to current regulations.

***Adverse reaction (AR)** is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure.

**"PV Data": Any report of misuse (with or without adverse events), any medical device incident, any medication error; any off-label use (with or without adverse events), any overdose (accidental and/or Intentional), any drug abuse; any lack of efficacy, any suspected transmission of infectious agents; any drug exposure during pregnancy or child exposure during breastfeeding or conception (with or without adverse events), cancer, any occupational exposure (with or without adverse events).

12. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

12.1. Ownership and use of data and study results

The ownership of data arising from the study resides with Grünenthal. OXON will provide a full copy of the anonymized data to Grünenthal at the end of the study. No use of the data will be possible without the authorization of Grünenthal conducting the study.

12.2. Publication

A final study report will be developed and will serve as a basis for the development of publications and presentations in scientific journals, and press releases.

Abstracts, summaries, presentations and manuscripts will be prepared in line with dissemination guidelines of the International Committee of Medical Journal Editors (14) and Guidelines for Good Pharmacoepidemiology Practice (15) to help ensure the quality and integrity of epidemiological research and to provide adequate documentation of research methods and results.

13. REFERENCES

1. Mick G, Baron R, Correa-Illanes G, Hans G, Mayoral V, Frías X, et al. Is an easy and reliable diagnosis of localized neuropathic pain (LNP) possible in general practice? Development of a screening tool based on IASP criteria. Curr Med Res Opin [Internet]. 2014 Jul [cited 2016 Apr 13];30(7):1357–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24650347

2. Gilron I, Watson CPN, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. CMAJ [Internet]. 2006 Aug 1 [cited 2016 Apr 28];175(3):265–75. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1513412&tool=pmcentrez&rendertype=abstract

3. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol [Internet]. 2010 Aug [cited 2015 Nov 10];9(8):807–19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20650402

4. IASP Task Force. IASP Taxonomy [Internet]. Classification of Chronic Pain, Second Edition (Revised). 2012. p. 209–14. Available from: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions

5. O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics [Internet]. 2009 Jan [cited 2016 Apr 28];27(2):95–112. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19254044

6. Pilowsky I, Crettenden I, Townley M. Sleep disturbance in pain clinic patients. Pain [Internet]. 1985 Sep [cited 2016 Apr 28];23(1):27–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4058926

7. Wittig RM, Zorick FJ, Blumer D, Heilbronn M, Roth T. Disturbed sleep in patients complaining of chronic pain. J Nerv Ment Dis [Internet]. 1982 Jul [cited 2016 Apr 14];170(7):429–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7086403

8. Kosinski M, Janagap CC, Gajria K, Schein J. Psychometric testing and validation of the Chronic Pain Sleep Inventory. Clin Ther [Internet]. 2007 Jan [cited 2016 Apr 14];29 Suppl:2562–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18164922

9. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain [Internet]. 2006 May [cited 2014 Jul 9];10(4):287–333. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16095934

10. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain [Internet]. 2006 Apr [cited 2016 Apr 28];7(4):281–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16618472

11. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain [Internet]. 2008 Jun [cited 2016 Apr 27];136(3):380–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17888574

12. Kendrick DB, Strout TD. The minimum clinically significant difference in patient-assigned numeric scores for pain. Am J Emerg Med [Internet]. 2005 Dec [cited 2016 May 31];23(7):828–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16291435

13. Torrance N, Lawson KD, Afolabi E, Bennett MI, Serpell MG, Dunn KM, et al. Estimating the burden of disease in chronic pain with and without neuropathic characteristics: does the choice between the EQ-5D and SF-6D matter? Pain [Internet]. 2014 Oct [cited 2016 May 11];155(10):1996–2004. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4220009&tool=pmcentrez&rendertype=abstract

14. International Committee of Medical Journal Editors. Defining the role of authors and contributors

[Internet]. Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

15. International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (GPP). Pharmacoepidemiol Drug Saf [Internet]. 2008;17:200–8. Available from: http://pharmacoepi.org/resources/guidelines_08027.cfm

14. ANNEXES

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1		[Date]	LNP screening tool
2		[Date]	EQ-5D
3		[Date]	CPSI