

# BMJ Open Impact of a 12-week open-label placebo treatment on headache days in episodic and chronic migraine: a study protocol for a parallel-group, multicentre, randomised controlled trial

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## ABSTRACT

**Introduction** Migraine is the most common neurological disorder and one of the major causes of years lived with disability. Its treatment (especially of chronic forms) is often challenging and accompanied with adverse effects. Although new therapeutic approaches have recently emerged (eg, calcitonin gene-related peptide antibodies), these are linked to strict prescribing guidelines and therefore limited to only a minority of patients. Recently, randomised controlled trials have demonstrated that open-label placebo treatments can lead to significant and clinically relevant improvements of chronic pain conditions.

**Methods and analysis** This multicentre, randomised controlled clinical trial following a parallel group between-subject design aims to systematically investigate the impact of a 12-week open-label placebo treatment on moderate to severe headache days (primary outcome) in patients with episodic and chronic migraine in addition to treatment as usual. Secondary outcomes comprise the number of migraine days, pain intensity, intake of acute medication, quality of life, disability, global impression of change, tolerability and a responder rate. To systematically address potential predictors of placebo responses in patients with migraine, this study assesses potential psychometric predictors, salivary cortisol and alpha-amylase awakening responses, catechol-o-methyltransferase Val158Met polymorphisms, as well as functional and structural brain connectivity (ie, resting state functional MRI, diffusion tensor imaging). The data analysis will be performed on basis of the general linear model considering repeated measures (mixed model).

**Ethics and dissemination** This protocol and all corresponding documents were approved with regard to their content and compliance with ethical regulations by the Ethics Committee of the Medical Faculty of the University Duisburg-Essen, Germany and the Ethics Committee of the Landesärztekammer Hessen. The results from this study will be actively disseminated through manuscript publications and conference presentations.

**Trial registration number** German Clinical Trials Register (DRKS00021259).

## Strengths and limitations of this study

- This is the first multicentre, randomised controlled clinical trial investigating the impact of a 12-week open-label placebo (OLP) treatment on episodic and chronic migraine by assessing patient-reported, pain-related outcomes, disability and parameters of psychological well-being.
- This protocol provides OLP administration as add-on treatment to standard care, which prepares for direct clinical translation in further trials and offers a proof-of-concept investigation for OLP in migraine as a potential preventive treatment alternative for patients refraining from pharmacological preventive therapy because of fear of side effects.
- Moreover, this study addresses the urgent need for mechanistic approaches exploring underlying processes and predictors of OLP efficacy, such as functional and structural brain connectivity, genetic determination and psychometric variables.
- This trial minimises potential disappointment of patients randomised to the treatment as usual group by offering an OLP treatment after study completion, and satisfaction with randomisation will be systematically assessed.
- As a limitation to this study, despite the long treatment duration, which is novel for OLP trials, its rationale will not be repeatedly presented throughout the trial to refresh and boost potential expectation effects.

## INTRODUCTION

With an estimated 1-year period prevalence of about 12% (5.6% for men, 17.1% for women), migraine is the most common neurological disorder. As a top 10 cause of years lived with disability worldwide, migraine is not only an individually but also socioeconomically relevant disease.<sup>1 2</sup> As a primary headache, its diagnosis and classification are based on the criteria specified in



the International Classification of Headache Disorders, third edition (ICHD-III).<sup>3</sup> The threshold for differentiating episodic migraine (EM) from chronic migraine (CM) is set at 15 headache days per month in the last 3 months. While acute migraine attacks are often successfully treated with non-steroidal anti-inflammatory drugs or triptans, the prophylactic treatment of EM and especially CM is challenging and often leads to treatment discontinuation due to accompanying adverse effects, which frequently occur prior to the actual treatment effect.<sup>4</sup> In addition, due to restricting prescribing guidelines and limited resources, specific novel pharmacological (eg, calcitonin gene-related peptide (CGRP) and CGRP receptor antibody treatments, onabotulinumtoxinA) and non-pharmacological (eg, inpatient multimodal) treatments are restricted to a certain percentage of patients.<sup>5 6</sup>

Recently, randomised controlled trials (RCTs) have demonstrated that open-label placebo (OLP) treatments can lead to a significant and clinically relevant pain relief (ie, chronic low back pain, irritable bowel syndrome) and other symptoms (ie, chronic fatigue, depression, attention-deficit/hyperactivity syndrome).<sup>7–11</sup> In contrast to ‘traditional’ placebo treatments, which were usually given unbeknown to the patient, OLPs are administered with the patients’ informed consent and therefore conquer ethical and legal conflicts of deception. Many RCTs investigating migraine treatments reveal considerable symptom improvement in placebo arms,<sup>12 13</sup> pointing to the potential to benefit from placebo effects. Particularly vivid examples for the potential of placebo effects in EM and CM provide recently published trials of intravenously applied eptinezumab, a CGRP-ligand antibody.<sup>14 15</sup> In both trials, the control groups showed a relevant symptom relief after receiving a placebo treatment. In contrast to deceptive placebos usually used in clinical trials, Kam-Hansen *et al* reported positive effects of a non-deceptive (open-label) placebo in the treatment of acute migraine attacks.<sup>16</sup> However, to date systematic investigations regarding the impact of a regularly applied OLP as a migraine preventive treatment are missing.

To clinically harness placebo responses, it is essential to predict the capacity of an individual to develop placebo effects in a context-specific, physiological system-specific and disease-specific manner.<sup>17–19</sup> Growing evidence suggests that genetic polymorphisms involved in dopamine and opioid function might have an impact on the magnitude of placebo responses.<sup>20 21</sup> Further, neuroendocrine factors are discussed to predict the susceptibility to placebo interventions by modulating individual treatment expectations with effects on treatment outcome.<sup>22 23</sup> Moreover, structural and functional MRI (fMRI) studies revealed neural changes in patients with migraine<sup>24 25</sup> regarding the descending pain inhibitory system, which is significantly involved in placebo effects<sup>26</sup> and therefore, mainly affects placebo interventions in patients with migraine.<sup>27 28</sup> The identification of structural and functional predispositions also in terms of cognitive flexibility

is therefore crucial to predict these placebo responders who could best profit from OLP interventions.<sup>29</sup>

This RCT aims to systematically investigate the impact of a 12-week OLP treatment on headache days (refer to the Definitions section for definition of headache day) in patients with EM and CM in addition to treatment as usual (TAU). Secondary outcomes comprise the number of migraine days (refer to the Definitions section for definition of migraine day), pain intensity, intake of acute medication, global impression of change, quality of life, tolerability, as well as treatment expectation and experience. To systematically address further potential predictors of placebo responses in patients with migraine, this study assesses salivary cortisol and salivary alpha-amylase (sAA) awakening responses as measures of the activity of the hypothalamus–pituitary–adrenal axis and the sympathetic nervous system,<sup>30–32</sup> Catechol-o-methyltransferase Val158Met (COMT) polymorphism,<sup>20</sup> as well as potential predictors including psychometric parameters, and fMRI (resting state fMRI, rsfMRI) as well as structural (diffusion tensor imaging, DTI) brain connectivity.

## METHODS AND ANALYSIS

### Study design

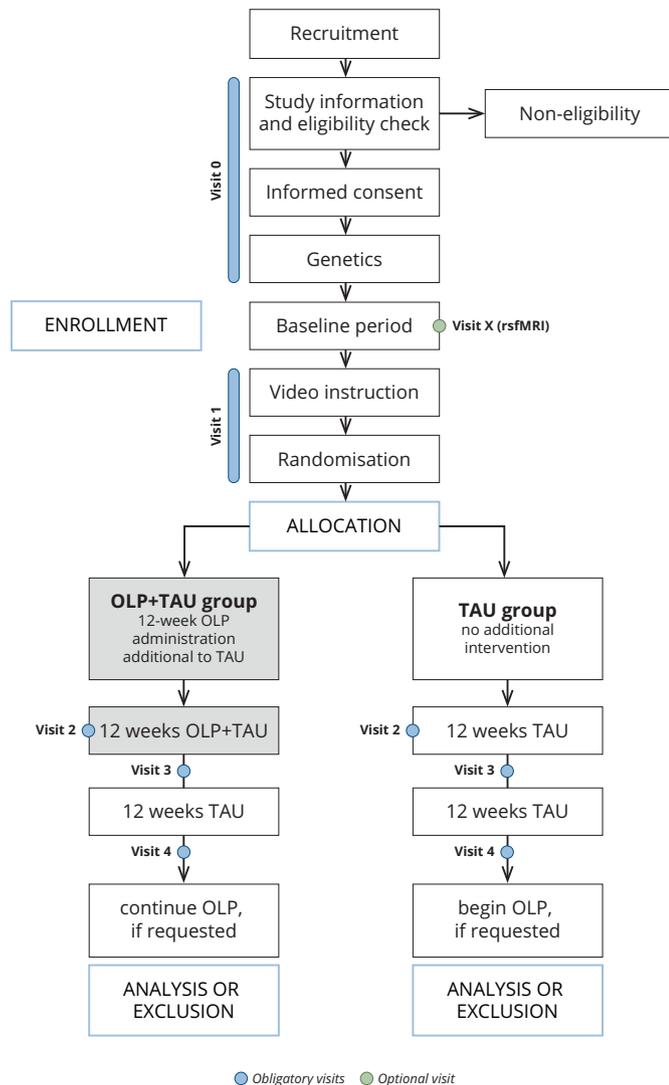
A multicentre, randomised controlled clinical trial of an OLP treatment on patients suffering from EM and CM using a parallel group between-subject design with two study groups: (1) OLP+TAU group, receiving a 12-week OLP intervention in addition to TAU and (2) TAU group, receiving no additional intervention. The first patient was included on 9 November 2020 and the trial is scheduled to end with a complete inclusion of N=150 patients. The study will be conducted at the primary study centre, University Hospital Essen, Department of Neurology, Essen, Germany, and the secondary study centre, Migraine and Headache Clinic Koenigstein, Koenigstein im Taunus, Germany. MRI scans will be assessed at the primary study centre only. The study design is depicted in [figure 1](#) and the visit schedule in [table 1](#). The study was preregistered at the German Clinical Trials Register on 9 October 2020.

### Patients and randomisation

One hundred fifty patients suffering from EM and CM will be randomly allocated to one of two study arms according to an a priori randomisation list generated by an independent member of the laboratory using R Studio (RStudio Team (2020), RStudio: Integrated Development for R, RStudio, Boston, Massachusetts, USA; V.1.2.5042). Patients will be asked to keep their treatment allocation confidential to ensure blinding of care providers, outcome assessors and data analysts.

### Patient and public involvement

Patients’ experiences and suggestions assessed via open question formats in a previous OLP trial in chronic back pain<sup>7</sup> were used to improve this study concept, for



**Figure 1** Flow of patients. For visit schedule and explanation, please see table 1. OLP, open-label placebo; rsfMRI, resting state functional MRI; TAU, treatment as usual.

example, by adding the intention to continue or begin OLP treatment post-study as explorative outcome. Also, this study protocol will comprise open questions assessing the patients' own ideas regarding the mechanisms underlying the effects of OLPs (ie, 'What do you think makes open-label placebos work?', 'What made you decide to participate in the study?', 'Would you continue taking placebos after participating in this study?').

### Patients' eligibility

Inclusion criteria comprise age  $\geq 18$  years, history of EM or CM (patient self-report and diagnosed by a specialist in neurology according to the ICHD<sup>3</sup>)  $\geq 12$  months prior to screening, migraine frequency  $\geq 4$  days per month on average across 3 months prior to screening (refer to the Definitions section for definition of migraine day). Furthermore, patients have to be capable of consent and fluent in German. A 4-week baseline period after inclusion ensures a stable medication prior to randomisation. Exclusion criteria comprise substance or alcohol abuse,

major depression, schizophrenia, suicidality, hypersensitivity or allergy to any ingredient of the placebo pills, participation in another study using investigational drugs within the last 3 months prior to inclusion, and any acute or chronic pain condition apart from migraine as well as pregnancy or breast feeding in women. Patients volunteering to attend the optional MRI session must not suffer from claustrophobia or have any implants or devices unsuitable for MRI, self-reported exclusion criteria will be assessed by the investigators and study personnel. Exclusion after trial completion comprise self-reported change of TAU and protocol violations (eg, not attending obligatory visits, withdrawal of consent).

### Definitions

All definitions are based on the recommendations of the Guidelines for Controlled Trials of Preventive Treatment of Episodic Migraine in Adults<sup>33</sup> and in accordance to the ICHD-III.<sup>3</sup>

### Migraine day

A migraine day is defined as a day with a headache that lasts at least 4 hours and meets ICHD-III criteria C and D for migraine without aura or criteria B and C for migraine with aura, or ICHD-III criteria for probable migraine; or a day with a headache that is successfully treated with a triptan, ergotamine, or other migraine-specific acute medication. For ICHD-III criteria, see Olesen.<sup>3</sup>

### Headache day

A headache day is defined as a day with moderate or severe pain that lasts at least 4 hours or a day with a headache lasting at least 30 min that is successfully treated by an acute headache medication.

### Treatment as usual

TAU is defined as any preventive migraine-related treatment recommended by national guidelines.<sup>34</sup> This includes both pharmacological and non-pharmacological approaches (eg, endurance sports, relaxation techniques, biofeedback, cognitive-behavioural techniques).

### Recruitment

Participants will be recruited via regional advertisement at both study centres, surrounding practices and via multiple online platforms (eg, study centres' websites, social networks, etc). Potential participants will be informed that participation in the study is voluntary, withdrawal of consent is possible at any time without reason, and refusal of study participation will not lead to any negative consequences. Informed consent procedure includes all relevant information and the opportunity to clarify questions. Enrolment is only possible after written informed consent.

### Trial treatments and study arms

Study eligibility will be verified at inclusion visit (visit 0, see table 1 for details) and during a following 4-week baseline period. At inclusion visit, all patients will be asked to

**Table 1** Visit schedule

	Visit 0 (inclusion)	Visit 1 (baseline+R)*	Visit 2 (R+1 month)	Visit 3 (R+3 months)	Visit 4 (R+6 months)	Visit X (MRI)
<i>Difference to inclusion (in months)</i>	0	+1	+2 months	+4 months	+7 months	Indep.
Medical history, validation of eligibility	X	X	–	–	–	–
Demography	X	–	–	–	–	–
<b>Primary outcome</b>						
Headache days (last 4 weeks)	–	X	X	X	X	–
<b>Secondary outcomes</b>						
Migraine days (last 4 weeks)	–	X	X	X	X	–
Mean pain intensity (last 4 weeks)	–	X	X	X	X	–
Acute medication intake days (last 4 weeks)	–	X	X	X	X	–
Global Impression of Change (PGIC)	–	–	X	X	X	–
Quality of Life (SF-12)	–	X	X	X	X	–
Disability (PDI, HIT-6)	–	X	X	X	X	–
Side effects (GASE)	–	X	X	X	X	–
Proportion of patients with a 50% reduction of headache days from baseline (responder rate)	–	–	X	X	X	–
<b>Exploratory outcomes/predictors</b>						
Functional connectivity (rsfMRI)	–	–	–	–	–	X†
Structural connectivity (DTI)	–	–	–	–	–	X†
Salivary cortisol and sAA awakening responses	X‡	–	–	–	–	–
Genetics (COMT polymorphism)	X	–	–	–	–	–
Treatment expectation (TEX-Q)	–	X	–	–	–	–
Generic Rating for Treatment Pre-experiences, Treatment Expectations, and Treatment Effects§	–	X	X	X	X	–
Fear of pain (FPQ-III)	–	X	–	–	–	–
Pain catastrophising (PCS)	–	X	–	–	–	–
Behavioural approach system sensitivity (BIS BAS)	–	X	–	–	–	–
Personality (BFI-10)	–	X	–	–	–	–
Somatisation (SASS)	–	X	–	–	–	–
Depression, anxiety (STADI)	–	X	–	–	–	–
Stress (PSS)	–	X	–	–	–	–
Request of (further) OLP intake	–	–	–	–	X	–
<b>Treatment</b>						
OLP distribution to OLP+TAU	–	X¶	–	–	–	–
OLP distribution to TAU	–	–	–	–	X**	–

\*All assessments will be performed prior to randomisation.

†Facultative visit, only at primary study centre within 4-week baseline period between visit 0 and visit 1.

‡Assessment prior to randomisation.

§In-house questionnaire.

¶Post-outcome assessments.

\*\*After visit 4, if requested.

BFI-10, Short Version of the Big Five Inventory; BIS BAS, Behavioral Inhibition and Approach System; COMT, catechol-o-methyltransferase; DTI, diffusion tensor imaging; FPQ-III, Fear of Pain Questionnaire; GASE, General Assessment of Side Effects; HIT-6, Headache Impact Test; OLP, open-label placebo; PCS, Pain Catastrophizing Scale; PDI, Pain Disability Index; PGIC, Patient Global Impression of Change; PSS, Perceived Stress Scale; R, randomisation; rsfMRI, resting state functional MRI; sAA, salivary alpha-amylase; SASS, Scale for Assessment of Somatic Symptoms; SF-12, Short Form Health Survey; STADI, State-Trait Anxiety Depression Inventory; TAU, treatment as usual; TEX-Q, Treatment Expectation Questionnaire.

provide basic demographic information, current medication, complete medical history, alcohol and drug use via a standardised in-house questionnaire.

At visit 1, all participants will be asked to watch an instruction video (for transcript, see online supplemental file) containing general information about the placebo effect and results of recent OLP trials.<sup>7</sup> Patients will then be randomised (see above) to one of two study arms: (1) the treatment arm: OLP+TAU, (2) the control arm: TAU. Following, participants in both groups will receive a cardboard box containing either a labelled dispenser with 168 placebo tablets (P Tabletten, 7 mm weiß, Lichtenstein, Zentiva Pharma, Germany), a note emphasising that the tablets contain no active ingredient and instructions to take one placebo pill two times per day for 12 weeks in addition to their stable treatment as usual (OLP+TAU group) or only a note stating the assignment to the control group with no requirement of further action (TAU group). This OLP regimen was chosen based on previous trials.<sup>7-9</sup> Boxes will be matched for weight and sound upon shaking. The white placebo tablets will contain lactose monohydrate, cellulose, magnesium stearate (European Pharmacopoeia), and microcrystalline cellulose. Self-reported daily OLP intake will be documented on a standardised headache diary (see below). To minimise a potential disappointment of patients randomised to the TAU group, which might impact adherence, patients in the TAU group will be offered an OLP treatment after completion of visit 4.<sup>7,8</sup> Furthermore, satisfaction with randomisation will be systematically assessed on a 101 mm visual analogue scale ('How satisfied are you with your group assignment (placebo group or control group)?', 'not satisfied at all'–'very satisfied') on randomisation.

### Primary, secondary and exploratory outcomes

All outcomes will be either assessed via online questionnaires (Lime Survey, Lime Survey, Hamburg, Germany) or at the study centre (ie, MRI scans and blood sample) by a blinded investigator.

The primary objective of this study is to test the effectiveness of an OLP treatment in patients suffering from EM and CM. In accordance to the guidelines of the International Headache Society for controlled trials of preventive treatment of CM in adults,<sup>33</sup> efficacy will be evaluated by the number of moderate to severe headache days from a 4-week baseline period (baseline) to visit 3 (visit 3, end of 12-week treatment period) assessed by a standardised headache pain diary<sup>33</sup> as primary outcome. Both the duration of the baseline assessment and treatment period were chosen according to international guidelines<sup>33</sup> (see figure 1 for details).

Secondary outcomes will comprise the change in migraine days from baseline to visit 3. A migraine day will be defined as specified in the international guidelines for clinical trials in preventive treatments for migraine<sup>33</sup> and in accordance with the ICHD-III.<sup>3</sup> In addition, the change in mean pain intensity in the last 4 weeks will be assessed on a numerical rating scale (0–10, 'no pain', 'unbearable

pain') and days of use of acute medication in 4 weeks will be recorded on the headache diary. Furthermore, (1) disability, that is, the degree to which patients' daily life activities are disrupted by the migraine-related pain, by the Pain Disability Index,<sup>35</sup> and the Headache Impact Test<sup>36</sup> as these measures have been shown to be susceptible to change migraine-related disability in placebo treatment arms of clinical trials<sup>37</sup>; (2) global impression of change by the Patient Global Impression of Change,<sup>38</sup> which has been shown to reflect the general improvement in chronic pain in patients that is associated with the clinical status as a function for perceived treatment response<sup>39</sup>; (3) the physical and mental component of quality of life by the Short Form Health Survey<sup>36</sup> will be assessed. For the latter, the mental component is expected to be more susceptible to modulation by the OLP rationale as compared with the physical component.<sup>7</sup> Safety and tolerability will be recorded by the General Assessment of Side Effects,<sup>40</sup> as the assessment of side effects via this questionnaire has previously been linked to expectation effects as well as genetic predispositions.<sup>41</sup> Finally, we will calculate a responder rate, that is, the proportion of patients who reached a 50% reduction in headache days from baseline to visit 3.<sup>33</sup>

Exploratory outcomes address potential moderators and predictors of OLP responses. These include functional and structural brain connectivity assessed by rsfMRI and DTI at the primary study centre at scanning visit X (facultative, within 4-week baseline period). Participants will provide single-assessment samples of salivary cortisol and sAA awakening responses between visit 0 and visit 1. Furthermore, a blood sample will be taken at screening visit in order to identify COMT polymorphisms by PCR analysis. In addition, (1) treatment expectation will be assessed by the Treatment Expectation Questionnaire (TEX-Q<sup>42</sup>), which distinguished between symptom-specific effects and effects related to quality of life and functional capability; (2) fear of pain by the Fear of Pain Questionnaire<sup>43</sup>; (3) pain catastrophising by the Pain Catastrophizing Scale,<sup>44</sup> as these personality traits have been shown to be positively related to subjective pain intensity and fear of pain has further been shown to be the most robust predictor of pain chronification<sup>45-47</sup>; (4) personality traits using the Behavioral Inhibition and Approach System<sup>48-50</sup> and the Short Version of the Big Five Inventory<sup>51</sup> due to the close link between personality traits associated to dopamine release, reward processing and expectation effects of treatment outcome<sup>52</sup>; (5) anxiety and depression by the State-Trait Anxiety Depression Inventory<sup>53</sup> and stress by the Perceived Stress Scale<sup>54</sup> as depression, anxiety and psychological distress have been reported to be susceptible to modulation through OLP treatment<sup>7,55</sup>; and (6) somatisation by the Somatosensory Amplification Scale<sup>56</sup> as a predictive role of somatosensory amplification in the development of side effects or negative expectation effects has been observed.<sup>41,54,57</sup> Further, a questionnaire (Generic Rating for Treatment Pre-experiences, Treatment Expectations, and Treatment

Effects; G-EEE<sup>58</sup>) will assess previously gained treatment experience, expectation and subjective ratings of treatment effects over time and therefore expanding the rational of the TEX-Q. The G-EEE is a novel screening tool to assess treatment expectations and relevant treatment experiences with regard to positive and negative aspects as well as side effects. Further analysis comprises the change in primary and secondary outcomes from baseline to visit 2 (short-term effects), from baseline to visit 4 (long-term effects), as well as visit 4 will investigate potential long-term effects of OLP on all primary and secondary outcomes (OLP+TAU group, TAU group, respectively). Moreover, we will include the assessment of motivation in participating in the trial at visit 0 and presumed mechanisms of OLP effects by open question as well as patient's openness to begin or continue an OLP treatment post-study (TAU group, OLP+TAU group, respectively) at visit 4.

### Sample size calculation

We performed a sample size calculation using the statistical software G\*Power.<sup>59</sup> For our primary outcome, to reach a power of 0.9 with an alpha level of 0.05 and an effect size of  $f=0.2$  (ie,  $d=0.4$ ), a total sample size of  $N=134$  is needed. We decided for a sample size calculation based on our recent OLP trial investigating pain relief in chronic back pain with an effect size of  $d=0.44$ .<sup>7</sup> However, other OLP trials report higher effect sizes (ie, chronic low back pain:  $d=0.77$ <sup>8</sup>; irritable bowel syndrome:  $d=0.79$ <sup>9</sup>). To account for a potential dropout rate of 10%, we plan to enrol  $N=150$  patients ( $N=75$  patients per group).

### Statistical analysis

The data analysis will be performed on basis of the general linear model considering repeated measures (mixed model). All main and interaction effects of the experimentally controlled factors *group* (between-group) and *time of measurement* (within-group) will be considered. The focus is on the interaction effect, which represents the differences in the change between both groups. This model will be equally applied to all outcome variables. Possible correlations between different outcome variables as well as possible predictive genetic factors and cortisol levels will be examined exploratively by extending the model by further linear cofactors.

The rsfMRI data will be preprocessed using the fmripipeline.<sup>60</sup> Voxel-wise descriptors of resting state activity (eg, amplitude of low frequency fluctuation, independent component analysis large-scale resting state networks), inter-regional connectivity values (correlation, partial correlation, tangent), graph theoretical parameters (eg, weighted model strength) will be obtained. For dynamic connectivity analysis, sliding-window analysis is performed on the above measures of resting state activity and connectivity. The DTI data will be preprocessed with FSL<sup>61</sup> and parametric maps will be obtained via nipy and TractoFlow pipeline.<sup>62</sup>

We would like to clarify that the assessment of genetic, psychometric and neurobiological trait variables performed in this study will contribute to a large-scale pooled analysis of potential variables that predict or modulate an individual's placebo and/or nocebo response across different physiological systems as part of the collaborative research centre CRC/TRR 289 'treatment expectation'.<sup>63 64</sup>

Genotyping for COMT Val158Met polymorphism will be carried out as described in Wendt *et al.*<sup>41</sup> Briefly, genomic DNA will be extracted from whole blood using peqGOLD Blood DNA Mini Kit (PEQLAB Biotechnologie, Erlangen, Germany) and genotyping will be performed on a 7500 Fast Real-Time PCR System using the TaqMan SNP Genotyping assay for rs4680 (C\_25746809\_50) and TaqMan genotyping master mix (Applied Biosystems, Darmstadt, Germany) according to the manufacturer's instructions and cycling conditions. Allelic discrimination analysis will be performed using SDS software V.1.4 (Applied Biosystems, Foster City, USA).

Based on previous findings from patient samples suffering from chronic back pain,<sup>7 8</sup> irritable bowel syndrome<sup>9</sup> and acute migraine attacks,<sup>16</sup> we expect a significant reduction of headache days in the OLP+TAU group compared with the TAU group over time (primary outcome). Also, we expect significant improvement in mean pain intensity, migraine days and parameters of psychological well-being, and a reduced need for acute medication and side effects (secondary and exploratory outcomes). We hypothesise that methionine/methionine homozygotes in the OLP+TAU group show stronger improvement in all outcomes compared with valine/valine homozygotes, and heterozygotes.<sup>20 21</sup> Moreover, we hypothesise that higher awakening responses in salivary cortisol and sAA activity will be associated with weaker improvements in all outcomes and less susceptibility to OLP treatment. All analysis steps will be accompanied by professional statisticians.

### Data management

Behavioural study data will be collected via a web server-based survey system (LimeSurvey, LimeSurvey, Hamburg, Germany) independently installed on a server provided by the University of Duisburg-Essen. All data will be securely stored on a local storage provided by the University Medicine Essen with an implemented access and file management system (Seafile, Beijing, China). Identifiable patient data will be stored, preserved and destroyed locally at the site in accordance with governmental regulations. Data will be stored and processed with Microsoft Office 365 applications (Microsoft Corporation, Redmond, Washington, USA) provided by the sites. Only authorised study personnel are able to view and manage data according to their study role. Data management has been reviewed and authorised by the data protection officer of the University Medicine Essen.

For the imaging data acquisition, personal data of the participants will be pseudonymised with a software

solution developed by the collaborative research centre TRR/CRC 289 implementing a two-factor authenticated, decentralised, encryption-based, deterministic pseudonymisation technique. Imaging data will be anonymised during conversion by defacing anatomical images and omitting possibly personal identifiable data from the file headers. Imaging data will be stored at an object storage of the University of Duisburg-Essen in (anonymised) Brain Imaging Data Structure<sup>65</sup> format. Changes in both the raw data and derivatives will be tracked by DataLad (<https://www.datalad.org/>).

### Ethics and dissemination

This protocol and all corresponding documents were approved with regard to their content and compliance with ethical regulations by the Ethics Committee of the Medical Faculty of the University Duisburg-Essen, Germany (20-9182-BO) and the Ethics Committee of the Landesärztekammer Hessen (2020-1841-zvBO) and will be carried out with principles enunciated in the current version of the Declaration of Helsinki.<sup>66</sup>

Patients interested in study participation will receive a patient information sheet and an informed consent form, describing the study and providing sufficient information for an informed decision about participation and data confidentiality. Furthermore, detailed oral information is provided by a trained investigator. The results of the planned analyses will be published in peer-reviewed journals.

### DISCUSSION

In view of its high prevalence and impact on functional disability, migraine is a neurological disorder with high relevance not only on the individual but also on the socio-economical level.<sup>1 2</sup> Moreover, preventive treatment of CM is often hampered by lack of efficacy or side effects that limit patients' adherence to the therapeutic regimen. Novel therapeutic approaches (eg, CGRP and CGRP receptor antibody treatments, onabotulinumtoxinA) are limited to a minority of patients due to limited resources and restricting prescribing guidelines.<sup>5 6</sup>

Here we investigate the preventive effect of an OLP effect on EM and CM as treatment add-on or potential alternative. Furthermore, this trial assesses outcomes of disability, tolerability, and psychological well-being and aims to identify potential predictors of OLP effects in a very large sample enrolling N=150 patients (75 patients per group).

This study protocol can be seen in light of some limitations. First, since previous OLP treatments usually were limited to a treatment period 3–6 weeks, to our knowledge, this is the first study protocol providing OLPs for a 12-week duration. Since the development of OLP effects over a longer period of time is unknown, it might have been beneficent to refresh the OLP rationale in order to foster treatment expectations.<sup>67</sup> Second, this study protocol does not include a deceptive placebo arm

allowing for direct comparison of the effect of open-label versus deceptive placebos. However, this decision was made for the benefit of the trial's translational/clinical approach and prevents any ethical conflicts deception might cause.<sup>68</sup> Third, only the primary study centre provides rsfMRI sessions, which might increase placebo responses due to the fact that these patients experience an additional study visit resulting in enhanced experience of medical environment and contact to healthcare personnel.<sup>69</sup> However, due to MRI exclusion criteria and the fact that the MRI visit is voluntary, not all patients enrolled at the primary study centre will participate.

Our study design presents relevant improvements of limitations discussed in previous OLP studies, such as short duration of OLP administration (3 weeks in previous trials<sup>7–9 11</sup>), insufficient blinding and lack of control groups,<sup>70</sup> as well as missing mechanistic approaches.<sup>71</sup> First, with a 12-week OLP intake, the present study design allows an evaluation of the effects of a long-term administration, its safety and tolerability. Second, we implemented a blinding procedure allowing distribution of either OLP or empty, but noise-adjusted and weight-adjusted boxes by a blinded team member. Third, the outcome assessment via headache diary and online assessment ensures that patients in both groups will have comparable contact to the blinded study team. Furthermore, our multicentre design strengthens generalisability to the population. Finally, we intend to analyse psychometric variables, functional and structural brain connectivity, salivary cortisol and sAA awakening responses, as well as a genetic polymorphism to identify predictors and therefore address the urgent need of mechanistic understanding of OLP effects.<sup>71 72</sup>

In summary, previous OLP trials have demonstrated that OLPs are effective in a variety of conditions including chronic pain and psychological disorders and are safe and well tolerated. Although first evidence suggests OLP efficacy on acute migraine attacks,<sup>16</sup> a systematic investigation of OLP's preventive effects is missing. The presented study protocol is capable to form the basis for translational research, by providing strategies to clinically harness OLP effects, and gaining further mechanistic information about the underlying processes involved in OLP efficacy.

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