Dr Tatiana Besse-Hammer
Centre Hospitalier Universitaire Brugmann
Clinical Research Unit
Place A. Van Gehuchten, 4
1020 Bruxelles
Téléphone : 02/477.33.12
Tatiana.besse-hammer@chu-brugmann.be

At the attention of the EMA

Brussels, 16 July 2021

To whom it may concern,

EudraCT clinical trials results – clinical trial with no patients included

Sponsor	Centre Hospitalier Universitaire Brugmann (CHU Brugmann)		
Title	A randomized controlled trial of lidocaine patch for lower limb amputation pain		
EUDRACT	2016-000864-41	**Sponsor reference**	CHUB-Patch lidocaine

I hereby notify you that the study identified above was closed on 05 September 2019 with no patients included.

The clinical trial had already been placed on hold (temporary halt) since 02 June 2017. The reasons for not including patients in this clinical trial were: lack of recruitment and lack of human resources to perform the trial. The accumulation of delays furthermore caused the placebo patches to expire: new ones could not be obtained, therefore making the clinical trial impossible to perform.

The study design is annexed to this letter.

I remain at your disposition for further information on this clinical trial.

Kind regards,
Dr Besse-Hammer

C.H.U. BRUGMANN BRUXELLES
UNITÉ DE RECHERCHE CLINIQUE
DR BESSE H. TATIANA
1-94145-58-001

CHU | UVC BRUGMANN

Title	A randomized controlled trial of lidocaine patch for lower limb amputation pain
EudraCT	2016-000864-41
Sponsor	CHU Brugmann 4 Place A. Van Gehuchten 1020 Brussels
Justification	Phantom limb pain (PLP) and scar hyperalgesia (SH) are frequent problems after amputation: in particular most persons who undergo limb amputation will experience phantom pain. The neuropathic nature of PLP suggests the involvement of both peripheral and central neurological mechanisms, including neuroplastic changes in the central nervous system. PLP as other central nervous system-related pain syndromes remains a challenge for treatment. Scar hyperalgesia involves peripheral mechanisms and results from the production of substances liberated by damaged skin cells. These inflammatory substances lower the pain threshold by altering the chemical environment of the skin nerve endings. Scar hyperalgesia is associated with secondary mechanical hyperalgesia in the skin area around the scar. The lidocaine patch 5% is a topical analgesic acting by blocking sodium channels of peripheral nerve endings and by inhibiting ectopic discharges in sensitized and hyperactive cutaneous nociceptors. The patch is noninvasive, with minimal systemic absorption resulting in a reduced risk of drug-drug interaction. In addition, a central analgesic effect of lidocaine has been suggested. The lidocaine patch 5% is currently licenced for the treatment of symptomatic postherpetic neuralgia. It also has been successfully used in patients with other neuropathic pain states, such as entrapment neuropathies, painful idiopathic distal sensory polyneuropathies and postoperative/post traumatic neuropathic chronic cutaneous pain. The lidocaine patch has not been studied for the management and prevention of phantom limb pain. The aim of the present research is to investigate if a lidocaine patch 5% is effective for reducing PLP and primary/secondary scar hyperalgesia. The hypothesis is that persistent peripheral nociceptive input from the stump after surgery may drive maladaptive cortical reorganization leading to chronic central pain and thus promote chronic phantom limb pain. Treating scar hyperalgesia on the stump with topical lidocaine may reduce the activity of peripheral nociceptive afferents and thus decrease the likelihood of developing persistent phantom limb pain.
Primary outcome	- Patient reported overall daily pain intensity (stump, scar and PLP) rated on a 0 to 100 visual analogue scale with anchors of 0 (no pain) to 100 (worst pain experienced) - Pain as assessed with the following tools -DN4 neuropathic pain at baseline (defined as 7 days before patch placement) -Neuropathic Pain Symptom Inventory at baseline, one day, 6 weeks and 6 months after patch placement -Short Form McGill Pain Questionnaires sensitive to the effects of pain treatment administered at baseline, one day and after 6 weeks after patch placement -Quality of life: SF36 at baseline, 6 weeks and 6 months after patch placement -Sleep quality: assessed with the Pittsburgh Sleep Quality Index at baseline, 6 weeks and 6 months after patch placement.
Secondary outcome	- Delay of dress of provisory prosthesis (number of days between surgery and delivery of temporary prosthesis) - Delay of dress of provisory prosthesis (number of days between inclusion in the study and delivery of temporary prosthesis) - Cumulative analgesic consumption score (CACS): at baseline, one day and six

	weeks after patch placement - Phantom pain occurrence (PLP) 6 months after patch placement
Phase	II
Study design	Randomized controlled multicentric double blind trial (5% lidocaine patch vs sham)
Inclusion criteria	All above or below knee amputations in the first two months after surgery, after complete wound healing (no clips, no stitches, no seepage)
Exclusion criteria	- Younger than 18 years old - Patients with an history of central nervous system disease - Patients with an history of major psychiatric disease (MMS<23/30, HADS >8/20) - Pregnancy - Known hypersensitivity to local anesthetics (lidocaine, bupivacaine, etidocaine, mepivacaine, prilocaine) - Skin irritation of the stump
Planned recruitment	20 patients
Actual recruitment	0 patients
Study duration	Start date: 02 June 2016 Temporary halt date: 02 June 2017 End date: 05 September 2019
Study location	CHU Brugmann
Statistical analysis	Sample size was determined as follow. Fourteen patients (n=7) in each group are sufficient to detect a 30% difference in pain intensity score (i.e minimal clinical significant change) between the two treatment groups with 80% power assuming two-sided significance level of 0,05. Descriptive statistics (e.g means, standard deviations) were meant to be calculated and examined prior to statistical analysis. All quantitative variables were meant to be assessed for normality using normal probability plots and Kolmogorov-Smirnov test statistics and transformations will be applied as necessary. If transformations were not successful in normalizing the data, non-parametric methods would be used. All statistical tests for the primary study outcomes were meant to be performed at two-sided alpha=0,05 level. Secondary hypotheses tests were meant to be adjusted using Bonferroni correction. Covariates were meant to be entered into the models below as necessary. The primary outcome measure was meant to be the overall pain intensity score on the VAS scale. We planned to use mixed models with the pain score as the dependent variable, treatment (= type of patch) as a within-subject factor, time as a within-subject factor and the interaction between treatment and time. Unstructured variance-covariance was meant to be used to incorporate the correlations between repeated observations on the same subject. Mixed effects models use all available data on each individual, incorporate the correlation structure of the data and are flexible in testing specific hypothesis regarding change over time. A significant interaction between treatment and time was meant to be considered supportive of our hypothesis. Mixed models were meant to be used to assess differences in QST, neglect and MRI-DTI variables between treatments and across time. Mixed models were meant to be used to assess correlations between pain intensity change and other clinical characteristics (SF-MPQ total sensory score, NPSI dimensions, SF36, CACS, Pittsburgh sleep quality index, delay of dress of temporary prosthesis).
Expected benefits	- Reduction of subacute pain after amputation - Reduction of chronic phantom pain development - Reduction of the waiting period before the placement of a prosthesis on the amputated limb - Improvement of the sleep quality and the quality of life