Executive Summary:
Migraine is a common brain disorder, typically characterised by recurring, incapacitating attacks of 1-3 days of severe headache, autonomic dysfunction, and sometimes aura symptoms. The disease affects 15% of all European citizens including children, ranks among the WHO top 12 of most disabling and undertreated disorders, and is responsible for the highest socio-economic burden of any brain ailment in Europe.

Migraine attacks typically strike bi-monthly, and in 25% of patients once a week or more. Many patients may progress to 'chronic migraine' with near-daily headaches and high disability (chronification). There is
desperate need of effective prophylactic treatments to prevent attacks and chronification. Current medications are only moderately effective and often poorly tolerated, mainly due to lack of understanding of how attacks are triggered and why their frequency may increase so dramatically. Overuse of painkillers and triptans, are recognised risk factors for chronification, as are comorbid depression, stress, and obesity. Central sensitisation of pain signalling pathways appears to be pivotal to the chronification process.

EUROHEADPAIN research uses established and evolving human and translational animal models to: (a) identify pathways and biomarkers for the triggering and chronification of migraine attacks; (b) decipher the modulatory effects of (hypothalamic) brain circuitries on trigeminal processing, sensitisation, and chronification; (c) assess the effects and mode of action of migraine-provoking molecules; and (d) evaluate the efficacy and mode of action of neuromodulation (in collaboration with an SME) and second messenger-blocking drugs in the treatment of chronic migraine. We expect important spin-offs to the understanding of other chronic pain disorders. The pharmaceutical industry will be engaged once treatable targets have been identified to develop novel treatments to reduce the disability and socio-economic burden due to migraine.

Project Context and Objectives:
The EUROHEADPAIN project (http://www.euroheadpain.org) investigated mechanisms and treatments of migraine and its chronification by integrating pre-clinical and clinical research in a multidisciplinary manner, combining research efforts of 11 Participants (including one SME) of 9 countries. The project addressed both the clinical and scientific problem of migraine.

THE CLINICAL PROBLEM
Migraine: clinical features, epidemiology, and socio-economic impact
Migraine is a common, disabling, episodic brain disorder, typically characterised by recurring, usually incapacitating attacks of severe head pain and associated symptoms of autonomic and neurological dysfunction (migraine without aura). Migraine attacks last between 4-72 hours (median one day). In one-third of patients attacks are associated with neurological aura symptoms (migraine with aura). The disease affects 15% of all European citizens, ranks among the most disabling and undertreated disorders, and is responsible for the highest socio-economic burden of any brain ailment in Europe. Migraine attacks typically strike bi-monthly, and in 25% of patients once a week or more.

Some migraineurs may experience only a few attacks in their life, but the vast majority will get hit over and over again by ever recurring migraines. The individual attack frequency and severity may fluctuate due to factors such as hormonal changes, misuse of acute headache medication, stress, sleep-deprivation, intercurrent diseases, and other unknown factors. By and large, half of all migraineurs experience two or more attacks per month, and a quarter one or more per week. One in ten patients will progress from episodic to chronic migraine, experiencing headaches on 15 or more days per month (= chronification). Such patients may easily experience several hundreds of attacks. Chronic migraine is considered the most severe and most difficult-to-treat form of migraine. The chronification process may start spontaneously but is usually triggered by overuse of acute headache medication and/or caffeine, in particular in patients with overweight and/or depression. Comorbid depression is one of the psychological factors responsible for the severely reduced quality of life (QoL) seen in many migraine patients. Hence, improving QoL is regarded one of the targets when treating migraines.

Failing treatment
There is a huge unmet need of effective and well tolerated treatments for migraine. Although the acute treatment options for attacks have significantly improved with the advent of triptans, more than half of the patients are still dissatisfied. For prophylactic treatments, aimed at reducing attack frequency, the situation is even worse. All current migraine prophylactics were originally designed for other indications and were accidentally found to show “some efficacy” in “some patients” for only “some time”. Most patients have to undergo a long process of trial-and-error before they may experience at least some relief. A major reason for this delay is that physicians cannot predict who will respond to what treatment. Notably, overuse of painkillers and triptans are recognised risk factors for chronification, as are comorbid depression, stress, and obesity. The development of novel adequate migraine-specific medication is dearly needed but seriously hampered by patient heterogeneity in clinical trials and incomplete understanding of the disorder’s mechanisms, specifically the lack of understanding of how attacks are triggered and why their frequency may increase so dramatically.

Adequate treatment of migraine is further complicated by the unfortunate clinical reality that most physicians perceive the current diagnostic process of migraine (based on a careful, extensive and detailed medical history) as too impractical, cumbersome, and time-consuming. Although widely accepted validated and accurate diagnostic clinical criteria are available, migraine patients often are misdiagnosed and consequently undertreated. Improving means of diagnosing patients, including means for stratification of patients with respect to migraine subtypes and the who are more likely to respond to (specific) treatments would not improve patient care and benefit clinical trials.

THE SCIENTIFIC PROBLEM
Towards prevention of the triggering, initiation, recurrence, and chronification of migraine attacks
Although the mechanisms for the migraine headache and aura are reasonably well understood, much less is known about: (i) why migraine patients are predisposed to migraine attacks?; (ii) how migraine attacks are triggered?; (iii) why attacks recur?; (iv) why the attack-frequency may progress so dramatically to chronic migraine. The absence of a good understanding of how migraine attacks may begin has hampered the development of prophylactic treatments to prevent migraine attacks and chronification.

Human and animal studies have shown that glutamatergic-mediated cerebral hyperexcitability leading to increased susceptibility to spreading depression (SD) is pivotal to the initiation of attacks of familial hemiplegic migraine and other monogenic migraine subtypes. Whether similar mechanisms are involved in common migraines, is uncertain. In analogy to other chronic pain syndromes, central sensitisation of pain-signalling pathways is believed to be at the core of the chronification process leading to chronic migraine. How sensitisation in migraine might begin and progress is unknown. Studies to understand what makes the migraine brain different and predisposed to chronification are desperately needed.

THE EUROHEADPAIN PROJECT: APPROACHES AND OBJECTIVES
The EUROHEADPAIN consortium aimed to use and integrate knowledge of established and evolving human and translational animal models to: (i) better understand how migraine attacks have changed the biology in migraine patients; (ii) decipher modulatory effects of brain circuitries relevant to various aspects of migraine attacks; and (iii) generate novel treatment options for migraine patients. By unravelling disease mechanisms and effects and modes of action of migraine-provoking molecules and neuromodulation the project aims to increase the number of (potential) treatment options for patients. By understanding interindividual variations in migraine disease characteristics (by investigating various groups of migraine patients) and investigating how they may rely on distinct migraine mechanisms, the project is expected to
make an impact on migraine research, patients and society.

The EUROHEADPAIN project used specific approaches to understand and control pain in migraine:
1. Identification of biomarkers (clinical neurophysiological, neuroimaging, biochemical, molecular, and genetic) biomarkers for better diagnosis, identification of disease mechanisms, and stratification of migraine patients;
2. Dissection of neurobiological mechanisms, in animal models and patients, to understand why migraine attacks occur and identify possible new treatment targets for mechanism-based prevention of migraine;
3. Identification (and testing) of novel prophylactic pharmacological treatment targets for mechanism-based prevention of attacks and chronification;
4. Optimising neuromodulation treatment protocols and devices to improve treatment of migraine.

The EUROHEADPAIN project had defined objectives for 5 so-called Work Packages (WP) aimed at translating cardinal clinical and pre-clinical questions into: a) pathogenic answers; b) improved means to diagnose and stratify patients; c) therapeutic solutions; and d) education to the medical and scientific communities as well as to patients and the general public. Our research had the objective to:
1. Identify (and validate) clinical neurophysiological, neuroimaging, biochemical, molecular, and genetic interictal biomarkers for (WP1 and WP2):
   a. The diagnosis of migraine, to enable better diagnosing of patients with episodic or chronic migraine.
   b. The pathophysiologiical changes in the “interictal migraine brain”, to gain insight into the neurobiological mechanisms underlying susceptibility to migraine pain-provoking triggers.
   c. The pathophysiologiical changes in the “chronic migraine brain state”, to increase our understanding of the neurobiological mechanisms underlying chronification and to assess the functional and structural consequences of chronification to the brain.
   d. The predisposition to chronification, to enable identification of patients who are at risk of chronification and should receive prophylactic treatment.
   e. The prediction of treatment response, to enable improved stratified care for migraine.
2. Establish clinical neurophysiological, neuroimaging, biochemical, and molecular preictal/periictal biomarkers, i.e. those that are particularly relevant to the onset of migraine attacks (WP3).
3. Dissect mechanisms for the triggering and chronification of migraine attacks (WP1 and WP3) to identify novel treatment targets for mechanism-based prevention of attacks and chronification.
4. Unravel neurobiological mechanisms modulating migraine pain and chronification (WP4), by deciphering the effects of hypothalamic and cortical and subcortical brain circuitries on: a) trigeminal processing; b) other migraine-relevant pain-pathways; c) central sensitisation of the brain; d) other mechanisms involved in the process of chronification.
5. Determine effects and modes of action of second messenger-modulating molecules in provoking and treating migraine attacks (WP5) to identify: a) new pain-inducing pathways; and b) novel treatment targets for the alleviation and prevention of migraine pain.
6. Optimise protocols and devices for neuromodulation treatment of migraine (WP5).
7. Disseminate knowledge generated by EUROHEADPAIN on: a) how migraine can be diagnosed with the aid of biomarkers; b) how migraine attacks are initiated and how this process can be prevented; c) how migraine pain is generated and how this process can be blocked, alleviating the pain; d) how chronification of migraine may begin and progress, and how this process can be prevented, halted, and reversed.
The combined research of EUROHEADPAIN addressed most relevant aspects of migraine. Our biomarker research will improve patient diagnosis and stratification. Our experimental animal research will unravel important pathophysiological mechanisms relevant to specific migraine subgroups in relation to their attacks. Our investigations in patients will reveal how attacks may change the migraine brain and how we can modulate these changes by pharmacological interventions or non-invasive neurostimulation. Therefore, we expect EUROHEADPAIN research will have an important impact, not only by advancing our understanding of migraine pain processes, but also because it will yield novel treatment targets and solutions to the benefit of patients. In addition, we are training young scientists in Europe at the highest level in translational research on pain mechanisms, not only of migraine but also in general. Finally, EUROHEADPAIN will create a unique network of top Centres in Europe that will provide a unique source of basic knowledge that can be translated to clinical solutions to treat pain, in collaboration with pharmaceutical or biotech companies. Dissemination of knowledge on migraine throughout the scientific community and to other stakeholders, such as patient organisations and pharmaceutical companies is an essential part of the project.

Project Results:
EUROHEADPAIN aimed to identify, investigate, diagnostic, predictive and pathophysiological biomarkers for the susceptibility for and initiation, modulation and chronification of migraine attacks to improve diagnostic and treatment options for episodic and chronic migraine. The multidisciplinary EUROHEADPAIN consortium has direct access to over many thousand well phenotyped genoptyped migraineurs. Our extensive clinical resources consist of a rich phenotypic data set with additional clinical, pharmacological, genetic, biochemical, neurophysiological and (functional) neuroimaging information. Within the consortium we have developed complementary animal and in vitro experimental models that provided detailed insight into the mechanisms for the generation and modulation of migraine pain.

EUROHEADPAIN research combined activities using various approaches (described in section 2) to investigate migraine patients and relevant cellular and animal models of migraine to investigated mechanisms and treatments of migraine and its chronification by integrating pre-clinical and clinical research in a multidisciplinary manner. The research is structured in 5 scientific work packages WPs (WP1-WP5).

Patients with episodic or chronic migraine were studied outside an attack and when possible longitudinally followed through the transition from pre-ictal to ictal until an attack has occurred (e.g. neuroimaging data of patients that were subjected to fMRI for 30 days in a row to capture spontaneous attacks and link those to brain changes that gave insight into where attacks started and how they progress). Profiling of biochemical changes (in plasma and CSF), (functional) neuroimaging changes, and neurophysiological changes, whenever possible in the same patients – which had never been done before –, was performed to obtain interictal biomarkers for the diagnosis of and susceptibility to migraine and chronification. Neurophysiological and neuroimaging profiling was performed to investigate the transition from pre-ictal to ictal to dissect the initiation pathway of attacks and obtain predictive and initiation biomarkers and networks. Detailed mechanistic insight on brain changes relevant to migraine pathophysiology were obtained from translational studies in transgenic mice carrying migraine mutations previously identified in patients with a monogenic form of migraine. Complementary read-outs from cell culture systems and animal studies made it possible to dissect peripheral and central (hypothalamic) mechanisms for the
generation and modulation of migraine pain. This information was fed by genetic profiles with many identified genetic factors and associated molecular pathways. In addition the genetic findings highlight risk factors for episodic and chronic migraine and have the possibility to predict or assess treatment response. Finally, attacks were provoked in interictal patients and healthy subjects using pharmacologically different molecules to develop provocation target tests and decipher triggering pathways for migraine attacks towards novel treatments. Improved options for non-invasive neuromodulation for chronic and episodic migraine were developed both by optimising neurostimulation protocols and improving the equipment (in close collaboration with an SME) as well as advancing the understanding of how neuromodulation works using neurophysiological and neuroimaging tools.

A more detailed description of the main S & T results/foregrounds is provided below. Only a short general description of the main results can be provided as most of the specific information is confidential and publication would undermine the protection of commercial interests, including intellectual property, or privacy and the integrity of the individuals. Per WP a short highlight of the main result in relation to the objectives is provided.

WORK PACKAGE 1 - INTERICTAL AND PRE-ICTAL BIOMARKERS AND PATHWAYS FOR EPISODIC AND CHRONIC MIGRAINE

Partners P2-ULG (Lead beneficiary) and P1-LUMC, P3-UKE had the objective to: (1) identify and validate interictal biochemical, neuroimaging, and neurophysiological biomarkers to establish objective diagnostic tests for migraine; (2) stratify migraine patients for treatment based on biomarker profiles; (3) identify patients that are at risk for chronification; (4) identify subgroup specific pathways for migraine pain; and (5) identify novel migraine prophylactic treatment targets.

Patients with episodic or chronic migraine (and matching controls) were recruited for the studies at the various research sites aimed at the identification of biomarkers linked to the interictal phase of the migraine attack. A total of 15 number, in line with Annex 1, were performed aimed at (1) biochemical profiling of CSF/plasma, (2) neuroimaging profiling; and (3) neurophysiology profiling. The objectives and deliverables were met.

Most notable results: 1) The combined structural, functional and metabolomic assessment in the same patient, which had never been done before, revealed promising biomarkers (brain changes) relevant to episodic and chronic migraine. 2) Novel approaches based on neurophysiological visual evoked potential (VEP) sub-analyses yielded three biomarkers. These biomarkers, after further validation after the end of the project, are likely to lead to an accurate inexpensive and easy accessible objective biomarker for the diagnosis of migraine and the stratification of patients. 3) On the mechanistic level, it was shown that chronic migraine is associated with atrophy (decreased grey matter volume) and hypometabolism in the (orbito)frontal regions of the brain. 4) Using a modified high-resolution MRI sequence, daily scanning for 30 days of migraine patients that underwent one or more spontaneous attacks identified the hypothalamus as important in the actual headache phase, whereas the anterior hypothalamus serves as a neuroimaging biomarker for chronic migraine.

Other significant results:
1. Cerebrospinal fluid (CSF) and plasma was collected from migraine patients with hemiplegic migraine (N=19), migraine patients with aura (N=99), migraine patients without aura (N=98), and healthy controls
and analysis was performed of these samples on various platforms for proteomics, peptidomics, and metabolomics measurements, as described in Annex 1. Proton magnetic resonance spectroscopy (1H-NMR)-based metabolomics quantified sixteen metabolites in CSF and revealed several compounds that were significantly different in hemiplegic migraine patients compared to healthy controls; one was significantly lower in both migraine with and without aura patients compared to healthy controls.

2. A longitudinal study was performed to investigate biomarker profiles reflecting changes associated with the triggering or initiation of migraine attacks in male episodic migraine patients and controls with saliva and serum measurements (4 measurements/day) leading to a spontaneous migraine attack. Biomarker information from these body fluids was combined with neurophysiological blink reflex measurements. In saliva, the primary focus was on measuring CGRP levels, as CGRP is implicated in migraine pathophysiology, and serum levels of reproductive hormones.

3. Neuroimaging using (1H-MRS) was performed to study: (i) the interictal phase of episodic migraine and measure differences in concentrations of metabolites in vivo in the brain of migraine patients and healthy controls; (ii) different phases of a glyceryl trinitrate (NTG) provoked migraine attack; and (iii) brain networks and biochemical profiles associated with the initiation of migraine attacks in female patients with menstrually related migraine and control subjects that were daily followed until their first migraine day (episodic migraine) or the first day of menstruation (controls).

4. Different multimodal studies were conducted aimed to: (i) establish interictal electrophysiological and neuroimaging profiles of patients with episodic and chronic migraine, including those with medication overuse headache, by comparing physiological (i.e. evoked potentials), structural, metabolic and functional differences between healthy controls and patients; and (ii) correlate electrophysiological patterns (i.e. habituation) with imaging data.

5. As conventional analyses of broad-band VEP did not reveal significant differences between migraine subtypes and controls in terms of habituation or latencies, novel approaches of VEP analysis were applied. A reproducible machine learning classifier based on VEP subcomponents allowed us to establish a diagnostic biomarker of migraine with an accuracy of 86% in episodic migraineurs and 70% in controls.

6. Assessing cold and heat sensory and pain thresholds in patients between attacks using quantitative sensory testing (QST) revealed two distinct sensory profiles in the general population: 'Hyper-' and 'Hypo'-sensitive. A significant difference in pain threshold was found between 'hypersensitive' controls and chronic migraine patients. Distinct central correlates of pain sensitivity were found in migraine patients and could therefore represent a biomarker of migraine and perhaps its chronification.

7. Neuroimaging of various groups of migraine patients revealed that: (i) chronic migraine, with or without medication overuse, is associated with decreased grey matter volume and hypometabolism in (orbito)frontal regions; (ii) glutamate level is increased in the thalami of episodic migraineurs; and (iii) functional coupling between the visual cortex and the thalamus is lacking in migraineurs.

8. By daily neuroimaging using fMRI in migraineurs and controls challenged by trigemino-olfactory stimulation a unique data set was obtained that recorded a number of spontaneous migraine attacks that will be instrumental to assess the brain state of a migraineur in the interictal phase and will reveal relevant changes in the peri-ictal and pre-ictal phases, and the dynamics over several migraine cycles.

9. Spinal imaging was optimised for brainstem imaging by involving 21 healthy volunteers, and the protocol was subsequently used in migraineurs and controls challenged by trigemino-olfactory stimulation to identify brainstem structures involved. Significant BOLD responses to noxious ammonia stimulation were observed in areas typically involved in trigeminal nociceptive processing, cerebellum, and a pain-modulating network. Activations of certain brain regions were positively correlated with pain intensity.
ratings. Employing Psychophysiological-Interaction-(PPI)-analysis enhanced functional connectivity of specific brain regions was found following trigeminal nociception.

WORK PACKAGE 2 - GENETIC BIOMARKERS AND MOLECULAR PATHWAYS FOR EPISODIC AND CHRONIC MIGRAINE

Partners P5-UH-FIMM (Lead beneficiary) and P6-QUT had the objective to: (1) obtain genotypic data from EUROHEADPAIN and IHGC patient collections; (2) identify novel genetic risk factors for migraine pain and subgroups of migraine, including patients with frequent attacks; (3) understand the genetic structure of migraine subgroups by patient stratification; and (4) mine pain- and migraine-relevant pathway information from available genotype data sets.

By combining efforts from EUROHEADPAIN and other initiatives it was possible to genotype and obtain imputed data of a large number of migraine cases that in fact exceeds the target number of 9,500. At the end of the project, EUROHEADPAIN has access to an imputed data set of no less than 59,674 migraine cases and 316,078 controls. The objectives and deliverables were met.

Most notable results. EUROHEADPAIN research identified 38 novel genetic risk factors for common migraine (far more than the 5 planned indicators); seven of which are most relevant for migraine without aura. The observation that no such loci were identified for migraine with aura underlines the polygenic nature and different genetic architecture, i.e. for variants with the highest impact in migraine subtypes. Further investigations revealed a significant overlap for associated genes of migraine subtypes, which can explain their co-occurrence within the same patient or family and provides a rationale for developing drugs that treat patients irrespective of their migraine type. With respect to the molecular pathways involved, the genetic data revealed enrichment for vascular and smooth muscle genes. The research highlighted the existence of shared genetic factors shedding light on the comorbidity between migraine and depression and the involvement of epigenetic mechanisms in the chronification of headache.

Other significant results:
1. Overall genetic overlap between migraine subtypes was assessed using SNP effect concordance analysis (SECA) at over 23,000 independent SNPs. Significant heterogeneity of SNP effects (Phet < 1.4 x 10−3) was observed between the migraine with aura and migraine without aura subgroups (for SNP rs9349379), and between clinic- and population-based subgroups (for SNPs rs10915437, rs6790925 and rs6478241). For all 12 SNPs the risk increasing allele was the same, and SECA found the majority of genome-wide SNP effects to be in the same direction across the subgroups. Hence, it was concluded that any differences in common genetic risk across these subgroups is outweighed by the similarities.
2. Gene-based overlap (pleiotropy) was identified between migraine with aura and migraine without aura using various statistical approaches by mining the available genetic data, beyond the inspection of only the genome-wide significant loci, of 4,505 patients with migraine with aura, 4,038 patients with migraine without aura, and over 75,000 control subjects. Findings suggest a significant overlap in genes associated with both migraine subtypes; with genes enriched for functions related to inflammation, the cardiovascular system and connective tissue.
3. Systematic evaluation of 27 previously identified candidate genes (from association studies) in relation
to migraine subgroups was performed in GWAS data of 5,175 clinic-based migraine patients and 13,972 controls - so far the most powerful study sample (power > 95%) than any previous publication - indicated that most likely all previous studies had been severely underpowered as none of the previous findings could be replicated in a much larger data set, thus providing an important message that previous candidate gene studies should be critically interpreted.

4. Evaluation of shared genetic contribution among co-morbidities of migraine revealed a significant overlap of genetic risk loci between migraine and coronary artery disease (CAD). When stratified by migraine subtype, this was limited to migraine with aura; the overlap was protective in that patients with migraine had a lower load of CAD risk alleles than controls. Genes indicated by 16 shared risk loci point to mechanisms with potential roles in migraine pathogenesis and CAD, including endothelial dysfunction (PHACTR1) and insulin homeostasis (GIP). In another, similar genetic study evidence was obtained for shared genetic factors underlying migraine and depression. Findings suggest a bi-directional association between migraine and depression, with an increased risk for depression in relatives of probands reporting migraine, and vice versa. However, the observed risk for migraine in relatives of probands reporting depression was considerably higher than the reverse. These results add further support to previous studies suggesting that patients with comorbid migraine and depression are genetically more similar to patients with only depression than patients with only migraine.

5. Exome chip analysis combining datasets of 13,532 migraineurs and 40,370 matching controls, aimed to find low frequency variants in migraine subtypes, identified several SNP variants (at exome-wide significance threshold) that had already surfaced in the large migraine GWAS. For migraine with aura no exome-wide significant variants were detected (probably due to lack of statistical power).

6. Cell-type specific association analysis in migraine GWAS data of 4,954 clinic-based patients with migraine and 13,390 controls, using curated sets of synaptic genes and sets of genes predominantly expressed in astrocytes, microglia and oligodendrocytes, showed that gene sets containing astrocyte- and oligodendrocyte-related genes are associated with migraine, which is especially true for gene sets involved in protein modification and signal transduction. Observed differences between migraine with aura and migraine without aura indicated that both migraine types, at least in part, seem to have a different genetic background.

7. Brain-region specific association analysis in migraine GWAS data of 23,285 migraine cases and 95,425 controls combined with high-resolution spatial gene expression data of normal adult brains from the Allen Human Brain Atlas, identified specific brain regions and molecular pathways, including: (i) neurotransmission, protein catabolism and mitochondria in the cortex; (ii) transcription regulation in the cortex and cerebellum; and (iii) oligodendrocytes and mitochondria in subcortical areas that are possibly involved in migraine pathophysiology. The results provide support that these brain regions and pathways are involved in migraine pathophysiology.

8. A genetic study aimed at identifying cross neurological and psychiatric disorder gene sharing with migraine, conducted by IHGC as part of the Brainstorm consortium - a world-wide collaboration among GWAS meta-analysis consortia from 23 brain disorders - systematically evaluated the evidence for genetic sharing of risk alleles across this wide spectrum of brain disorders. In total data of 214,981 cases and 719,477 controls was analysed and the manuscript submitted for publication so specific results cannot be revealed in this report.

WORK PACKAGE 3 - PREDICTIVE BRAIN CHANGES AND MECHANISMS FOR THE TRIGGERING
AND INITIATION OF MIGRAINE ATTACKS

Partners P1-LUMC (Lead beneficiary) and P3-UKE had the objective to: 1) identify neurophysiological brain changes relevant for the prediction of migraine attacks; 2) elucidate neurobiological network mechanisms and modulatory factors in mice relevant to attack initiation in patients; and 3) build computational models for predicting brain network stability in migraine.

Various studies were performed towards the identification of human neurophysiological markers for the attack initiation and chronification that reflect neurophysiological brain changes reflecting “early-warning signals” in migraine. In addition, two neuroimaging studies were preformed, including one aimed at revealing cycling dynamics of migraine attacks with information on brain changes (and likely mechanisms) responsible for the pre-, peri- and ictal phases of attacks was performed successful. Also the establishment of a state-of-the-art platform for assessing attacks in migraine mice – and the generation of a novel mouse mutant – was completed. Even without the establishment of an actual computation model of trigeminovascular pain pathways to predict the stability of brain network dynamics (specific deliverable 3.5) essentially, objectives and deliverables were met.

Most notable results. 1) The developed Leiden Visual Sensitivity Scale test showed that migraine patients are visually more sensitive to light, both interictally and ictally; patients with migraine with aura are more sensitive than migraine patients without aura. 2) Functional MRI in patients, daily scanned for 30 days, revealed brainstem alterations that may reflect overall susceptibility to an upcoming attack with a functional change in hypothalamic-brainstem connectivity that could be the direct driver of a migraine attack. 3) A novel conditional knockin S218L mutant strain that allows the investigation of specific brain regional differences after a switch induced by expression of Cre recombinase after crossing of the conditional mice with a specific Cre transgene or injection of a virus (in which expression is driven by the relevant promoter).

Other significant results:
1. The data show that visual sensitivity is related to cortical excitability, which can be used as an easy measure of altered cortical excitability, likely a day-to-day implementation of this questionnaire is well possible which will allow tracking of a patient’s visual sensitivity over the migraine cycle as a possible early-warning signal for upcoming attacks. The development of portable EEG equipment methodology will soon enable measurements of VEP-EEG to the participant’s own home.
2. Multi-sine light stimulation combined with novel nonlinear EEG analysis method ‘multi-spectral phase was developed and tested to discriminate between the migraine with aura group and groups of healthy controls and migraine-without-aura providing a means to test how differences in cortical excitability can result in migraine attack initiation.
3. Transcranial magnetic stimulation (TMS) induced potentials (TEP’s) using 64-channel EEG were recorded in migraine patients with aura and healthy controls. Observed altered timing of cortical evoked responses help understand the multi-sine results.
4. An integrated unique platform for longitudinal intracortical MUA and EEG recordings, with the possibilities for VEP analysis and optogenetic triggering of attacks was established in freely behaving mice that revealed (i) changes in hippocampal excitability and long-term plasticity, (ii) revealed increased gamma power in the visual cortex, (iii) and occurrence of spontaneous CSD events in mutant mice.
5. Using optogenetics it was shown that (i) CSD events can be evoked by shining light of the appropriate wavelength through the intact skull of mice expressing light-sensitive ChR2 ion channels in the cortex (Tolner et al. Pain 2015); (ii) epileptic events can be optogenetically controlled by making use of such light-sensitive channels expressed in cerebellar nuclei of mice that also express mutated voltage-gated calcium channels; and (iii) that optogenetically non-invasively induced CSD has characteristics that are well comparable to those of invasive KCl application (through a burr hole in the cortex) but with the huge advantage that CSD can be applied for various days – a paradigm that fits the investigation of brain changes involved in the chronification of attacks and assessed behaviourally (e.g. grip test).

6. With respect to reversing treatment modalities assessed in mice, effects of stress as a migraine-trigger investigated in anaesthetised transgenic migraine mice (those that express the milder R192Q gene mutation) revealed that acute rises of the level of stress hormone corticosterone enhanced the susceptibility for experimentally induced CSD specifically in migraine mutant mice by activation of glucocorticoid receptor pathways.

7. Mass spectrometry imaging revealed CSD- and genotype-specific molecular changes in the brain of FHM1 transgenic mice.

8. A theoretical framework of dynamic network biomarkers in patients was established. Although EUROHEADPAIN yielded very promising data set (including data of neuroimaging and neurophysiology in the same patients), the development and measurement of such data sets was done too late into the project to be the basis of meaningful modeling. Such research will however be continued after the end of the project.

9. The framework of point 8 was used to investigate attack symptoms with symptoms of the premonitory phase in over 1000 German migraine patients. In more detail, premonitory symptoms with an onset of 2 or more hours prior to the headache were present in 38.9% of migraine patients, the most frequent being a tense neck, phonophobia and difficulty concentrating. There was a clear overlap of certain trigger factors and the presence of corresponding premonitory symptoms: flickering or bright light as a trigger was associated with higher frequency of photophobia in the premonitory phase. The same applied to the presence of food craving and osmophobia in the premonitory phase and certain foods or odours as trigger factors. These data support the view that commonly reported trigger factors of migraine are not so much independent precipitators of migraine pain, but that they are most likely just misinterpreted results of enhanced attention to certain stimuli mediated by typical premonitory symptoms of migraine pain.

10. Multimodal neuroimaging was performed as an approach towards detecting early warning signs of an imminent transition towards a migraine attack; foremost collecting data of neuroimaging and neurophysiology measurements in the same patients. To this end patients with episodic migraine, chronic migraine and healthy volunteers underwent a 18-FDG-PET scan and a MRI with different sequences (T1, T2 flair, Diffusion Tensor Imaging 64 directions, Proton NMR Spectroscopy and Resting-state fMRI), in addition to neurophysiological testings (VEP, QST, nBR, CHEPS).

WORK PACKAGE 4 - UNDERSTANDING NEUROBIOLOGICAL MECHANISMS OF MIGRAINE PAIN

Partners P7-SISSA (Lead beneficiary) and P3-UKE, P8-FAU, P13-KCL had the objective to: (1) dissect brain stem and hypothalamic circuitries and molecular mechanisms relevant to trigeminal processing of pain signals, to find out the relative contribution of peripheral and central neurons to sensitisation; (2) validate and manipulate these structures to understand episodic and chronic migraine pain; and (3)
explore, by manipulating mechanisms relevant to migraine pain, the therapeutic potential of novel targets against migraine pain.

The research identified various mechanisms relevant to migraine pain and means to manipulate these mechanisms. Studies in rats and humans identified risks and therapeutic potential of manipulations relevant to the migraine pain cycle. The objectives and deliverables were met.

Most notable results. 1) Chemical derivatives of TNP-ATP are strong blockers of purinergic P2X3 receptor activity on trigeminal neurons suggest a potential pharmacological mechanism to control trigeminal pain. 2) A rat model of migraine showed the impact of hypoglycaemia on TCC neuronal responses as a potential mechanism for dietary induced alterations in trigeminovascular processing. 3) The ability of LY466195 to inhibit trigeminovascular nociceptive processing in an animal model highlights the potential of targeted GluK1 mechanisms as a potential therapy for migraine. 4) The NO-H2S-HNO-TRPA1-CGRP signalling cascade has been established in mechanisms of meningeal nociception. Other endogenous signalling substances (5-HT, ATP) are differentially involved in meningeal nociception and can also be preventive in headache generation. 5) Several neuropeptides involved in the regulation of blood glucose levels were shown to modulate trigeminal nociceptive responses thus highlighting that trigeminal pain processing neurons are responsive to alterations in energy metabolism that may help explain the association between the regulation of appetite and migraine. 6) A novel differential role for the brainstem locus coeruleus was identified in migraine. Ablation of the locus coeruleus noradrenergic neurons reduced trigeminal nociception, but decreased cortical spreading depression thresholds.

Other significant results.
1. A model of hemisected rat cranial preparation indicated the involvement of purinergic receptors in meningeal nociception possibly generating headaches.
2. Evidence was obtained from animal research that trigeminal neurons responsible for headache generation in humans are activated by nociceptive events in pericranial muscles and can be silenced by anaesthesia of pericranial afferent inputs.
3. BNP is an endogenous biomarker of trigeminal sensory neuron excitability and its inhibitory action is lost in a genetic migraine mouse model.
4. Trigeminal sensory neurons express a full complement of the receptor for the migraine mediator CGRP, indicating a site of action for anti CGRP migraine treatment.
5. Nociceptive processes within extracranial periosteum and deep pericranial muscles can contribute to headache generation by direct innervation through collaterals of meningeal afferents, which implicates the usefulness of extracranial manipulations for headache therapy.
6. Levels of CGRP in different compartments (meningeal tissues, CSF, blood) vary dependent on the release sites; they are far too low to explain any effects on CGRP receptors, which is important regarding new strategies in migraine therapy.
7. The nasal mucosa is innervated by chemoreceptive afferents responding to ammonia, the chemical test stimulus used in neuroimaging in humans to examine the migraine pain cycle. The afferents project to the trigeminal nuclear brainstem complex, which is in accordance with the activation sites detected with fMRI.
8. Spinal imaging for brainstem in humans was optimised and validated.
9. A specific role of the cerebellum in trigeminal nociceptive transmission was established.
10. The optimised method for brainstem imaging revealed differences in brainstem. activations/modulation
between migraine (chronic and episodic) and healthy controls; in total 9 patients and 6 controls were scanned every day for 30 consecutive days.

11. Specific functional inhibition of trigemino-cortical projections is one of the reasons that triptans, unlike pain killers, act highly specific on headache and migraine but not pain as such.

WORK PACKAGE 5 - EFFECTS AND MODE OF ACTION OF PHARMACOLOGICAL AND NEUROMODULATION TREATMENT OPTIONS FOR MIGRAINE

Partners P10-REGIONH (Lead beneficiary) and P2-ULG, P11-Cefaly, P12-USZ had the objective to: 1) test several novel classes of drug targets for their ability to provoke migraine headaches in double-blind, placebo-controlled, cross-over studies; 2) elucidate modes of action of these drug targets in an experimental rat model of migraine; and 3) test existing, and develop novel, non-invasive magnetic or direct current stimulation devices for their potential to change brain changes, connectivity, and metabolism, and efficacy to reduce pain.

Various studies were performed aimed at (i) testing novel migraine provocation treatment targets and (ii) elucidating modes of action of migraine drug targets in rats. In addition optimised protocols and novel devices were obtained for neuromodulation to treat migraine patients. Also efforts (using neurophysiology and neuroimaging) were made to understand the neurobiological basis for why neuromodulation can be effective. The objectives and deliverables were met.

Most notable results. (1) Phosphodiesterase 3 inhibitor cilostazol induces migraine-like attacks via cyclic AMP increase. These data suggest that compounds that either inhibit the production or increase the degradation of cyclic AMP may be new antimigraine drug targets such as activators of PDE3 or inhibitors of the membrane-associated or cytosolic site of adenylate cyclase. (2) Hypoxia may be used to provoke migraine and aura attacks, allowing us to investigate aura and headache mechanisms under controlled conditions. (3) Isosorbide-5-mononitrate (5-ISMN) may be used to provoke migraine like attacks in healthy volunteers. (4) 5-ISMN and cilostazol models may be used to test current and future anti-migraine drugs. (5) Neuromodulation techniques represent an efficient therapeutic alternative for chronic migraine treatment. (6) The clinical benefits observed after transcutaneous occipital nerve stimulation are accompanied by modifications in key pain processing regions of the central nervous system that can be illustrated through neuroimaging techniques. (7) Successful registration of Cefaly technology towards the Belgian competent authorities.

Other significant results.
1. Natriuretic peptides in physiological and pharmacological doses do not cause headache and do not affect blood flow velocity in the middle cerebral artery or dilate extracerebral arteries in healthy volunteers.
2. The hypersensitivity of migraine patients to infusion of CGRP and PACAP38 shows no association to family history of migraine.
3. Endovascular therapy results in temporary increase in headache in the first 3 months after procedure, which normalizes over time.
4. The novel NTG and CSD combined rat model may be suitable for testing compounds with only moderate or subtle effects via the assessment of the ratio of propagation of CSDs.
5. Two of the tested kynurenic acid analogues were able to restore the ratio of propagation to the control level, thus were able to interfere with CSD propagation.

6. While both transcutaneous occipital nerve stimulation and transcutaneous direct current stimulation offer similarly beneficial clinical results, favourable electrophysiological changes were only observed with the former.

Potential Impact:
A short description of the socio-economic impact and the wider societal implications of the project (so far) and the main dissemination activities and exploitation of results is provided below.

THE SCOPE OF THE PROBLEM

Migraine is largely neglected
Migraine is one of the most prevalent, disabling, misdiagnosed, and undertreated disorders, and the associated economic burden to society is astronomical. Yet, migraine is a wholly misunderstood, underappreciated, and largely neglected phenomenon in the EU and other parts of the world. The near ubiquity, the broad public familiarity, and the perceived near-absence of fatal complications, combined with a century of direct-to-consumer promotion of inexpensive but mostly ineffective over-the-counter analgesics, has reinforced an impression that migraines are only a minor problem, except for those with a low tolerance for pain. Despite the high disease-associated disability and socio-economic burden, migraine is stigmatised and dismissed, and caught in a blind spot of public inattention and lack of empathy.

Migraine is a highly prevalent disorder with frequent attacks
Nearly one in four people, i.e. up to 33% of all women and 13% of all men, will have recurring attacks of migraine during (at least some stage of) their life. The vast majority of migraineurs start getting migraine attacks at young age, between age 5 and 25. In at least two-thirds of patients attacks will continue to recur for many decades, not rarely even into very old age. The prevalence of 'active migraineurs', i.e. the proportion of subjects in the general population who was suffering from migraine attacks in the previous year, is approximately 12%, i.e. 17% of all women and 7% of all men. The peak age is between 20 and 50 years, when most people build up and expand their professional career. The median migraine attack frequency is approximately two per month and the median duration of attacks is about one day. One in ten migraineurs will develop chronic migraine with migraine headaches on at least 15 days a month.

The personal and socio-economic burden of migraine is enormous
The World Health Organisation (WHO) has listed migraine as one of the 20 most disabling and most undertreated disorders worldwide, and among the top ten in women. In fact, migraine is listed well above many other diseases which were previously regarded as having greater impact on society, including diabetes, asthma, osteoarthritis, bipolar disorders, schizophrenia, epilepsy, and Alzheimer. The economic burden due to migraine is the second highest of all brain diseases. The estimated migraine-related annual loss is 190 million working days and €55 billion in the EU alone.

Migraineurs have a high comorbidity of other incapacitating disorders
Migraine increases the risk of other incapacitating diseases, including depression, anxiety, epilepsy,
substance abuse, obesity, which adds to impaired quality of life (QoL) and days living with disability. Migraine, in particular with aura, also increases the risk of cardio- and cerebrovascular disease and is linked to several thousands of deaths in the EU annually, even after all other known risk factors have been accounted for. Europeans with migraine with aura or frequent migraine are also more than 3 times more likely to attempt suicide than those without migraine, irrespective of the presence of depression. Comorbid depression is one of the psychological factors responsible for the severely reduced QoL seen in many migraine patients. Hence, improving QoL is regarded one of the targets when treating migraines.

Migraine is often unrecognised, misdiagnosed and thus mistreated
Many migraineurs are misdiagnosed, as simple objective diagnostic tests are lacking. Many physicians prefer avoiding the detailed, time-consuming, clinical interviews, necessary to reliably establish diagnoses by carefully checking the diagnostic criteria. As a results, less than half the patients have formally received the correct diagnosis and thus have not been treated with appropriate medication.

Lack of adequate treatment
There is a huge unmet need of effective and well-tolerated preventive and attack medication. Therapeutic options for migraine are few. Over the past 50 years, only one novel class of drug, the triptans, has been developed specifically for the acute treatment of migraine. Even these treatments are fully satisfactory in less than half of the patients and are contraindicated in patients with comorbid cardiovascular disease. Mainstream migraine prophylactic treatments have been largely based on serendipitous observations and presumed class effects, and have disappointing efficacy and tolerability. Prescribing migraine-prophylactic treatments is a trial-and-error process as current medications are non-specific and the response to treatment is erratic. This is mainly due to lack of understanding of how attacks are triggered, whether different patients have different patient-specific trigger factors, and why and in which patients the attack frequency may suddenly rise so dramatically.

Migraine research is underfunded
Despite the very high prevalence and impact, headache research has been dramatically underfunded in the EU, in particular when compared to other disorders which are much less frequent and are associated with much less disability and socio-economic burden. In the past decade, there has been only one small EU call specifically for headache, and only one consortium was funded. Clearly, there is a mismatch here between clinical needs and efficient use of tax payer’s money.

IMPACT ON THE UNDERSTANDING OF THE MECHANISMS FOR THE GENERATION, MODULATION, CHRONIFICATION, INHIBITION, AND PREVENTION OF MIGRAINE PAIN
The multidisciplinary approach of EUROHEADPAIN increased understanding of a wide range of mechanisms involved in the pathophysiology of migraine, in particular how migraine attacks are triggered and initiated. These include the following specific mechanisms and pathways:
• The molecular and neurobiological mechanisms for susceptibility to migraine and migraine attack provoking triggers;
• How migraine attacks are initiated and how this process can be prevented;
• The role of spreading depression in triggering migraine attacks and pain;
• The role and mode of action of second messenger-modulating molecules in provoking migraine attacks;
• How migraine pain is generated and how this process can be modulated and blocked;
• The role of hypothalamic circuitries in modulating migraine pain and chronification;
• How chronification of migraine may begin and progress, and how this process can be prevented, halted, and reversed.
• How comorbid depression as one of the psychological/social trigger factors may affect triggering mechanisms.

Because of the many overlapping mechanisms and clinical and preclinical issues, other chronic pain disorders may benefit as well from the research by the EUROHEADPAIN consortium.

IMPACT ON DIAGNOSTIC AND PREDICTIVE TESTS

Research from EUROHEADPAIN has revealed various promising biomarkers for the diagnosis and stratification of patients that, when – for some of them – further evaluated, will have the clear potential:
• To objectively establish better diagnosis of migraine facilitating and improving the diagnostic process for:
  a. Physicians, thereby enabling improved patient care; and
  b. Clinical studies such as medication trials that require uniformly and reliably diagnosed large cohorts of patients;
• To assess which patients are at a particularly high risk of developing chronic migraine to enable implementation of preventative measures precluding transition from episodic to chronic migraine;
• To predict treatment response, enabling improved stratified care of migraine patients;
• To predict the effect of psychological/social trigger factors, mainly depression, on disease initiation and outcome.

IMPACT ON IMPROVED TREATMENT

The multidisciplinary research programme of EUROHEADPAIN improved our understanding of how migraine attacks begin, how migraine chronification may start and progress, and how these processes may be prevented, halted, or reversed. More specifically, EUROHEADPAIN research led to:
• Novel pharmacological targets for desperately needed, mechanism-based, improved acute and prophylactic treatments to treat and prevent attacks of episodic migraine, and to prevent, halt and reverse chronic migraine;
• Novel neuromodulation treatment options and improved treatment protocols for existing neuromodulation treatment options for (medication-intractable chronic) migraine;
• Promising biomarkers to help predict patient’s treatment response.

IMPACT ON PATIENT WELL-BEING

The personal burden of migraine to patients is high. European migraine patients (and their family members) will likely benefit from the following important outcomes of EUROHEADPAIN:
• Increased awareness and recognition that migraine is a real and highly disabling disorder with enormous socio-economic impact;
• Biomarkers for migraine that will improve and facilitate the diagnosis of patients and thus management and care of them;
• The risk factors for chronification and attack-provoking factors and triggering mechanisms that enables the implementation of targeted (psychological/social (focussing on depression), pharmacological or neuromodulation) measures preventing attacks and chronification;
• The biomarkers, brain circuitries, and other neurobiological mechanisms for the triggering and chronification of migraine attacks that will guide further identification of treatment targets for improved prevention and treatment of migraine attacks and chronification.
IMPACT ON HEALTH ECONOMY
Given the astronomical socio-economic burden of migraine, reducing the number of migraine attacks by only a few percent already will have a dramatic cost-saving effect on both direct (acute treatments) and indirect (absenteeism from work) migraine-related expenses. Within the duration of the project, for logical reasons, no estimate can be given.

IMPACT ON INNOVATION AND EUROPEAN COMPETITIVENESS
Multiplatform biochemical profiling of CSF coupled to MRS in vivo measurement of brain chemistry is not done anywhere else at the large scale and sophisticated scientific level EUROHEADPAIN is proposing. The multidisciplinary approach combining clinicians, geneticists, neurobiologists, and an SME has ensured that European research will remain the major player in the field of migraine and other headache types. Clearly, the project is a major impetus for the development of novel bio-analytical and statistical methods for biochemical profiling of CSF, and the understanding of metabolic processes in the brain and CSF, now and in the future. Similarly, the integrated use of several complementary neuroimaging tools allows for a greatly improved understanding of brain chemistry and function in vivo that is not found elsewhere. So the improved understanding of how migraine attacks begin and are modulated has given Europe a major advantage in developing new treatments for migraine.

IMPACT ON INDUSTRY
Several of the outcomes of EUROHEADPAIN research (towards biomarkers for improved diagnoses and stratification of patients, novel molecular targets and neurobiological mechanism relevant to how attacks begin, progress and can be modified) may be commercialised in collaboration between Academia and Industry. This knowledge (through dissemination via scientific publications, conferences, and direct interaction with companies) will definitely promote and guide further identification of pharmacological and neuromodulation treatment targets for improved prevention of migraine attacks and chronicification.

IMPACT ON SME PARTICIPATION
EUROHEADPAIN research has addressed and to large extent overcome shortcomings neuromodulation strategies, i.e. their relatively low efficacy (by modifying the devices and treatment protocols by and in collaboration with SME Cephaly (partner (P) 11)), lack of knowledge about the mode of action (by neuroimaging and neurophysiological findings); and the invasiveness and impracticality of most of the devices (by making the device portable, again by SME Cephaly). The outcome of the research is that it is realistic to use neuromodulation treatment in clinical practice to treat patients with chronic migraine. In fact, this led to the registration of Cephaly technology towards the Belgian competent authorities. The project has created important business potential for Cefaly (and all its European partners and sub-contractors). The expected gain in efficacy by optimal non-invasive neuromodulation will give access to a potential market which is ± 2% of the general population in developed countries. According to its current experience in medical device distribution around the world, Cefaly evaluates at 25 M€ the potential yearly turnover within three years after a positive outcome of the research.

DISSEMINATION AND EXPLOITATION
1. Dissemination to the scientific community
Scientific dissemination of the project results was at large be achieved through publications in high-ranking
scientific journals. The achievements of EUROHEADPAIN are also made available via presentations on the EUROHEADPAIN website and via oral and poster presentations at scientific meetings and key conferences on clinical (neurological) and basic science (neuroscience, pain) topics. After approval of the 2nd Periodic and Final Report, a newsletter on the results of the EUROHEADPAIN project will be distributed under the scientific community.

2. Dissemination to pain researchers outside the field of headache
To specifically connect to headache specialists and specialists in other areas of pain research EUROHEADPAIN researchers participated in the 'International Association for the Study of Pain' (IASP). Principal Investigators of EUROHEADPAIN were involved in organising sessions or in giving presentations at the bi-annual IASP World Congress or at the IASP/HIS joint meetings. The IHS/IASP meetings are intended to capitalise on joint initiatives of these organisations, such as the 'Global Year Against Headache' initiative which was part of their 'Global Campaign Against Headache' (with the World Health Organisation (WHO) to lift the burden of headache world-wide. The cross-fertilisation of basic and clinical research of various pain syndromes, one of which being migraine, generated new ideas for research and novel important insights in pain mechanisms operating in head pain and in other types of pain.

3. Dissemination to educate young scientists
The EUROHEADPAIN project encouraged young scientists, appointed on the project, to interact with each other and with other research groups within and outside the project. Training comprised the following aspects: (i) Learning how to exchange experiences from different disciplines in migraine pain research; (ii) Better understanding of their individual needs in becoming leading scientists; (iii) Tailoring their training needs related to migraine pain research by specific; (iv) Participating actively in national and international meetings, or co-organising scientific sessions at relevant migraine/pain meeting; (v) Participating in the generation of reporting to get first experience with managing larger scientific projects, such as EUROHEADPAIN. To stimulate young researchers in their early career of headache research EUROHEADPAIN organised a successful dedicated teaching and training event, the iHEAD meeting on 'How to become a next leader in headache science'. The meeting was organised in Leiden (NL) from 31 October to 2 November 2014. The PhD students appointed on the EUROHEADPAIN project are enrolled in the Graduate School of the participating institutes, where high-standing and adequate training and teaching is provided and regular monitoring and evaluation are part of the PhD programme. Supervision of the PhD students is guaranteed by the guidance of top-level scientists in headache research. We are confident that participating or linking to EUROHEADPAIN will give the majority of the appointed young researchers a career in scientific research.

4. Dissemination to the general public
Whenever possible, appropriate steps were taken to inform the general public of breakthrough findings in clinical and basic science research of migraine and headache pain. Means used were press releases on institutional website in the local language, interviews in written press or on radio and/or television.

5. Dissemination to patients and patients associations
All clinical PI’s of the project are world experts in clinical primary headache and migraine research, and also see patients. Outreach to patients in the Netherlands, Germany Denmark and Belgium was guaranteed since the clinical PI’s from these countries head the national referral clinic of their country. In
addition, there is a very active collaboration between the international patient organisations 'World Headache Alliance (WHA)' and the professional organisations (e.g. International Headache Society (IHS), European Headache Federation (EHF), and the 'American Headache Society' (AHS)). All EUROHEADPAIN participants have close ties with WHA as Profs Ferrari (P1), Schoenen (P2), Olesen (P10) and Prof. Goadsby (P13) are all past presidents of the IHS and EHF some are board members of AHS.

6. Dissemination to policy makers (health care authorities and caregivers)
We made an effort in extending existing contacts with policy makers, in particular health insurance companies, regulatory bodies and relevant government bodies, to make the results of the project known and to alert the policy makers on potential implications. We will continue to make them aware of the unmet needs for patients with pain, in migraine and other pain syndromes, even beyond the scope of this project. We will not only spread the message that the treatment of pain is unsatisfactory in about half of the patients, but also that migraine is seriously undertreated and misdiagnosed. We will continue to try to convince them that appropriate measures are needed to increase awareness of these atrocities and that researchers and policy makers should try to make efforts that benefit millions of patients in Europe.

7. Dissemination to pharmaceutical industries
The development of reliable biomarkers and novel treatment targets that will come from the project will be instrumental to attract pharmaceutical companies. Several of EUROHEAD’s PI’s (Profs. Ferrari, Schoenen, Goadsby, and Olesen) are well-connected to pharmaceutical/medical device industry. At an early stage they recognised very well the potential of certain treatment targets, i.e. serotonin agonists, orexins, and CGRP antagonists, and have worked successfully together with ‘big pharmaceutical companies’ (e.g. Pfizer, GSK, and MSD) to bring these compounds to the market. In fact serotonin agonists are the current preferred acute treatment option for migraine attacks, and CGRP antagonists are now being prepared as a possible new treatment. We expect that the outcomes of EUROHEADPAIN, like what happened for SME Cefaly, will lead to the development of optimised treatment options.

FURTHER EXPLOITATION OF RESULTS
After the conclusion of the EUROHEADPAIN project, we intend to further exploit acquired knowledge of biomarkers and neurobiological mechanisms of pain in episodic and chronic migraine that are aimed to produce more reliable tests for diagnosing and stratifying patients of migraine subgroups (episodic vs chronic, migraine with aura vs migraine without aura) based on our Biomarker discoveries (WP1). Knowledge on Genetic factors and molecular pathways (WP2) has already been instrumental to guide mechanistic studies aimed at discovering the underlying biology of migraine pain in animal and human research and our multidisciplinary research yielded novel Mechanisms of pain (WP4) and Novel treatment options (WP5). Several of the novel pharmacological treatment targets are ready to be taken up by pharmaceutical companies. The optimized and validated non-invasive transcutaneous neurostimulation devices and protocols developed together with an SME (WP5) is a clear first example of a successful exploitation of results of the project.

List of Websites:
www.euroheadpain.org
Contact details:
Coordinators:
prof. dr. M.D. Ferrari, Neurology: (m.d.ferrari@lumc.nl)
prof. dr. A.M.J.M. van den Maagedenberg: Human Genetics and Neurology: (a.m.j.m.van_den_maagdenberg@lumc.nl)
Project manager:
B.M.E. Teng, Human Genetics: (b.m.e.teng@lumc.nl)

Address:
Leiden University Medical Center
Human Genetics, S4-P
P.O. Box 9600
2300 RC Leiden - NL

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