SAPIENZA
UNIVERSITÀ DI ROMA
Dipartimento di Neuroscienze Umane
Unità di Malattie Neuromuscolari

IMI-PainCare

A Truini

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IMI-PAINCARE

“Improving the care of patients suffering from acute or chronic pain” is the ambitious goal of the IMI-PAINCARE Consortium. This Consortium is composed of 40 participants from 14 countries; 6 are EFPIA (European Federation of Pharmaceutical Industries and Associations) participants with strong traditions in pain research and development, 23 are internationally renowned academic and clinical institutions, 5 are specialist SMEs with cutting-edge technologies, 3 are patient organizations and 3 are professional pain/anesthesia societies.

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777500. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.

The Consortium addresses three important topics:
- Patient reported outcome measures to improve management of acute and chronic pain (PROMPT);
- Pharmacological validation of functional pain biomarkers in healthy subjects and animals (BioPain);
- Improving translation in chronic pelvic pain (TRiPP).

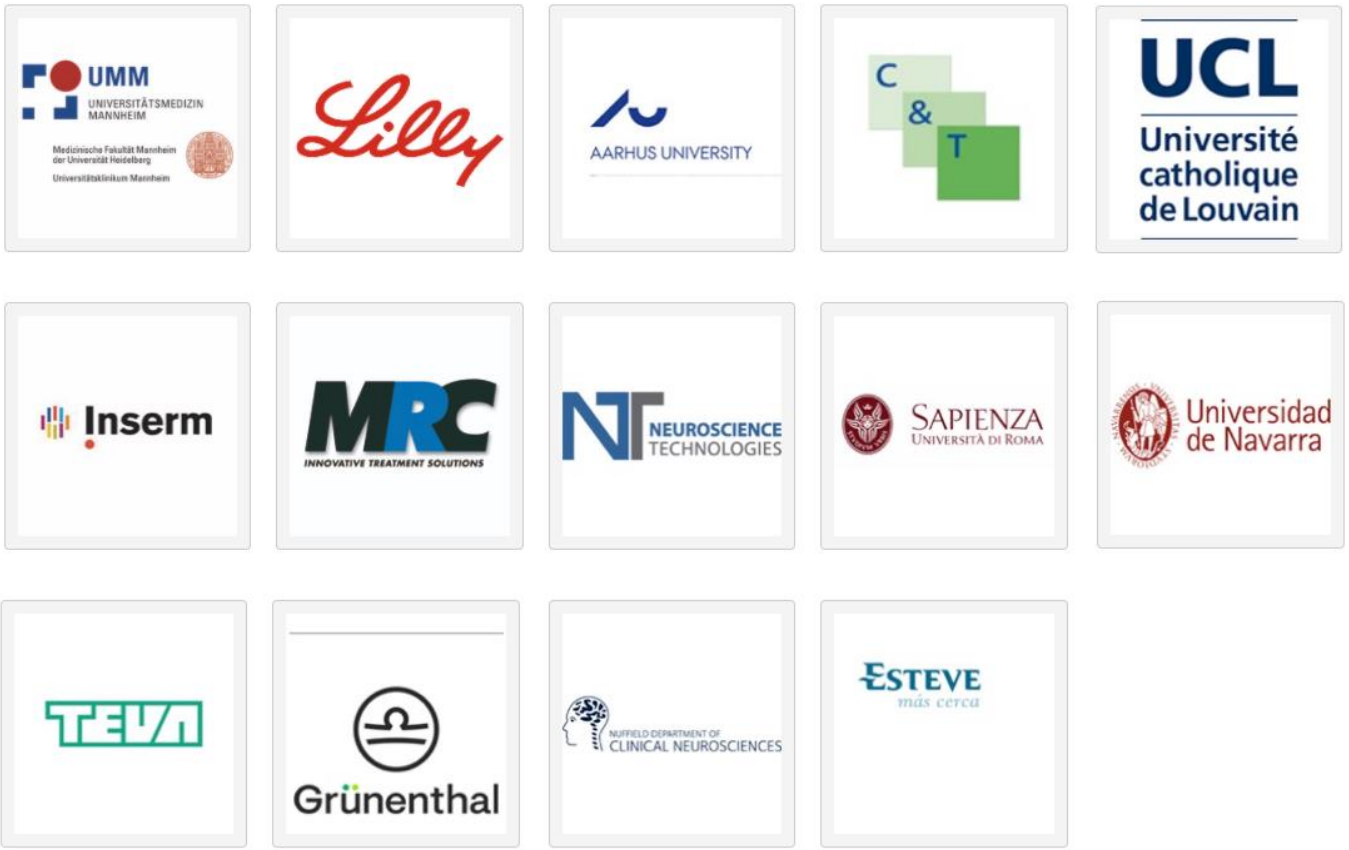
Subtopic TRiPP - Translational Research in Pelvic Pain

TRiPP is focusing on two specific types of chronic pain: endometriosis-associated pain (EAP) and bladder pain syndrome (BPS). Both conditions are currently treated by targeting the periphery (the endometriotic lesions in the pelvis or the bladder), but these treatments are often ineffective. The main hypothesis of **TRiPP** is that the pain symptoms experienced by women with these conditions are generated and maintained by mechanisms similar to those found in other chronic pain conditions, but occur in combination with specific pathological lesions and symptoms

Subtopic PROMPT - Providing Standardised Consented PROMs for Improving Pain Treatment

PROMPT aims at improving management of acute and chronic pain by identifying a core set of PROMs (patient reported outcome measures) that are predictive indicators of treatment success in clinical practice and controlled trials. These will not only address pain intensities as well as the functional consequences of pain for individuals but also identify patients at risk of experiencing chronification of acute post-operative pain. Results will help health care professionals to individualize pain management, and thus improve the quality of life of pain patients.

Subtopic BIOPAIN - Functional pain biomarkers



BioPain will address problems in the translation of analgesics from preclinical to early clinical drug development. The main hypothesis is that effect sizes of analgesic actions on at least some objective biomarkers of nociceptive signal processing can be translated between rodents, healthy volunteers undergoing surrogate models of pain sensitization and patients suffering from chronic pain. Powerful electro-physiological and imaging techniques are now able to accurately assess peripheral nociceptor activation as well as spinal and supra-spinal nociceptive signal processing.

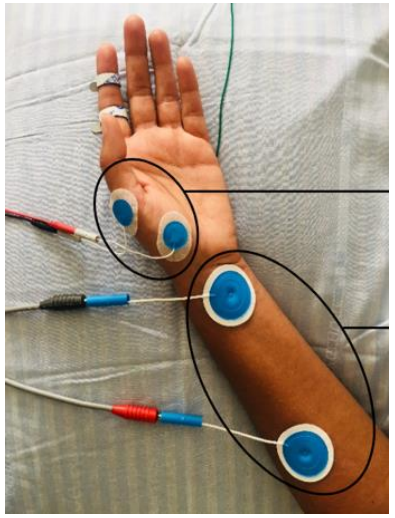
Subtopic BIOPAIN - Functional pain biomarkers

Drug Development of the pain field:
Promising preclinical data are often not reproduced in the clinic
Only 2 percent of new therapeutics for pain — compared to 10 percent of new therapeutics for other conditions — advance from Phase 1 clinical trials to approval (https://heal.nih.gov/research/preclinical-translational/biomarkers).

The scope of the BioPain subtopic is reducing the high drug attrition rate in the pain field validating pharmacodynamic biomarkers as measurable indicators of peripheral, spinal and central neuronal activities in response to drug exposure in animals and humans.

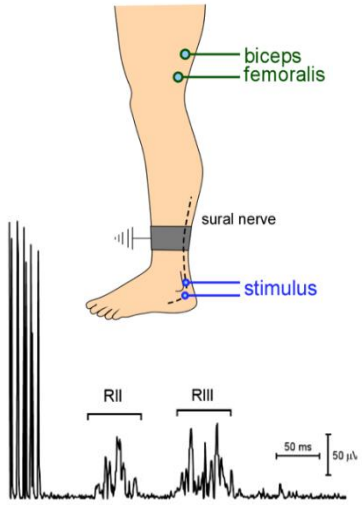
WP5 – Study Design

Aarhus



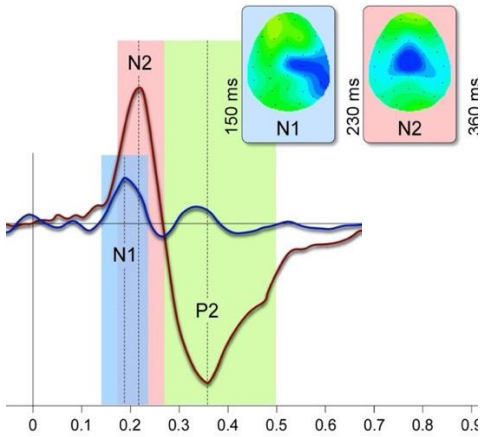
Peripheral biomarkers

Rome



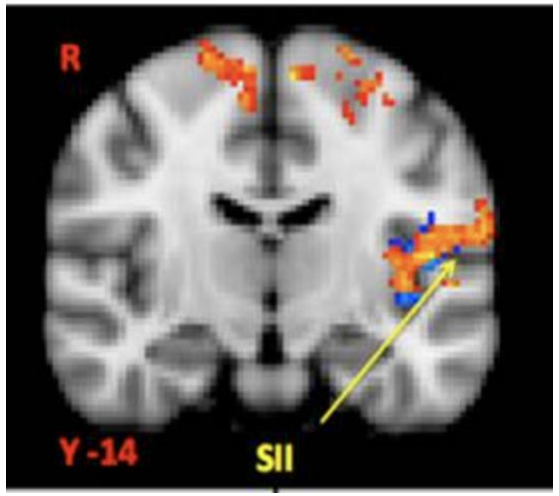
Spinal biomarkers

Louvain



Brain/EEG biomarkers

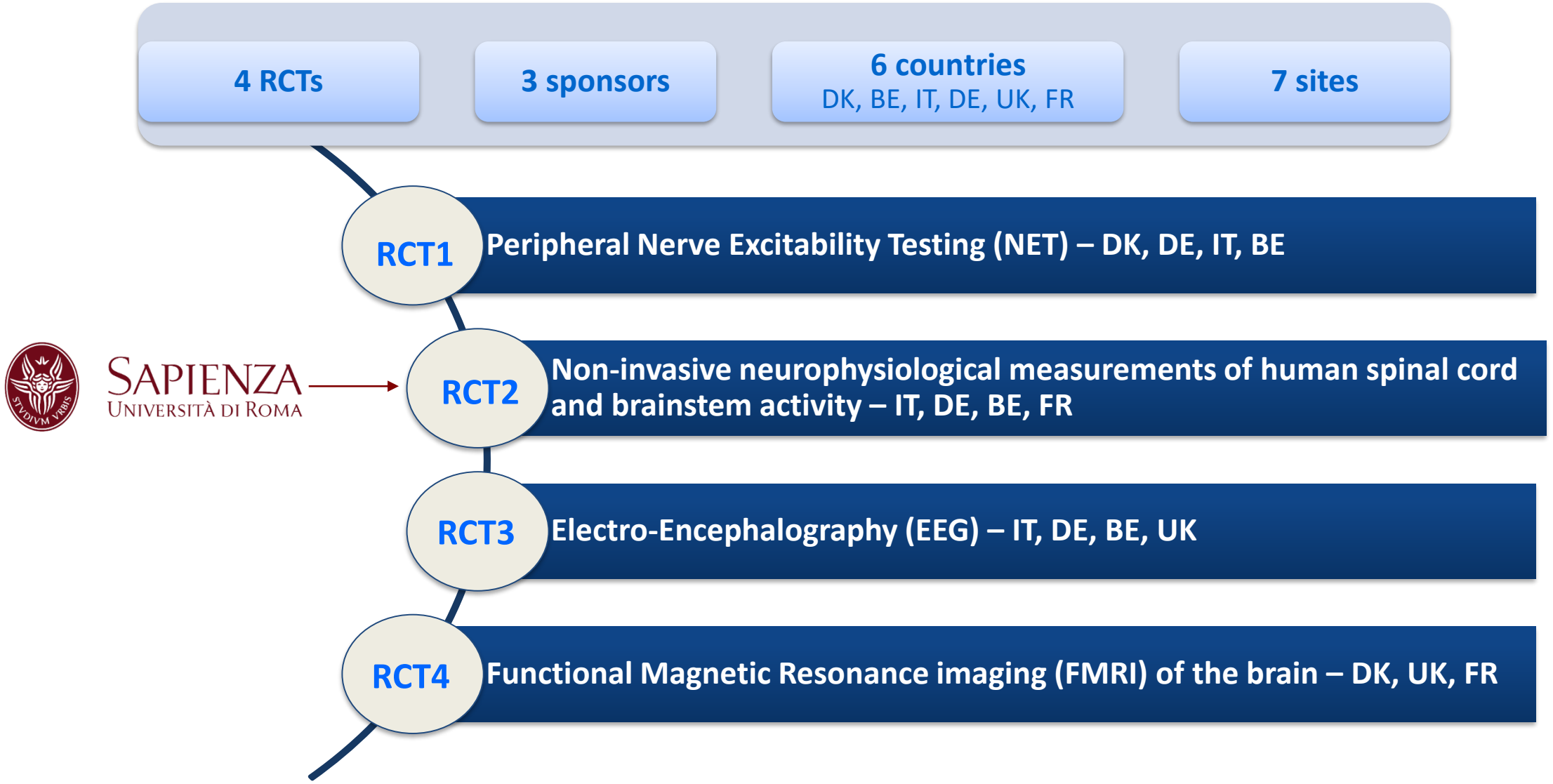
Oxford



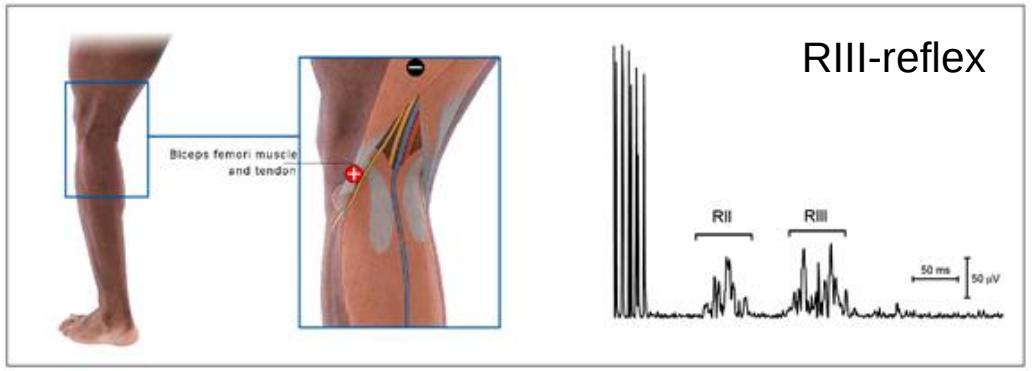
Brain/fMRI biomarkers

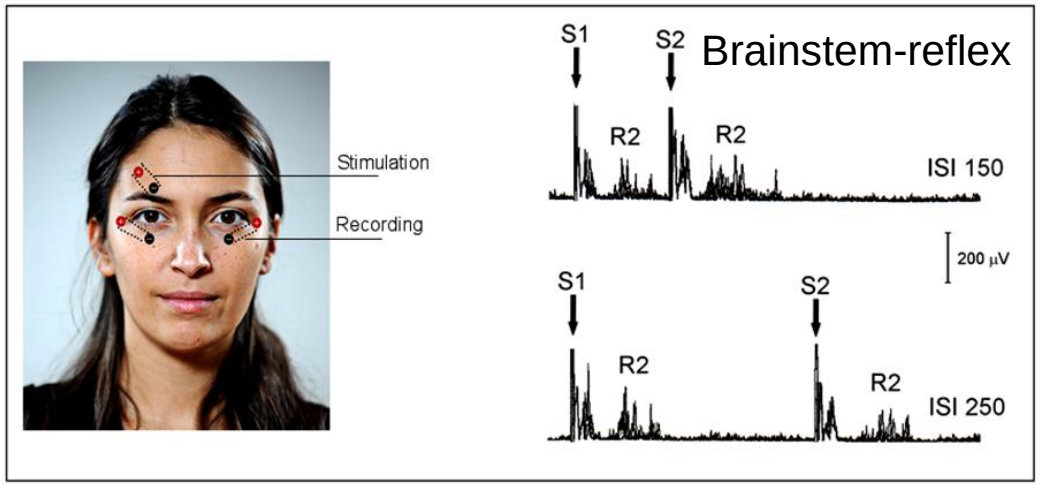
We aimed to test how different peripheral and central nervous system variables are influenced by standard of care drugs (lacosamide, pregabalin, tapentadol) during experimental pain models (high-frequency stimulation).

Subtopic BIOPAIN - Functional pain biomarkers



RCT2-BioPain in humans





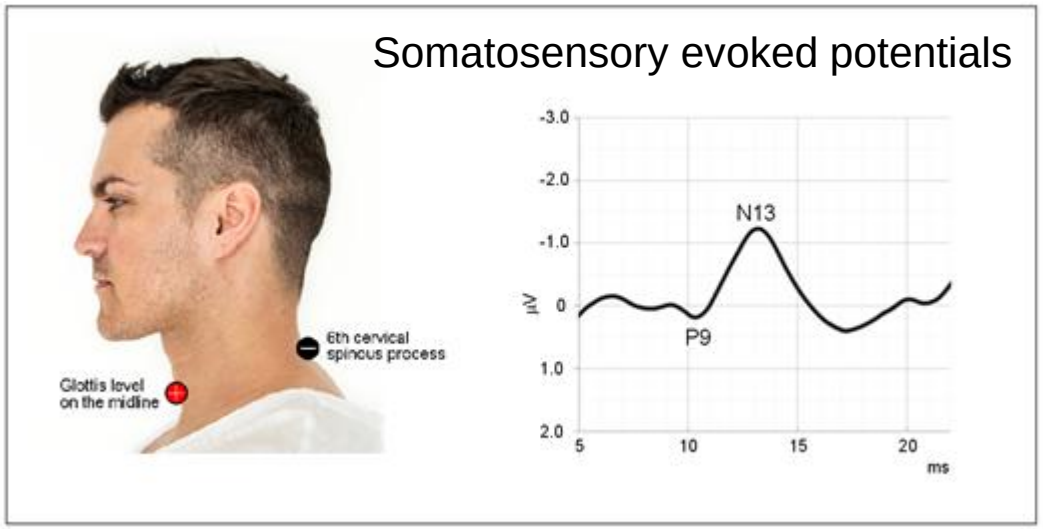
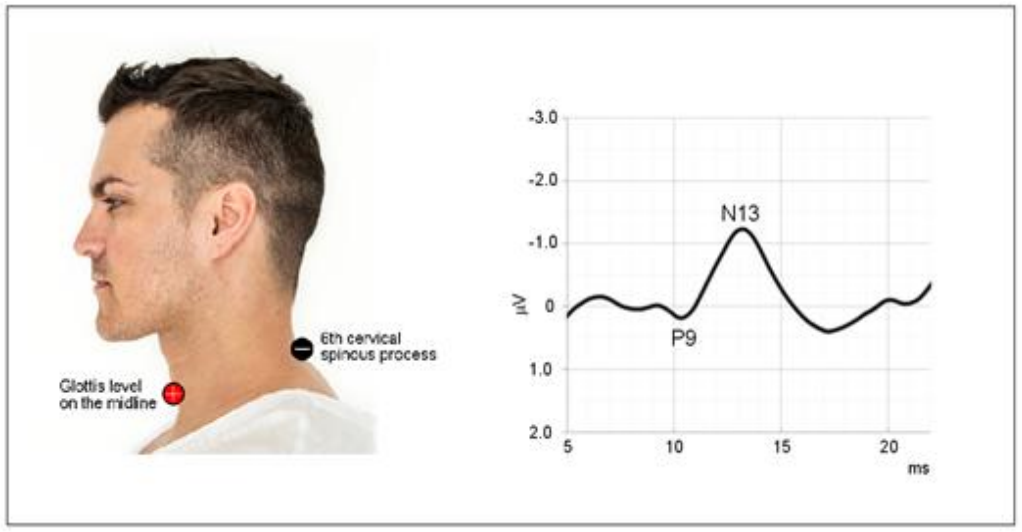


Table 1: Detailed time table of procedures and assessments in Periods 1, 2, 3 and 4

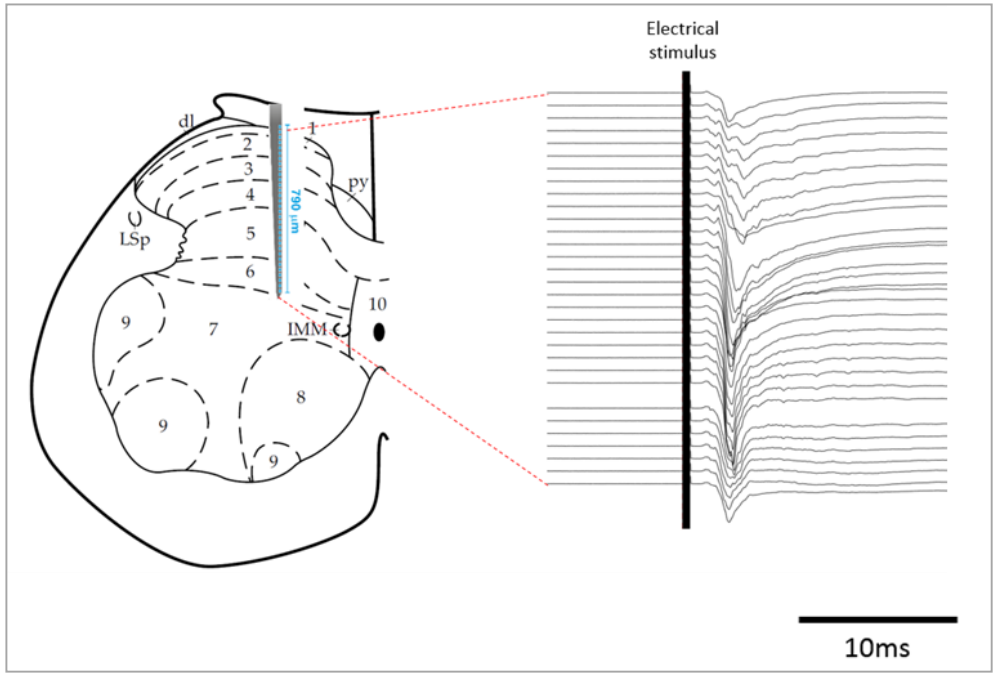
Clock time	Time relative to dose (min)	Time relative to HFS (min)	Dose	HFS	PK	PD	Hyper-algesia testing**	PROMs	(D)rink (M)eal
08:00	-150	-60							
08:30	-120	-30						X***	
09:00	-90	0		X					
09:30	-60	30				(1)			
10:00	-30	60							
10:30	0	90	X					X****	D
11:00	30	120							
11:15	45	135			(1)				
11:30	60	150				(2)			
12:00	90	180							
12:30	120	210					X		D
13:00	150	240			(2)				
13:30	180	270				(3)			
14:00	210	300							
14:30	240	330			(3)				M
15:00	270	360							
15:30	300	390						X	
16:00	330	420							
16:30	360	450				(4)			
17:00	390	480							
17:30	420	510			(4)				D
18:00	450	540							
Next day					(5)*				

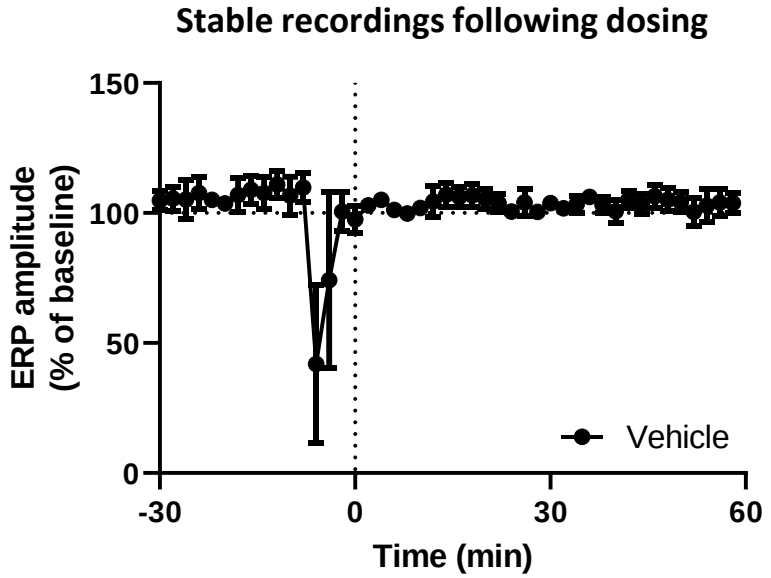
* The PK sample on next day can be taken at any suitable time provided that the exact time of sampling is precisely recorded

RCT2 equivalent in animals



- N13-SEP is a spinal evoked potential
- Elicited by electrical stimulation of the ulnar nerve
- Similar protocol can be performed clinically and pre-clinically
- In humans it is recorded with an electrode placed over the 6th cervical spinous process (Cv6).
- In rodents, high density silicon probe electrodes can be implanted in dorsal horn to simultaneously acquire data at multiple levels of the spinal cord





BioPain WP Structure and organisation

Hans vanNiel Grunenthal WP5 Leader

Andre Mouraux University of Louvain

WP 5
Consensus on clinical study designs

WP 6
Data engineering and statistics

Rolf-Detlef Treede University of Heidelberg WP6&8 Leader

WP 7

Nanna Finnerup Aarhus University

WP7 Leader

Andrea Schuckelt Grunenthal

WP7 Leader

WP 7
Clinical study implementation and operations

BioPain RCT 1 | BioPain RCT 2 | BioPain RCT3 | BioPain RCT4

e-room

Nanna Finnerup Aarhus University

RCT Lead

Andrea Truini Sapienza University RCT Lead

Andre Mouraux University of Louvain RCT Lead

Irene Tracey Oxford University RCT Lead

WP 8
Preclinical biomarker back-translation, with PK

Keith Phillips UK Pain Lilly UK Subtopic leader WP6&8 Leader

Difficoltà e vantaggi nella partecipazione ad un progetto EU funded

Difficoltà

Validate Application Results

EudraCT Number: 2019-000755-14
Sponsor's Protocol Code Number: IMI2-PainCare-BioPain-RCT2
National Competent Authority: Italy - Italian Medicines Agency
Validation Date and Time: 2019-05-17 16:09:22 CEST

The Clinical Trial (EEA CTA) has passed all validation rules.

DIPARTIMENTO DI NEUROSCIENZE UMANE

SAPIENZA UNIVERSITÀ DI ROMA

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Heads of Medicines Agency
Clinical Trials Facilitation Group

Rome 9th April 2019

VHP1461 (VHP2019036) -Response to validation comments received from participating Member States on 8th April 2019

VHP-No: VHP1461 (VHP2019036)
EudraCT-No: 2019-000755-14
IMP: Vimpat / Lyrica / Palexia
Study title: A randomized, double-blind, placebo-controlled, cross-over, multicenter trial in healthy subjects to investigate the effects of lacosamide, pregabalin and tapentadol on biomarkers of pain processing observed by non-invasive neurophysiological measurements of human spinal cord and brainstem activity
Participating Member States: Belgium, Germany BfArM, Italy

COMUNICAZIONE AL RICHIEDENTE, AGLI ALTRI COMITATI ETICI E AD AIFA DELLA DECISIONE DEL COMITATO ETICO RELATIVA AL PARERE UNICO

Il parere finale (favorevole o non favorevole) deve essere trasmesso entro trenta giorni dalla data di ricevimento della domanda nella forma prescritta (entro sessanta giorni in caso di sperimentazione monocentrica)

SC/MGM-ML/DG

AIFA/SC/P/146366

AIFA AGENZIA ITALIANA DEL FARMACO
Ufficio Sperimentazione Clinica

Roma, 20 DIC 2019
UMBERTO I - POLICLINICO DI ROMA Andrea Truini Viale dell'Università 30 00185 - Roma Italia andrea.truini@uniroma1.it

OGGETTO: EudraCT number: 2019-000755-14

TITOLO: Studio randomizzato, in doppio cieco, controllato con placebo, cross-over, multicentrico su soggetti sani, volto ad indagare gli effetti di lacosamide, pregabalin e tapentadolo sui biomarcatori del dolore mediante misure neurofisiologiche non invasive del midollo spinale e del tronco dell'encefalo.

Ministero della Salute

DIREZIONE GENERALE DEI DISPOSITIVI MEDICI E DEL SERVIZIO FARMACEUTICO
PEC: dgfdm@postacert.sanita.it
Ufficio VII– Ufficio Centrale Stupefacenti - Viale Giorgio Ribotta. 5 - 00144 Roma

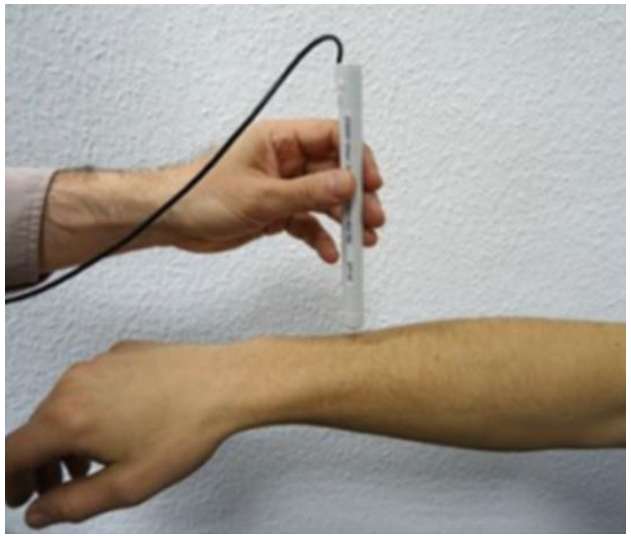
Ministero della Salute
DGDMF
0057570-P-14/09/2020
403429612

Università degli Studi di Roma La Sapienza
Dipartimento di Neuroscienze Umane
Viale dell'Università n.30
00185 Roma

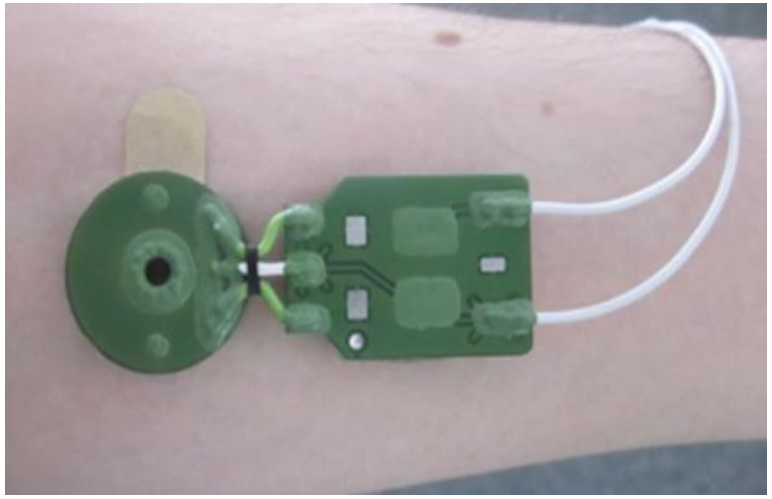
Fascicolo: DGDMF/VII/1.5.i.f.3.1/2020/3

OGGETTO: Autorizzazione ai sensi dell'art. 49 del D.P.R. 309/90
Decreto n. SC/14 del 14/09/2020 e permesso di importazione n.20 del 14/09/2020
Studio clinico EudraCT: 2019-000942-36, EudraCT: 2019-000755-14, EudraCT: 2019-001204-37
Codice protocollo IMI2-PainCare-BioPain.

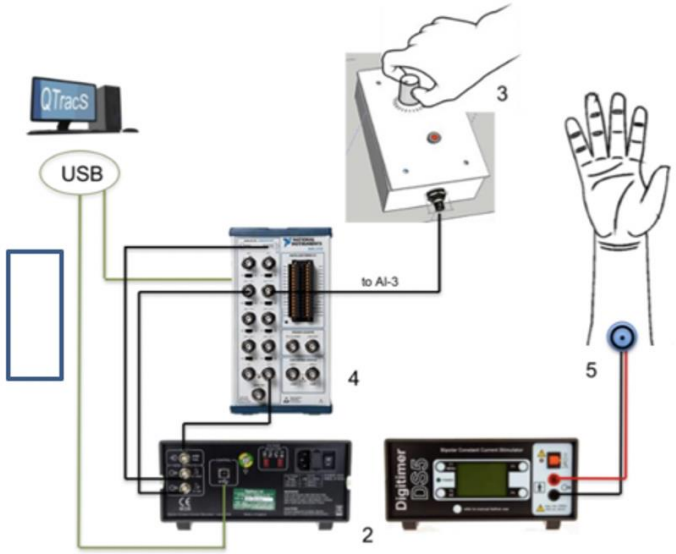
New tools for medical diagnosis and research



MRI-safe triggered pinprick stimulator for all RCTs (MRC)



Multi-pin electrode for the experimental induction of secondary hyperalgesia (MRC)



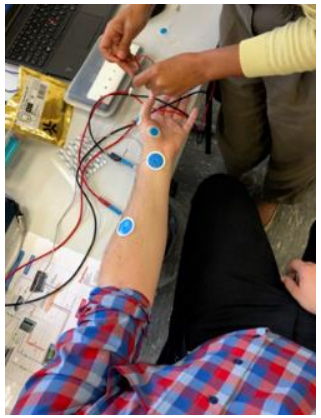
Psychophysics response box for RCT1 (NT)

See Innovation Radar

Training and certification of all centers on in-study procedures completed for all RCTs

- Study procedures standardized across centers
- Research fellows received training and certification
- Alignment on techniques, on-site demonstration and practicing
- Other trainings on CRF completion, PROMS and data flow, PK blood sample handling, GCP training and recruiting plan

BioPain RCT Alignment meeting, 25-27 Sep 2019
Location: Human Subject Laboratory, Medical Faculty Mannheim, Heidelberg University, Germany

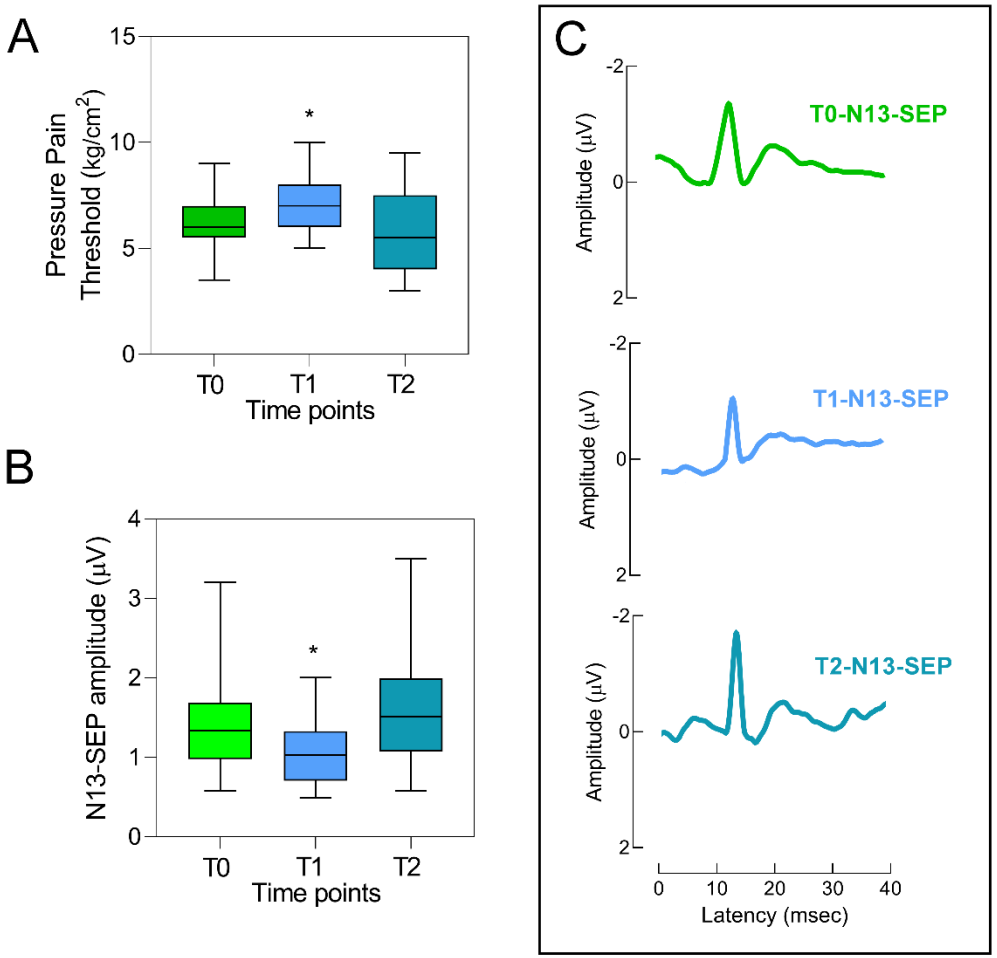
European Commission IMI-PainCare imi innovative medicines initiative

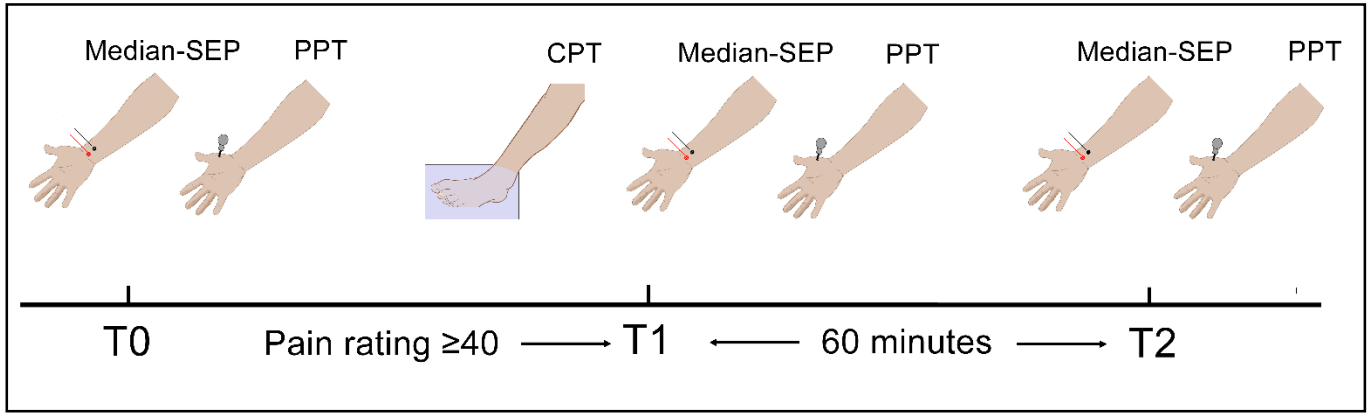
Andrea Di Lionardo

Giulia Di Stefano

Caterina Leone

Giuseppe Di Pietro





Di Pietro et al., Diffuse noxious inhibitory control modulates the N13 spinal component of somatosensory evoked potentials. Submitted to NCCN

Di Lionardo et al., The N13 component of the somatosensory evoked potential: a segmental dorsal horn field potential as a biomarker for testing central sensitization in humans. Submitted to Sci Rep

Leone et al., How different experimental models of secondary hyperalgesia change the nociceptive flexion reflex. Submitted to CLINPH

Sapienza is there