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A double blind parallel group randomised placebo controlled trial of Propranolol and Pizotifen in preventing migraine in children

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Acronym:	**P3MC**
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SYNOPSIS

Title	Two double blind parallel group randomised placebo controlled trial of Propranolol and Pizotifen in preventing migraine in children
Acronym	P3MC
Short title	Preventing migraine in children and young people
Chief Investigator	Dr William Whitehouse
Objectives	To test whether Propranolol is superior to placebo and whether Pizotifen is superior to placebo for the prevention of migraine attacks in children aged 5 - 16 years referred to secondary care out-patient settings with frequent migraine (2-6 / 4 weeks)
Trial Configuration	Two parallel group randomised controlled trials of a) Propranolol vs placebo and b) Pizotifen vs placebo each with a 6 month post trial follow-up
Setting	Comprise 10 secondary care paediatric headache or paediatric neurology clinics in Glasgow, Hartlepool, Manchester, Liverpool, the Wirral, Nottingham, Derby, Birmingham, Goodmayes, and London
Sample size estimate	The sample size estimate for each trial assumes a power of 80%, and 5% two-sided significance, and a 2:1 allocation of active:placebo treatment within each trial. On these assumptions the required sample size is 226 evaluable participants for each trial, i.e. 452 in total, to detect a reduction in mean attack rate in both arms from 3 to 2 per month, during weeks 11 to 14. The target of 600 for recruitment also leaves a margin for drop out of up to 25% (=1-452/600) for the primary outcome but only 2% (=1-588/600) for the proportion of responders outcome.
Number of participants	588 evaluable participants, 600 to be recruited
Eligibility criteria	Children and young people aged 5 years-16 years with Migraine with Out aura (MO), Migraine with Aura (MA), or Probable Migraine (PM) as defined by the International Headache Society (IHS)[1] with 2 to 6 migraine or probable migraine attacks per 4 week period by history during the previous 3 months and 2 to 6 migraine or probable migraine attacks per 4 week period during the 4 week baseline *and* treating paediatrician and parent / guardian and child or young person believe the attacks are currently frequent and severe enough to merit a twice daily preventative medication
Description of interventions	<u>Propranolol</u> Preparation: 10 mg / 10 ml or 10 mg tablet Dose: Up to 30 mg twice a day for children aged 5-7 years; to 40 mg twice a day for those age 8-11 years; to 60 mg twice a day for those aged 12-16 years. <u>Pizotifen</u> Preparation: 500 microgram / 10 ml or 500 microgram tablet Dose: Up to 1.5 mg at bedtime for children aged 5-7 years; to 2 mg for those aged 8-11 years; to 3 mg for those aged 12-16 years.

Duration of study	This trial is estimated to last a total of 3.5 years, from initiation of the (first) study site to completion of the last patient. For any given participant, the duration of his or her involvement will be at least 6 months up to a maximum of 11 months
Randomisation and blinding	The randomisation will be based on a computer generated pseudo-random code using random permuted blocks of randomly varying size. Participants, their parents / guardians, research nurses, local investigators administering the interventions, and those assessing the outcomes will be blinded to group assignment.
Outcome measures	**Primary** The number of migraine attacks during weeks 11 to 14 **Secondary** Response defined as a 50% or greater reduction in number of attacks; headache intensity; use of rescue medication; school attendance; parent/guardian time off work during weeks 11 to 14; recalled attack frequency; quality of life and functional outcomes.
Statistical methods	The mean attack rate during weeks 11 to 14 will be compared between treatment arms by Poisson regression with adjustment for stratification variables, other covariates and robust standard errors (for over-dispersion)

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BASH	British Association for the Study of Headache
BPNA	British Paediatric Neurology Association
b.d.	Twice Daily
CACE	Complier Average Causal Effect
CPMP	Committee for Proprietary Medicinal Products
CI	Chief Investigator overall
CIOMS	Council for International Organisations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTM	Clinical Trial Material
CTU	Nottingham Clinical Trials Unit
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
EMEA	European Agency for the Evaluation of Medicinal Products
EOT	End of Trial
GCP	Good Clinical Practice
GCQ	Generic Children's Quality of Life Scale
HTA	Health Technology Assessment programme
ICD-10	International Classification of Diseases and Related Health Problems, Tenth Revision
ICF	Informed Consent Form
IHS	International Headache Society
MA	Migraine with Aura
MCRN	Medicines for Children Research Network
MHRA	Medicines and Healthcare products Regulatory Agency
MO	Migraine with Out aura
NHS	National Health Service
NRES	National Research Ethics Service
NSAIDs	Non-steroidal anti-inflammatory drugs
o.d.	Once daily
ONS	Office of National Statistics
PedMIDAS	Pediatric Migraine Disability Assessment Questionnaire
PBO	Placebo
P/GIS	Parent / Guardian Information Sheet
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PM	Probable Migraine
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
s.c.	Subcutaneous injection
SPC	Summary of Product Characteristics
SR	Sustained Release
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Trial Coordinating Centre
TMG	Trial Management Group
TSC	Trial Steering Committee

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

In the last 20 years the International Headache Society (IHS) has fostered the development of high quality research in headache and migraine in particular. The 2nd edition of the International Classification of Headache Disorders was published in 2004[1] and provides a framework for not only clinical practice but particularly headache research, including clinical trials. It is vital that trials use this classification which has become rather more child relevant in this last edition.

There are operational diagnostic criteria for Migraine with Out aura (MO), and Migraine with Aura (MA) e.g. with an associated neurological impairment or dysfunction such as a visual field defect or zigzag lines in the visual field. As many general paediatricians will be unfamiliar with the precise criteria we also include patients with Probable Migraine (PM), as defined in the classification. They have features of migraine, perhaps combined with those of Tension-Type Headache, but do not fulfil completely the operational diagnostic criteria for migraine. Inclusion of this category, previously called “migraine-like headache” or “mixed headache” is vital for the trial to be of general use to most children presenting to paediatricians with severe headaches.

A recent Cochrane Review[2] has demonstrated the remarkable lack of reliable clinical trials of migraine treatments for children, especially for the 2 most prescribed preventative treatments used in the UK, Propranolol and Pizotifen.

Furthermore trials in migraine rescue and preventative treatments in children and adults, have been complicated by high placebo responder rates, e.g. of 23%[3]. For a trial’s results to be of generalisable use it should reflect this characteristic, not exclude “placebo responders”. However for a drug to be worthwhile it should be clearly superior, both clinically and statistically, to placebo (see section on sample size, below).

The clinical course of migraine is notoriously difficult to predict at any age, and especially in children. Migraine will come for weeks, months or a few years then remit for months or years, sometimes returning unpredictably later on. Long term follow-up is difficult and studies have demonstrated this variability[4]. A strength of this trial is the participation of clinically well defined migraine patients who will also be approached to help with future longer-term follow-up studies.

The study consists of two separate parallel groups, double-blind randomised controlled trials: one of Propranolol vs placebo, the other Pizotifen vs placebo. One placebo will match the Propranolol, the other placebo will match Pizotifen. Each trial will consist of a 4 week "run-in" then a 2 week dose escalation, then 12 week maintenance phase, and finally a 2 week down-titration. This will be followed by a 3 month off-treatment phase, still blind, and finally, a 3 month unblinded follow-up.

The aim is to confirm or refute superiority of Propranolol to placebo and of Pizotifen to placebo for the prevention of migraine attacks in children aged 5 - 16 years referred to secondary care out-patient settings with frequent migraine (2-6 / 4 weeks).

Both the active trial treatments or “Investigational Medicinal Products” (IMPs), Propranolol and Pizotifen have been in common clinical use for this indication in children for over 20 years. The trial does not therefore expose this group of patients to a new therapeutic risk, but will systematically evaluate efficacy and adverse events. The results will ascertain if one or both are superior to placebo in the prevention of migraine in children, and quantify other useful clinical outcomes such as quality of life, school attendance, any prolonged benefit after drug withdrawal, and adverse effects.

No unpleasant or painful procedures such as blood sampling will be undertaken. Only children and young people who together with their parent / guardian and paediatrician believe preventative treatment is warranted and who experience frequent migraine during the baseline 4 week Assessment Block 1 will be recruited.

DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Propranolol

A non-selective beta-blocker which crosses the blood-brain barrier exerting central as well as peripheral effects has been used in migraine prevention since the 1960s[5]. It is generally well tolerated but in high dose can be associated with fatigue or sleep disturbance. It can cause bronchospasm and exacerbate asthma, so patients with asthma will be excluded.

The adult recommended dose is initially 40 mg twice a day increasing to a maintenance dose of up to 80 mg twice a day[6]. In children, "Medicines for Children"[7] is used as an authoritative source of prescribing advice and recommends 20 mg two or three times a day in 2-12 year olds and up to 40 mg three times a day in 12-18 year olds. The new "British National Formulary (BNF) for children"[8] recommends "200-500 micrograms/kg three times a day, usually 10-20 mg two or three times a day up to 4 mg/kg/day maximum" for children aged 2 -12 years, and 20-40 mg two or three times a day increasing up to maintenance of 80-160 mg/day, the same as the adult recommended dose, for people aged 12 – 18 years.

In the trial we have picked age banded starting, titration and maintenance doses for children aged 5-7 years, 8-11 years and 12-16 years. These correspond to the recommendations and are equivalent to 0.6 -4 mg/kg/day for 80% of 5 to 7 year olds, 0.7-4 mg/kg/day for 80% of 8-11 year olds, and 0.7-4 mg/kg/day for 80% of 12-16 year olds, by standard growth charts for the tablet preparations. The maximum dose for the liquid preparation is less (see Liquid formulation and ceiling dose below).

Pizotifen

An antihistamine with histamine-1 antagonist and serotonin (5-HT2) antagonist properties is structurally related to the tricyclic antidepressants. It has been used for over 20 years in the United Kingdom for migraine prophylaxis in children, young people and adults. It is generally well tolerated but can cause drowsiness, especially if given in the day-time. For this reason clinical practice has evolved in paediatrics and it is commonly given as a once a day evening dose. Other adverse effects include increased appetite and weight gain.

The recommended dose for young people aged 12-18 years is in line with the adult recommended dose of 1.5 mg at night increasing to a maximum of 4.5 mg/day[6]. In children "Medicines for Children" [7] and the BNF C[8] recommend starting with 500 micrograms/day in 5-10 year olds and 1 mg/day in 10-12 year olds increasing to a maximum maintenance of 1.5 mg/day (1 mg as single night time dose) in 5-12 year olds, and 1.5 mg/day increasing to a maximum of 4.5 mg/day (3 mg as single night time dose) in 12-18 year olds, as with the adult dose.

In the trial we have picked age banded starting, titration and maintenance doses for children aged 5-7 years, 8-11 years and 12-16 years, corresponding approximately to these recommendations and are equivalent to 14-100 micrograms/kg/day for 80% of 5 to 7 year olds, 18-100 micrograms/kg/day for 80% of 8-11 year olds, and 18-100 micrograms/kg/day for 80% of 12-16 year olds, by standard growth charts for the tablet preparations. The maximum dose for the liquid preparation is less (see Liquid formulation and ceiling dose below).

Formulation and maximum ceiling dose

A liquid formulation will be needed as we expect all 5-7 year olds and some 8-11 year olds will not be able to swallow tablets. We expect 12-16 year olds will prefer to take tablets, although some might prefer liquid: the highest dose in this age group will be 60 ml or 6 tablets twice a day.

The liquid preparation of Propranolol (Syprol) contains propylene glycol as a preservative and in order to comply with the World Health Organisation (WHO) recommended maximum intake of 25

mg/kg/day of propylene glycol, the manufacturers (Rosemont Pharmaceutical Limited) recommend a maximum of 160 ml/day for a 70 kg adult (2.3 ml/kg). This therefore sets a maximum ceiling dose of Propranolol 10 mg/10 ml of no more than 1ml/kg twice a day. As the trial is double blind this maximum dose applies to Propranolol, Pizotifen and placebo. This will reduce the maximum dose of Propranolol and Pizotifen the lightest children in each age band can receive. For Propranolol (10 mg/10 ml) the maximum will be 2 mg/kg/day and for Pizotifen (500 micrograms/10 ml) the maximum will be 50 micrograms/kg/day, as the total daily Pizotifen dose is given at night, with a dummy (placebo liquid) dose in the morning to maintain the blind treatment allocation.

Despite this restriction, the proposed liquid doses remain within the recommended ranges:
For Propranolol although the ceiling of 2 mg/kg/day is half the maximum dose recommended in the BNF C for 2 – 12 year olds, the BNF C states that the dose for this age group is usually up to a maximum of 40 or 60 mg/day, which would be allowed in all those of 20 or 30 kg or more i.e. in about 50% of 5 -11 year olds. For 12-18 year olds the BNF C recommends up to 80 -160 mg/day, in line with the proposed maximum of 120 mg/day for 12 – 16 year olds, which would not exceed the maximum ceiling dose in those weighing 60 kg or more i.e. in about 25% of 12 - 16 year olds.

For Pizotifen BNF C recommends a maximum evening dose of 1 mg for children aged 5 -12 years. More than 50% will weigh over 20 kg so will be able to take 20 ml BD equivalent to 1 mg/evening dose. For young people aged 12 -18 years the BNF C recommends a maximum evening dose of 3 mg i.e. 60 ml so only those weighing 60 kg or more, who can take the maximum ceiling dose of 60 ml twice a day, can reach the maximum recommended daily dose, i.e. about 25% of children aged 12 – 16 years.

For those taking tablets, mostly the older participants in the 12 to 16 year age group, no ceiling dose is needed and so higher doses will be used, up to a maximum of 60 mg BD (up to 4 mg/kg/day for 80% of participants) for Propranolol, and up to a maximum of 3 mg as an evening dose (up to 100 micrograms/kg/ evening for 80% of participants) for Pizotifen; doses as recommended in the BNF C.

A priori we decided to look at the effectiveness of each trial drug in mg/kg/day during the 4 week assessment block 2 (weeks 11-14): the number of migraine attacks during weeks 11 to 14 compared to baseline versus mean dose for each participant, in mg/kg/day, for the same period.

Description

Propranolol

Rosemont Pharmaceuticals will supply the liquid formulation of the propranolol, in the form of their licensed product Syprol Oral Solution 10 mg/10 ml (See Syprol SmPC for additional information).

Essential Nutrition a specialist manufacturer, with an IMP licence (ML/10324), will manufacture the Propranolol as tablets of 10 mg (see Propranolol Investigators Brochure for additional information).

Pizotifen

Novartis Pharmaceuticals UK Ltd will supply the liquid formulation of the pizotifen, in the form of their licensed product Sanomigran Elixir 0.5 mg/10 ml (See Sanomigran SmPC for additional information).

Essential Nutrition a specialist manufacturer, with an IMP licence, will manufacture the Pizotifen as tablets of 500 mcg (see Pizotifen Investigators Brochure for additional information).

Packaging and labelling

This will be in accordance with UK regulatory requirements. Morning and Evening tablet bottles will be clearly marked as such, and each bottle will have a unique identification number.

Bulk supplies of the Pizotifen, Propranolol and placebo tablets will be delivered to Brecon Pharmaceuticals Ltd a facility with an IMP manufacturers licence (ML/11724) for packaging into bottles with a fill count of 50 tablets and labelling to allow preparation of randomised and blinded supplies with final release by a QP.
In order to maintain the blind commercial stock of Propranolol liquid 10 mg in 10 ml (Rosemont Pharmaceutical) and Pizotifen liquid 500 mcg in10 ml (Novartis Pharmaceuticals) will be purchased and delivered to Nova Laboratories (ML/13581), a facility with an IMP licence, for repacking into 300 ml bottles to match the placebo bottles. Following repackaging these will then be delivered to Brecon Pharmaceuticals Ltd for labelling and preparation of the randomised and blind supplies.

To maintain maximum flexibility all bottles will have an identifying bottle number and generic dosing instructions which refer to a trial instruction leaflet to be provided to participants and parents / guardians at the randomisation visit.

Blinded supplies will require storage at a central site (Brecon Pharmaceuticals Ltd.) for distribution to an estimated 10 UK centres under the web-based system control.

All participants will be offered a choice of liquid or tablet preparations of the trial treatments. To maintain blinding, participants will take morning doses and evening doses from separate bottles. Propranolol and Pizotifen will have their own liquid and tablet placebo preparations matched for appearance and taste.

Table 3: Morning and evening trial treatments

Treatment	Morning medication	Evening medication
Propranolol	Propranolol liquid 10 mg in 10 ml or Propranolol tablet 10 mg	Propranolol liquid 10 mg in 10 ml or Propranolol tablet 10 mg
Pizotifen	Placebo liquid or Placebo tablet	Pizotifen liquid 500 mcg in 10 ml or Pizotifen tablet 500 mcg
Placebo	Placebo liquid or Placebo tablet	Placebo liquid or Placebo tablet

Tablet trial treatments will be supplied in 50 tablet bottles by the study nurse at home visits: 3 (week 0), 4 (in week 5 or 6), 5 (in week 9 or 10), or if more convenient, to the family at hospital visits within these windows.

Liquid trial treatments will be supplied in 300 ml bottles by the study nurse at home visits: 3 (week 0), 4 (in week 5 or 6), 5 (in week 9 or 10), or if more convenient, to the family at hospital visits within these windows,

Storage, dispensing and return

Trial treatments will be stored at room temperature below 25 ºC in the original bottles. In the local pharmacy, all trial treatments should be stored in a secure location, in a temperature controlled environment, with a temperature log maintained daily, if possible, and may be dispensed only by specifically authorised personnel.

Each participating centre pharmacy will take receipt of numbered supplies from the central distribution site (Brecon Pharmaceuticals Ltd.).

A medication request to the web-based system by local site trial investigator or pharmacy personnel will require input of participant number and the number of bottles of allocated treatment needed to allow dosing until the next study visit. The system will then provide the appropriate bottle numbers for that participant.

Details will be transferred to a trial specific prescription and the pharmacy will complete the dispensing process by addition of the participant's name and date of dispensing to each allocated bottle.

The local site investigator is responsible for ensuring trial treatment accountability, including reconciliation of trial treatment and maintenance of trial treatment records, throughout the course of the study in accordance with UK regulatory requirements. Responsibility may be delegated to the site pharmacy clinical trials staff. Upon receipt of trial treatment, delivery details will be checked for accuracy and receipt acknowledged by signing or initialling and dating the documentation provided. In addition, receipt will be acknowledged in the web-based system. Dispensing will be recorded on the appropriate accountability forms.

The research nurses will help families by supplying specific "a.m." and "p.m." bottles. They will emphasise the importance of using only the correct bottles, will help out if there are breakages and spillages and anticipate when supplies are running low, and talk openly about forgotten doses to encourage openness and accuracy. Forgotten "a.m." doses can be taken late up to 4 hours before the "p.m." dose; forgotten "p.m." doses will usually be left and the "a.m." dose taken the next morning, in any event the "p.m." dose should not be taken within 4 hours of the usual waking up time.

Unused trial treatment must not be discarded or used for any other purpose than the present study. Trial treatment that has been dispensed to a participant must not be re-dispensed to a different participant. Unused trial treatment and empty bottles will be picked up at the research nurse visits (visits 4, 5, 6) and returned to the local pharmacy. As there is a 2 week window for these visits the research nurse will ensure that enough trial treatment is left with the participants at visits 4 and 5 to last them to the end of weeks 6 and 10 respectively, before opening the new supply.

Residual numbers of tablets and residual volumes of liquid will be recorded and accountability completed before local destruction to assess compliance (see compliance section for more details).

Placebo

Both Liquid and tablet formulations of the placebo will be manufactured using all of the same excipient used in the active formulation of the drugs minus the active ingredients. Rosemont Pharmaceuticals will supply the liquid placebo in 300 ml standard bottles and Essential Nutrition will supply in bulk the tablet placebo. Packaging and labelling of placebo will take place at Brecon Pharmaceuticals Ltd, see packaging and labelling section above, for more detail.

Known Side Effects

See appendix B for a list of known side effects for Propranolol and Pizotifen.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose is to confirm or refute superiority of Propranolol to placebo and of Pizotifen to placebo for the prevention of migraine attacks in children.

PRIMARY OBJECTIVE

To test whether Propranolol is superior to placebo and whether Pizotifen is superior to placebo for the prevention of migraine attacks in children aged 5 - 16 years old with frequent migraine (2-6 / 4 weeks), who are referred to secondary care out-patient settings.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

The study consists of two separate parallel group, double-blind randomised controlled trials: one of Propranolol vs placebo, the other Pizotifen vs placebo. One placebo will match the Propranolol, the other placebo will match Pizotifen with 6 months post trial follow-up. Each trial will consist of a 4 week “run-in” followed by randomisation, then a 2 week dose escalation, then 12 week maintenance phase, and finally a 2 week down-titration. This will be followed by a 3 month off-treatment phase, still blind, and finally, a 3 month unblinded follow-up and option to consent for a possible future follow-up study (Figure 1).

PROCEDURES FOR EACH VISIT

Please refer to the Table 1 of the protocol for a summary of the observations that are made at each study visit.

Participants should be seen for all scheduled study visits, if at all possible, up to the end date of the trial, regardless of their compliance with the trial protocol. All living randomised participants are to be followed until the end date of the trial. Any participants who can no longer come to the study site for visits will be followed up by the research nurse by home visits, telephone, e-mail, letter, etc. or by contacts with relatives or family physicians. In the event of a participant withdrawing from trial follow-up a discontinuation visit will be arranged if at all possible (Figure 1).

Visit schedule

Refer to table 1. Randomisation occurs at visit 2. Whenever practical, trial treatment should start as close to randomisation as possible e.g. the same day. Each visit has a “window” of +/-2 weeks within which it is acceptable to complete the visit. Each patient’s actual visit schedule should first be determined and then written out, as closely as possible, taking into account practical considerations such as weekends, planned holidays, etc., and the allowed visit window.

Table 1: trial visits	screening & baseline assessment			trial drug treatment			blind follow-up		open follow-up		
Visit:	1	2	3	4	5	6	7	8	9	10 EOT[e]	DIS[f]
Hospital Clinic: doctor (+/- or nurse)	X	X				X		X		X	X
Home: nurse (+/- or doctor)			X	X	X		X		X		
Elapsed time (weeks from 1st dose)	-8 to -4	-3 to 0	0	5-6	9-10	15-16	23-24	29-30	35-36	41-42	Any time
Screening Clinical Data Sheet completed (screening history & exam)	X										
Concomitant headache / migraine medication check	X	X		X	X	X	X	X	X	X	X
Inclusion and exclusion criteria	X	X									
Informed consent[a]	X										
Start baseline assessment block 1 (4 weeks)[b]	X										
Headache Diary review		X				X		X		X	X
Adverse events check list[c]		X		X	X	X	X	X	X	X	X
If still eligible randomised		X									
Give / review trial & treatment plan		X	X	X	X	X					
PedMIDAS, GCQ, parent EQ5D, child EQ5D			X			X					
Dispense / deliver Investigational Medicinal Product (IMP)			X	X	X						
Study medication compliance check				X	X	X					
Check blinding patient, parent/guardian, nurse or doctor								X			
Reveal allocation								X			
End trial[e,f] check consent to follow-up										X	X

Footnote for table 1

a. The informed consent process begins before visit 1, with identification of possibly suitable patients, based on history of eligible headaches in previous 3 months, discussion of the trial and giving them and their parents / guardians the appropriate participant and parent / guardian information sheets. They will usually have these days or weeks before visit one and at least 24 hours before.

b. The 4 week baseline assessment block 1 begins at 00.00 hours, e.g. on the Monday, after the signing of the informed consent form at visit 1 and ends at 23.59 hours, e.g. on Sunday, 4 weeks later, followed as soon as possible by visit 2.

c. All serious adverse events (SAEs) will be reported using the SAE form; non-serious adverse events will be recorded just in the Headache Diary.

d. The 1st dose of trial treatments will be as close to the date of randomisation as practicable, usually within a few days, e.g. on the following Monday, and no more than 2 weeks after. The day (e.g. Monday) the 1st dose of trial treatment is given is the start of trial week 1.

e. End of Trial (EOT) visit (visit 10) will be scheduled to occur within 2 weeks of the end of assessment block 4 i.e. as soon as possible in weeks 41-42.

f. Discontinuation visit: following unplanned discontinuation of the trial treatment, i.e. before weeks 15-16, or withdrawal from the trial, this extra visit should be arranged, but can coincide with another visit if within the same 2 week window. Participants should be encouraged to remain in trial follow-up even if they discontinue trial treatment prematurely or decline some of the assessments.

NB Some participants will start their assessment blocks on a Monday but not all will. It will be an advantage for different participants at a site to start on different days of the week (at the discretion of the investigator, research nurse and family).

Definition of protocol deviations

A protocol deviation is an unanticipated or unintentional divergence or departure from the expected conduct of a study inconsistent with the protocol, consent document or other study procedures.

Violations of eligibility criteria and other deviations from protocol will be assessed by the TAC and discussed with the TSC during a study evaluability meeting, before data lock and unblinding.

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6. Romford (Children's Headache Clinic)
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7. London (Paediatric Headache Clinic)
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8. Manchester (Paediatric Neurology Clinic)
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9. Birmingham (Paediatric Neurology Clinic)
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rajat.gupta@bch.nhs.uk
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10. Wirral (Children's Headache Clinic)
Dr Adrian Hughes Principal Investigator
Consultant Paediatrician,
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Tel: 0151-604 7071

Primary endpoint

The number of migraine attacks during weeks 11 to 14, as recorded in the participant diary.

Migraine attack is defined as in the IHS International Classification of Headache Disorders1: headache attack fulfilling at least 2, or all 3 criteria B-D for MO 1.1, with or without aura (see Appendix 9.5).

Secondary endpoints

Efficacy

1. Response, defined as a 50% or greater reduction in number of attacks during weeks 11 to 14; 25 to 28; 37 to 40, relative to baseline, as recorded in the participant diary.

2. Headache intensity; headache intensity will be measured on the standard 4 point scale[23] (0 = no headache; 1 = mild headache, continues all activities; 2 = moderate headache, has to reduce activities; 3 = severe headache, stops all activities, just lies down or sleeps). As migraine headache is usually moderate or severe (with additional features), mild headaches will not be recorded, unless they are associated with sufficient additional features to meet the diagnostic criteria for migraine attack (see Appendix 9.5). Headache intensity as experienced during the worst part of the migraine attack will be averaged during weeks 11 to 14 for each participant.

3. Use of rescue medication, defined as the total number of rescue doses taken during weeks 11 to 14, as recorded in the participant diary.

4. School attendance, defined as % of school half days attended during weeks 11 to 14, as recorded by diary.

5. Recalled Attack Frequency: participants reply at visit 6 to “How many migraine attacks did you have in the 4 week assessment block (weeks 11 to 14)?” They may discuss with their parents / guardian and look at their diary if they wish. This will help in imputing missing values for those who can provide no diary information.

6. Quality of life & functional outcomes using:
6.1 the health-related quality of life tool PedMIDAS[9];
6.2 the non-health-related Generic Child Quality of Life measure GCQ[10].

Health Economics

Sufficient data to allow cost effectiveness comparisons from NHS and family perspectives will be collected but not analysed at this stage. If one or other active treatments proves effective in comparison to placebo, then funding for a formal cost comparison and cost effectiveness study will be sought.

7. Parent’s / guardian’s time off work mainly related to child’s migraine, for those in full time paid employment, or pro-rata for those in part-time paid employment, during weeks 11 to 14, as recorded in the participant diary.
8. Costs of Propranolol, Pizotifen, and placebo (study medications):
9. Cost of rescue medications
10. Number and length of emergency hospital admissions and Emergency Department attendances, and non-trial hospital and GP surgery appointments, related to migraine, with dates and place will be recorded in the participant diaries so the cost of investigations can be determined later
11. Cost of “child half days off school” (4 above)

12. EQ-5D[11] for parents / guardian and participants aged 12-16 years; UK Proxy EQ-5D[12] for younger participants (a UK child friendly EQ-5D may be available for use during the trial for participants aged 7-11 years).

Additional supporting demographic data will be collected including:

13. parent's / guardian's stage at leaving full-time education (record highest of two parents / guardians). The education levels are grouped as follows:
    • No qualifications: no academic or professional qualifications
    • Level 1: one or more O levels/CSEs/GCSEs (any grade); NVQ level 1; Foundation GNVQ; or equivalents
    • Level 2: five or more O levels; 5 or more CSEs (grade 1); five or more GCSEs (grade A – C); one or more A levels/AS levels; NVQ level 2; Intermediate GNVQ; or equivalents.
    • Level 3: two or more A levels; four or more AS levels; Higher School Certificate; NVQ level 3; Advanced GNVQ; or equivalents.
    • Level 4/5: First degree; Higher Degree; NVQ levels 4-5; HNC; HND; Qualified Teacher Status; Qualified Medical Doctor; Qualified Dentist; Qualified Nurse, Midwife, Health Visitor; or equivalents.
    • Other qualifications/level unknown: other qualifications (for example City and Guilds); other professional qualification

14. full post code (to derive deprivation score).
15. Office of National Statistics (ONS) self-coded NS-SEC of one parent / guardian.[26]

If both are effective compared to placebo, then the outcomes for each active drug will be compared, but the trial was not powered specifically to compare the two active treatments.

Safety and tolerability variables

These include:

1. Adverse Event (AE) reports:
    a) spontaneous,
    b) elicited by routine enquiry using the AE check list,
    c) findings from physical and neurological examinations

2. Vital signs: ,Weight, Height and Blood Pressure, Heart Rate at baseline and visit 6.

3. Participant's wish to continue (or parent / guardian's where child unsure) with allocated trial medication after week 14.

4. Time until withdrawal from allocated trial medication, from randomisation to end of week 14, with censoring at week 14 of those participants who do not withdraw. Reasons for withdrawal will be recorded in CRF.

RANDOMIZATION AND BLINDING

Participants will be allocated with equal probability to the Pizotifen, the Propranolol and the two Placebo treatment arms. Those allocated to Placebos will have an equal probability of receiving either the Propranolol Placebo or the Pizotifen Placebo. Thus, for example, for 600 participants randomised 200 will be allocated Propranolol, 100 Propranolol Placebo, 200 Pizotifen, and 100 Pizotifen Placebo.

The randomisation will be based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their standard operating procedure (SOP) and held on a secure server. The

randomisation will be stratified by age (5-11 years vs 12-16 years), type of migraine (two categories: migraine and probable migraine) and recruiting centre (10 centres).

Access to the sequence will be confined to the CTU Data Manager. Investigators will access the treatment allocation for each participant by means of a remote, internet-based randomisation system developed and maintained by the Nottingham CTU. The sequence of treatment allocations will be concealed until interventions have all been assigned and recruitment, data collection, and all other trial-related assessments are complete.

Participants, their parents / guardians, research nurses, local investigators administering the interventions, and those assessing the outcomes will be blinded to group assignment. The statistical analysis for each trial will also be blind. The DMC may have access to unblinded data but will have no contact with study participants.

The placebo formulations will match their respective active formulations in terms of colour, taste and volume. The majority of individual participants will only take one of the 3 treatments, however in order to preserve blinding of the treatment allocation, those randomised to Pizotifen will take a dummy treatment (Pizotifen Placebo, tablets or liquid) in the morning and Pizotifen in the evening, blinded.

Maintenance of randomisation codes and procedures for breaking code

The local Principal Investigator paediatrician or paediatric neurologist or other doctor in an emergency, e.g. in a hospital emergency department, may need to break the treatment allocation code and or withdraw the participant from the trial drug. This will happen only in exceptional circumstances. The code will not need to be broken, nor the participant withdrawn, for most intercurrent illnesses or medical emergencies, except when the participant is in the trial drug treatment phase (weeks 1 to 16) and Pizotifen or Propranolol would have a significant bearing on the diagnosis or treatment of an intercurrent illness. For example if the participant was admitted with acute severe bronchospasm or a cardiac conduction disorder requiring hospital treatment or other condition that could be caused by or exacerbated by either Propranolol or Pizotifen, then the code should be broken urgently.

The doctor is advised to discuss the case with the Chief Investigator or Trial Coordinating Centre staff (contactable by pager or telephone) if time allows. If there is no time to do this or it is agreed, after discussion, to break the code then the centre pharmacy / on call pharmacist will have 24 hour access to the code (both by internet and by master code break list stored in the coordinating centre hospital Pharmacy Department) and he or she or the Trial Coordinating Centre staff will inform the enquiring doctor of the trial treatment allocation for that patient.

The doctor will then decide if the trial drug treatment needs to be stopped temporarily or permanently or if it can continue and whether the participant and their parent / guardian should be unblinded. In any event the doctor will record what was decided in the child or young persons medical notes and inform the Trial Coordinating Centre. The participant should if at all possible continue in the trial follow-up schedule, even if they are withdrawn from trial drug treatment.

The code should not be broken for mild or unrelated adverse events or intercurrent illness e.g. mild asthma not requiring hospital admission, uncomplicated acute appendicitis etc.

TRIAL MANAGEMENT

The sponsor is the University of Nottingham, which will clarify with the funding body (the HTA) and local centre R&D departments their precise responsibilities. The sponsor is responsible for the proper conduct and management of the trial. A number of committees will be assembled to help

ensure the proper management and conduct of the trial, and to ensure the safety and well-being of the patients enrolled.

The following committees have been formed:
Trial Steering Committee (TSC)
Trial Management Group (TMG)
Trial Adjudication Committee (TAC)
Data Monitoring Committee (DMC)

The general purpose, responsibilities, and structures of the committees are described in this protocol. However, it is assumed that these committees will develop their own rules and procedures which may evolve with time, during the preparation and conduct of the trial. The committees will have guidance, in the form of Standard Operating Procedures (SOP), from the University of Nottingham's Clinical Trials Unit (CTU).

Trial Steering Committee (TSC)

The TSC is composed of representatives from the academic and medical communities, and from the TMG. Members from the TMG will not have voting privileges on the TSC. The TSC has the overall responsibility for ensuring a scientifically sound study design, a well executed trial, and accurate reporting of the study results. The TSC must address and resolve scientific, medical, and practical issues encountered during the trial. The TSC will draw up its own guidelines, and will review the criteria and guidelines of the other committees in order to provide advice and suggestions if necessary. The TSC will convene, either in person or via teleconference, as often as deemed necessary to carry out its responsibilities, but at least once per year.

The CTU will provide statistical support to the TSC to investigate any additional database questions that the TSC raises, which may include possible additional analyses to those outlined prospectively in the trial protocol. However these will not be undertaken without an appropriate protocol amendment or justified variation to the Statistical Analysis Plan.
The TSC will have administrative support from the Trial Coordinating Centre staff (the Trial Coordinator, based at the Nottingham Clinical Trials Unit.

The voting members of the TSC are:

Dr George Rylance (Chair)
Consultant Paediatrician
School of Clinical Medical Sciences (Child Health)
Sir James Spence Institute University of Newcastle upon Tyne
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tel: 0191 282 9568; fax: 0191 202 3022
george.rylance@ncl.ac.uk

Prof Paula Williamson
Prof of Medical Statistics
Director of MCRN Clinical Trials Unit
University of Liverpool Institute of Child Health
Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP, UK
p.r.williamson@liverpool.ac.uk

Mrs Trudie Lobban (consumer representative)
Chief Executive
STARS
PO Box 175, STRATFORD UPON AVON, CV37 8YD, UK

tel: 01789 450 564; fax: 01789 450 682
trudie@stars.org.uk

In addition, Dr William Whitehouse and other members of the TMG, such as the trial statistician, will normally attend meetings of the TSC, together with the Trial Coordinator.

Trial Management Group (TMG)

The TMG will oversee the "operational" aspects of the trial, which include the processes and procedures employed, and the day-to-day activities involved in study conduct. Day to day management of the trial will be undertaken by the trial Coordinating Centre at the Nottingham Clinical Trials Unit. The TMG will meet regularly, in person or by conference call to review the progress of the trial and to address any urgent issues. The TMG will provide recommendations and helpful suggestions to the TSC. The University of Nottingham, via the CTU, will employ its own systems and procedures in the conduct of this trial, using the CTU personnel such as database builder, Trial Statistician, Trial Coordinator and Data Entry Administrator, in liaison with the Chief Investigator

The TMG consists of:

Dr William Whitehouse (Chair & Chief Investigator)
Clinical Senior Lecturer in Paediatric Neurology,
School of Human Development, University of Nottingham,
E Floor East Block, Queen's Medical Centre, Nottingham, NG7 2UH, UK
william.whitehouse@nottingham.ac.uk
tel: 0115 924 9924 ext 64476; fax 0115 823 0626

Dr. Helen Sammons (Principal Investigator)
Associate Professor of Child Health
School of Graduate Entry Medicine and Health,
Academic Division of Child Health, The Medical School,
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helen.sammons@nottingham.ac.uk
tel: 01332 724694, fax: 01332 724697

Diane Whitham, Clinical Trials Development Manager,
University of Nottingham, Clinical Trials Unit, B39 Medical School, Nottingham, NG7 2UH, UK
diane.whitham@nottingham.ac.uk
tel: 0115 823 0514; fax: 0115 823 0501

Mrs Sheila Hodgson (Trial Pharmacist)
Queen's Medical Centre, Nottingham, NG7 2UH, UK
sheila.hodgson@nuh.nhs.uk
0115 924 9924 ext 68451

In addition administrative support will be provided by the Trial Coordinator, and other members of the CTU and other investigators will attend as needs be.

Trial Adjudication Committee (TAC)

The Trial Adjudication Committee (TAC) will need to decide what actions should be taken for specific problems as they arise, e.g. what to do with particular protocol violations, missing data, contradictory data or other circumstances not anticipated and dealt with in the Trial protocol. The TAC will meet at least once a year, in advance of the DMC meeting. The TAC can consult with the TSC and other colleagues as needs be and will let the TSC know what it has decided.

The TAC comprises the following TMG members:

Dr William Whitehouse (Chair & Chief Investigator)
Clinical Senior Lecturer in Paediatric Neurology,
School of Human Development, University of Nottingham,
E Floor East Block, Queen's Medical Centre, Nottingham, NG7 2UH, UK
william.whitehouse@nottingham.ac.uk
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Dr Helen Sammons
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Prof P Goadsby, Professor of Clinical Neurology,
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The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N , UK
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Dr Carole Cummins
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Dr Paul Silcocks (Trial Statistician, CTU)
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paul.silcocks@nottingham.ac.uk; ctsu@nottingham.ac.uk
tel: 0115 823 0505; fax 0115 823 0501

Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will evaluate the outcome and safety data in the context of the overall trial and the currently existing information about the study drugs. The DMC will consider the appropriate timeframe for reviewing the data during the course of the study (currently the TSC suggests two inspections of the data), and will draw up a Charter delineating their guidelines for operating, and stopping rules for terminating a portion or all of the trial prematurely.

The DMC will have access to all trial data. It may request and will be provided with whatever data it deems necessary or useful for it to carry out its duties, including the provision of unblinded data. The DMC will provide their recommendations to the TSC and to the CTU over the course of the trial.

The DMC comprises:

Prof George Russell (Chair)
Emeritus Professor of Child Health
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Prof John Osborne, Consultant Paediatrician
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tel: 01225 824 218; fax: 01225 824 212
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Dr Stephen Walters, Senior Lecturer in Medical Statistics
School of Health and Related Research
University of Sheffield
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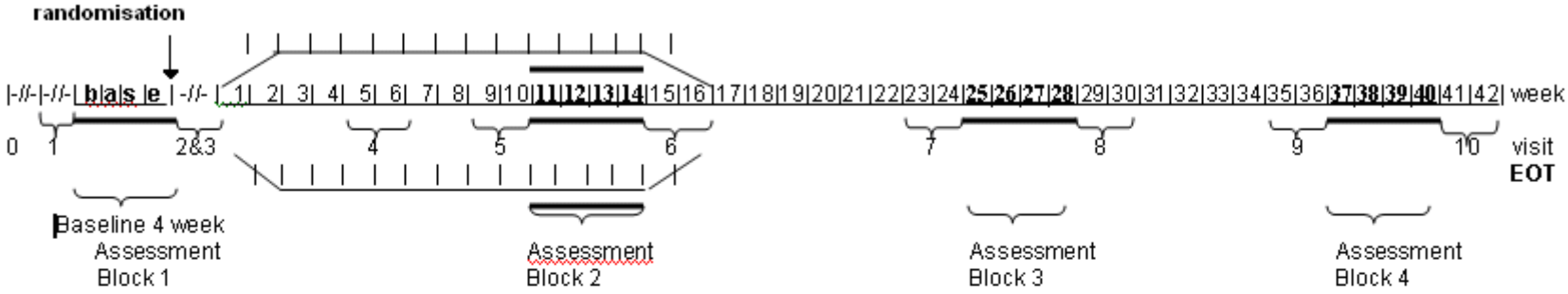
Tel: 0114 222 0730; fax: 0114 272 4095
S.J.Walters@sheffield@ac.uk

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

This trial is estimated to last a total of 3.5 years, from initiation of the (first) study site to completion of the last patient. For any given participant, the duration of his or her involvement will be at least 6 months up to a maximum of 11 months. For each trial there will be an initial 4 week "run-in" from baseline. This will be followed by randomisation and a 2 week dose escalation and a 12 week maintenance phase (the primary endpoint will be evaluated during the last 4 weeks of this period). There will then be a 2 week tail-off then a 3 month off treatment phase (still blind) and finally a 3 month unblinded follow-up.

We will ask participants and their parents / guardians to consent at visit 1 to be contacted at a future date for possible enrolment in a long-term follow-up and confirm this at the end of their active involvement in the trial. The TSC, in conjunction with the sponsor may terminate the trial early on the advice of the DMC (see Figure 1).

Figure 1 **Patient and family involvement over time**



visit (visits have +/- 2 week windows, week 1 starts with 1st trial drug dose)

0	Potential trial participant identified and information about trial given
1	Informed consent & assent and start 4 week run-in baseline assessment block 1
2-3	Review eligibility, consent, complete baseline documentation, randomise to 3 arms, deliver trial treatments
4&5	Home visit reviews and deliver trial treatments, remind family about assessment block, pick up used bottles
6	Review of assessment block 2 and general clinical review during tail of trial treatment, pick up used bottles
7	Review and remind family about assessment block 3
8	Review of assessment block 3, general clinical review, un-blinding
9	Review and remind family about assessment block 4
10	Review of assessment block 4, general clinical review, end of trial documentation

weeks

1-16	taking trial treatment
1- 2	trial treatment dose titration
3-14	maintenance dose of trial treatment
15-16	trial treatment dose tail
17-40	follow-up off trial treatment
41-42	end of trial visit

6 to 4 - 2 to 0 weeks pre randomisation baseline assessment block 1
11 -14 assessment block 2
25 -28 assessment block 3
37 -40 assessment block 4

There will be additional weekly contacts by phone, text, email at family and research nurses convenience, during weeks 1-16 and as appropriate weeks 17-40

End of the Trial

The end of trial is defined as the last visit (visit 10), scheduled to occur within 2 weeks of the end of assessment block, of the last participant.

STUDY POPULATION

NUMBER OF SUBJECTS PLANNED

A total of 600 patients will be randomised into this trial nationally thus allowing for ~25% drop out for the primary response variable and ~2% drop out for the responder rate. It is estimated that as many as 1000 patients may need to be screened in order for 588 evaluable randomised participants to be enrolled.

This trial will be conducted in 10 study centres throughout England and Scotland. The enrolment period (period during which new patients may be enrolled) is planned to last 24 months.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Potential participants may be identified in GP practices on the basis of clinical diagnosis and may chose to refer them to the relevant headache clinic. Potential participants will be identified in clinic by their clinic doctor or research nurse, on the basis of their clinical diagnosis and migraine or probable migraine attack frequency history for the previous 3 months. A standard clinical data sheet will be completed on all potential recruits, based on a tool in clinical use. If the potential participant and their parent / guardian are willing to participate but cannot estimate the migraine attack frequency in the previous 3 months they will be given a standard headache diary (in current clinical use) to fill in prospectively over the next 3 months, and appropriate advice and treatment will be given as is normal practice i.e. treatment will not be delayed. A check-list of Inclusion and Exclusion criteria will then be completed.

Once identified, the trial will be discussed with them and a Parent / Guardian Information Sheet (P/GIS) and consent form, and age appropriate Participant Information Sheet (PIS) and assent form given to them to review. Separate information sheets and assent forms for children age 5-8 years, 9-15 years, and aged 16 years will be given, as appropriate. There will be posters about the trial on display in the clinics and laminated pocket prompt cards to remind the clinic doctors of the trial and the inclusion and exclusion criteria, during clinics.

Potential participants and their parent / guardian will have as much time as they wish before giving formal informed consent and assent to enter the trial, sometimes a few weeks, usually several days and at least 24 hours. They can withdraw at any time, without giving a reason and without compromising their future care. They will be asked to talk through their reasons if they do not mind and will be asked to continue with the trial follow-up and data collection, even if they withdraw from the trial treatment.

In the event of their withdrawal data collected so far will not be erased and will be used in the final analyses where appropriate (this will be explained in the Participant Information Sheet).

Inclusion criteria

1. age 5 years 0 months to 16 years 11 months
2. with Migraine with Out aura (MO), Migraine with Aura (MA), Probable Migraine (PM) as defined by IHS1 (see Appendix E), with 2 to 6 migraine or probable migraine attacks / 4 weeks by history during the previous 3 months
3. and 2 to 6 migraine or probable migraine attacks / 4 weeks during the 4 week run-in
4. and treating paediatrician and parent / guardian and child or young person believe the attacks are currently frequent and severe enough to merit a try of twice daily preventative medication
5. Satisfactory completion of headache diary during the run-in period at discretion of the investigator

Exclusion criteria

1. Asthma, bronchospasm or nocturnal or exercise induced cough or wheeze within the last 12 months or currently on daily asthma preventative treatment
2. children under paediatric cardiology review, at the discretion of their paediatric cardiologist, e.g. if Propranolol or Pizotifen were contraindicated
3. children with any of the following: uncontrolled heart disease, the presence of second or third degree heart block, in cardiogenic shock, bradycardia, severe peripheral arterial disease, metabolic acidosis, sick sinu syndrome, untreated phaeochromocytoma, prone to hypoglycaemia (e.g. after prolonged fasting) or Prinzmetal's angina.
4. previous severe adverse event probably related to Propranolol or Pizotifen
5. on Propranolol, another beta-blocker, Pizotifen or Cyproheptidine in the last 3 months
6. currently in or have been in another prospective drug trial in the last 3 months
7. fewer than 2 or more than 6 eligible attacks during the 4 week run-in, and stay excluded for 3 months at least
8. child or family unable to identify their migraine or probable migraine headaches confidently (as may happen with some patients with both mild headaches and migraine on different days, e.g. with chronic daily headache [15 or more headache days / month]).
9. females of child bearing potential who are not using a reliable contraceptive strategy such as abstinence, barrier methods, oral contraceptive pills and contraceptive injections. See Pregnancy section below.
10. Informed consent not given by parents / guardian, or assent / consent not given by patient

PREGNANCY

The parent / guardian and participant information sheets and research nurse contacts will explain that while most unlikely, nevertheless should a participant become pregnant we would advise stopping the trial treatment but continuing the trial monitoring and seeking follow-up information on the pregnancy and any offspring at least until their second birthday. Note that this topic must be approached with judgement and sensitivity. A healthy pregnancy would not be recorded as an adverse event, unless there was an adverse outcome for the mother or infant. Any pregnancies will be specifically recorded and followed.

OBSERVATIONS

Measurements

A standard baseline clinical data sheet will be completed by the clinic doctor, recording baseline history and examination findings, based on one in clinical use in recent years.

A standard headache diary will be completed by the participant and their parent / guardian. This is adapted for the trial from a migraine clinic diary developed by the British Paediatric Neurology Association's (BPNA's) Governance & Audit group [23].

A standard Adverse Events check list developed for the trial.

Standard visit specific clinical data sheets to be completed by the doctor and research nurse at each trial visit.

Headache intensity scale[24]:

0 = no headache
1 = mild headache, does not interfere with usual activities
2 = moderate headache, inhibits but does not wholly prevent usual activities
3 = severe headache, prevents all activities; typically just lies down / sleeps

This is the functionally based scale, recommended by the IHS for many years, both to assist in diagnosis (migraine is almost always moderate or severe headache with additional criteria, see Appendix E) and monitoring treatment clinically and in trials. It will be rated by the participant and assisted if needs be by the parent / guardian. Each headache during each 4 week assessment block will be given a score based on the headache intensity at its worse. There will be at least 48 hours remission between separate migraine attacks: where there is a shorter remission it will be counted as a single attack. Children usually have short migraine attacks of a few hours duration only. We will also record migraine days as well as migraine attacks. Also height, weight, blood pressure and heart rate will be recorded at all clinical visits and in all cases at baseline and after the active treatment phase (visits 2 and 6) on the case report form.

Pediatric Migraine Disability Assessment Scale (PedMIDAS)[9]

A standardised validated health-related quality of life scale for children with migraine.

Generic Child Quality of Life Measure (GCQ)[10]

A standard validated non-health related quality of life scale for children.

EQ-5D[11]

A standardised validated health outcome measure providing a simple descriptive profile and a single index value for health status. For parents /guardians and participants aged 12-16 years old.

Child-friendly EQ-5D[12]

For younger participants; a child friendly version of EQ-5D has been developed and will be used during the trial for participants aged 7-11 years.

UK Proxy EQ-5D[13]

For younger participants unable to use the child-friendly EQ-5D; a proxy version of EQ-5D has been developed and will be used during the trial.

These quality of life scales will be applied by the research nurse, initially after randomisation and before the first dose is given (visit 3), after the main treatment assessment block (visit 6), and after the other 2 assessment blocks (visits 8 and 10).

Safety

No routine blood tests or other investigations will be undertaken. Any other tests may be undertaken at the clinic doctor's discretion with the participant and parent/ guardian's consent, as clinically indicated. If an adverse event is demonstrated then that will be recorded and reported in the usual way (see adverse event section).

Expected duration of participant participation

Study participants will be participating in the study for at least 6 months up to a maximum of 11 months.

Removal of participants from therapy or assessments

The following subject withdrawal criteria apply:

1) Adverse event (serious and non-serious) with clear contraindications
2) Participant or parent guardian withdraws consent
3) Lost to follow up
4) Participant develops an excluded/contraindicated condition
5) Investigator discretion (e.g. AE, participant needs treatment with prohibited drug, etc)
6) Unblinding, though adjudication from TAC is required

As this is a pragmatic intention to treat study compliance will only be measured and participants will not be withdrawn for non-compliance.

Please note that whenever a participant withdraws or is withdrawn then it will be made clear that their future clinical care will not be affected in any way.

It is important to distinguish temporary discontinuation of trial treatment, permanent discontinuation of trial treatment and early withdrawal from the study.

Participants must be withdrawn from the study if they or their parent / guardian withdraws consent. Such withdrawal of consent may take place at any time; no justification for such a decision is required but will be sought and recorded. They will be encouraged to continue with as much of the trial protocol as they will accept, e.g. they may wish to stop a trial treatment altogether but may agree to continue with complete or modified, partial follow-up. Data already accrued by the study will not be destroyed as even incomplete data sets will be of value to the study.

If an adverse event (serious or non-serious) occurs, the investigator or attending physician has the responsibility for and will take direct and appropriate action to provide care for the participant and to decide whether or not the trial treatment should be discontinued.
However, it is recommended that unless clear contraindications arise, the trial treatment be continued, or stopped only briefly. This is much preferred to permanently discontinuing the patient

from the trial treatment. Therefore, every attempt should be made to have the patient restart the trial treatment if medically appropriate.

In all cases, the reasons for discontinuation of trial treatment (and withdrawal from the study where applicable) must be recorded on the Case Report Form (CRF) and if the investigator has recorded more than one reason, they should indicate the main reason. The following will also be recorded: date of discontinuation or withdrawal, actions taken, date re-started if applicable, future follow-up assessments agreed.

Every effort should be made to encourage the participant to attend all planned assessments and visits, whether they continue to take the trial treatment or not.
Unblinding to participants or others involved in the conduct of the trial will be a protocol violation and notified to the Trial Adjudication Committee (TAC), who will decide what action to take.

Participants may be discontinued from the trial treatment at the discretion of the investigator, e.g. due to Adverse Events (AEs), or when the participant needs treatment with a prohibited drug during the study, or due to any other situation which the investigator judges to be relevant.

If there is violation of eligibility criteria and the participant is falsely enrolled they and their parent / guardian and medical team should be informed but encouraged to continue in the trial, including taking the trial treatments and follow-up. They will be included in the safety analysis but not in the other outcome analyses. The local investigator(s) will inform the TCC who will report to the TMG. The Chief Investigator (CI) will also discuss the circumstances with the TSC.

Following discontinuation or withdrawal a discontinuation visit should be completed, this can be done at the same time as the last follow-up visit they are able to attend.
Reasonable effort should be made to contact any participant lost to follow up during the course of the study in order to complete assessments and retrieve any outstanding data and study medication / supplies. The participants should not be accepted as lost without repeated telephone calls, texts, emails, letters, and visits to them and their third party contact (e.g. a grand parent or family friend).

Enrolled participants who withdraw from the study after randomisation will not be replaced.
Participants who withdraw before randomisation will keep their trial identification code but will be replaced (their replacement being assigned a separate trial identification code).
It is unlikely that abrupt termination of either trial treatment will affect participant safely and so no specific measures for this occurrence are advised.

Informed consent

The initial approach will be from a member of the child or young person's usual care team (which may include the investigator), and posters about the trial will be on display in the relevant clinical areas, e.g. the children's out-patient department, GP practices.

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant and their parents or legal guardian, or other individual or other body with appropriate jurisdiction, of all aspects pertaining to the child or young person's participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant and parent / guardian information sheets, and consent / assent forms, but the consent forms and information sheets will not be available printed in other languages.

The process for obtaining participant informed consent or assent and parent / guardian informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced.

The investigator or their nominee and the participant's parent / guardian or other legally authorised representative must both sign and date the Informed Consent Form before the child or young person can participate in the study. The child or young person will be encouraged to take an active role in the consent process and have an age-appropriate participant information sheet (separate sheets for children aged 5-8 years, 9 to 15 years and young people aged 16 years) and to sign an age-appropriate informed assent form. Young people aged 16 years old can consent to be a participant in the trial but will only be included if their parent / guardian also consent to their participation.

The clarity and usefulness of the participant and parent / guardian information sheets and consent and assent forms will be routinely assessed by an integrated, simple, brief questionnaire built into the consent and assent forms.

The participant and their parent / guardian will receive a copy of the signed and dated forms and the originals will be retained in the site study records. A copy of each will be filed in the participants medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study, made by both, the child or young person and their parent / guardian, is entirely voluntary. Only if the child or young person and the parent / guardian both agree will the child or young person be enrolled. The investigator or their nominee must emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions may be done before informed consent has been obtained.

The parent / guardian will be asked to provide a third party contact in the event of losing contact with the participant / parent / guardian. The third party and the parent / guardian will both be asked to consent to these details being kept on record until completion of the trial, at which time the information will be destroyed.

The investigator will inform the participant and their parent / guardian of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent and assent forms.

If the Informed Consent Form is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

Instructions on how to discuss and ask for informed consent and assent will be given to investigators who will ensure that their nominees, including research nurses, carry this out correctly without pressurising potential participants or their parents / guardian.

All investigators will have undertaken Good Clinical Practice (GCP) training prior to involvement in the study.

TRIAL / STUDY TREATMENT AND REGIMEN

Each active treatment will have a matched placebo. Treatments and their placebos will be available as identical tablets or for those who prefer, the younger participants in particular, as liquid preparations

Placebo tablet

Youngest children 5 to 7 years old (80% weigh 15-35 kg)
Titration

week 1	1 tab a.m.	1 tab p.m.
week 2	2 tab a.m.	2 tab p.m.

Maintenance

week 3-14	3 tab a.m.	3 tab p.m.

(reduce dose one step if possible or probable dose related adverse events)

Tail week 15-16

if was on 1 tab BD	reduce to ½ tab BD for 1 week then stop	
if was on 2 tab BD	reduce to 1 tab BD for 1 week then stop	
if was on 3 tab BD	reduce to 2 tab BD for 1 week	then 1 tab BD for 1 week then stop

Middle children aged 8 to 11 years old (80% weigh 20-55 kg)
Titration

week 1	2 tab a.m.	2 tab p.m.
week 2	3 tab a.m.	3 tab p.m.

Maintenance

week 3-14	4 tab a.m.	4 tab p.m.

(reduce dose one step if possible or probable dose related adverse events)

Tail week 15-16

if was on 2 tab BD	reduce to 1 tab BD for 1 week then stop	
if was on 3 tab BD	reduce to 2 tab BD for 1 week	then 1 tab BD for 1 week then stop
if was on 4 tab BD	reduce to 3 tab BD for 1 week	then 2 tab BD for 1 week then stop

Older children aged 12 to 16 years old (80% weigh 30-85 kg)
Titration

week 1	3 tab a.m.	3 tab p.m.
week 2	4 tab a.m.	4 tab p.m.

Maintenance

week 3-14	6 tab a.m.	6 tab p.m.

(reduce dose one step if possible or probable dose related adverse events)

Tail week 15-16

if was on 3 tab BD	reduce to 2 tab BD for 1 week	then 1 tab BD for 1 week then stop
if was on 4 tab BD	reduce to 3 tab BD for 1 week	then 2 tab BD for 1 week then stop
if was on 6 tab BD	reduce to 4 tab BD for 1 week	then 3 tab BD for 1 week then stop

Placebo liquid

Youngest children 5 to 7 years old (80% weigh 15-35 kg)
Titration

week 1	10 ml a.m.	10 ml p.m.
week 2	20 ml a.m.	20 ml p.m.

Maintenance

week 3-14	up to 30 ml a.m.	30 ml p.m. or maximum 1 ml/kg twice/day

(reduce dose one step if possible or probable dose related adverse events)

Tail week 15-16

if was on 10 ml BD	reduce to 5 ml BD for 1 week then stop	
if was on 20 ml BD	reduce to 10 ml BD for 1 week then stop	
if was on 30 ml BD	reduce to 20 ml BD for 1 week	then 10 ml BD for 1 week then stop

Middle children aged 8 to 11 years old (80% weigh 20-55 kg)
Titration

week 1	20 ml a.m.	20 ml p.m.
week 2	30 ml a.m.	30 ml p.m. or maximum 1 ml/kg twice/day

Maintenance

week 3-14	up to 40 ml a.m.	40 ml p.m. or maximum 1 ml/kg twice/day

(reduce dose one step if possible or probable dose related adverse events)

Tail week 15-16

if was on 20 ml BD	reduce to 10 ml BD for 1 week then stop	
if was on 30 ml BD	reduce to 20 ml BD for 1 week	then 10 ml BD for 1 week then stop
if was on 40 ml BD	reduce to 30 ml BD for 1 week	then 20 ml BD for 1 week then stop

Older children aged 12 to 16 years old (80% weigh 30-85 kg)
Titration

week 1	30 ml a.m.	30 ml p.m.
week 2	40 ml a.m.	40 ml p.m. or maximum 1 ml/kg twice/day

Maintenance

week 3-14	up to 60 ml a.m.	60 ml p.m. or maximum 1 ml/kg twice/day

(reduce dose one step if possible or probable dose related adverse events)

Tail week 15-16

if was on 30 ml BD	reduce to 20 ml BD for 1 week	then 10 ml BD for 1 week then stop
if was on 40 ml BD	reduce to 30 ml BD for 1 week	then 20 ml BD for 1 week then stop
if was on 60 ml BD	reduce to 40 ml BD for 1 week	then 30 ml BD for 1 week then stop

Propranolol tablet (10 mg)

Youngest children 5 to 7 years old (80% weigh 15-35 kg)
Titration

week 1	1 tab a.m.	1 tab p.m. (10 mg BD)
week 2	2 tab a.m.	2 tab p.m. (20 mg BD)

Maintenance

week 3-14	3 tab a.m.	3 tab p.m. (30 mg BD)

(reduce dose one step if possible or probable dose related adverse events)

Tail week 15-16

if was on 1 tab BD	reduce to ½ tab BD for 1 week then stop	
if was on 2 tab BD	reduce to 1 tab BD for 1 week then stop	
if was on 3 tab BD	reduce to 2 tab BD for 1 week	then 1 tab BD for 1 week then stop

Middle children aged 8 to 11 years old (80% weigh 20-55 kg)
Titration

week 1	2 tab a.m.	2 tab p.m. (20 mg BD)
week 2	3 tab a.m.	3 tab p.m. (30 mg BD)

Maintenance

week 3-14	4 tab a.m.	4 tab p.m. (40 mg BD)

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses from 0.7 to 4 mg/kg/day for 80% of the population this age
Tail week 15-16

if was on 2 tab BD	reduce to 1 tab BD for 1 week then stop	
if was on 3 tab BD	reduce to 2 tab BD for 1 week	then 1 tab BD for 1 week then stop
if was on 4 tab BD	reduce to 3 tab BD for 1 week	then 2 tab BD for 1 week then stop

Older children aged 12 to 16 years old (80% weigh 30-85 kg)
Titration

week 1	3 tab a.m.	3 tab p.m. (30 mg BD)
week 2	4 tab a.m.	4 tab p.m. (40 mg BD)

Maintenance

week 3-14	6 tab a.m.	6 tab p.m. (60 mg BD)

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses from 0.7 to 4 mg/kg/day for 80% of the population this age
Tail week 15-16

if was on 3 tab BD	reduce to 2 tab BD for 1 week	then 1 tab BD for 1 week then stop
if was on 4 tab BD	reduce to 3 tab BD for 1 week	then 2 tab BD for 1 week then stop
if was on 6 tab BD	reduce to 4 tab BD for 1 week	then 3 tab BD for 1 week then stop

Propranolol liquid (10mg / 10ml)

Youngest children 5 to 7 years old (80% weigh 15-35 kg)
Titration

week 1	10 ml a.m	10 ml p.m. (10 mg BD)
week 2	20 ml a.m	20 ml p.m. (20 mg BD) or max. 1ml/kg BD

Maintenance

week 3-14	up to 30 ml a.m	30 ml p.m. (30 mg BD) or max. 1ml/kg BD

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses from 0.6 to 2 mg/kg/day for 80% of the population this age
Tail week 15-16

if was on 10 ml BD	reduce to 5 ml BD for 1 week then stop	
if was on 20 ml BD	reduce to 10 ml BD for 1 week then stop	
if was on 30 ml BD	reduce to 20 ml BD for 1 week	then 10 ml BD for 1 week then stop

Middle children aged 8 to 11 years old (80% weigh 20-55 kg)
Titration

week 1	20 ml a.m.	20 ml p.m. (20 mg BD)
week 2	30 ml a.m.	30 ml p.m. (30 mg BD) or max. 1ml/kg BD

Maintenance

week 3-14	up to 40 ml a.m.	40 ml p.m. (40 mg BD) or max. 1 ml/kg BD

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses from 0.7 to 2 mg/kg/day for 80% of the population this age
Tail week 15-16

if was on 20 ml BD	reduce to 10 ml BD for 1 week then stop	
if was on 30 ml BD	reduce to 20 ml BD for 1 week	then 10 ml BD for 1 week then stop
if was on 40 ml BD	reduce to 30 ml BD for 1 week	then 20 ml BD for 1 week then stop

Older children aged 12 to 16 years old (80% weigh 30-85 kg)
Titration

week 1	30 ml a.m.	30 ml p.m. (30 mg BD)
week 2	40 ml a.m.	40 ml p.m. (40 mg BD) or max. 1ml/kg BD

Maintenance

week 3-14	up to 60 ml a.m.	60 ml p.m. (60 mg BD) or max. 1 ml/kg BD

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses from 0.7 to 2 mg/kg/day for 80% of the population this age
Tail week 15-16

if was on 30 ml BD	reduce to 20 ml BD for 1 week	then 10 ml BD for 1 week then stop
if was on 40 ml BD	reduce to 30 ml BD for 1 week	then 20 ml BD for 1 week then stop
if was on 60 ml	reduce to 40 ml BD for 1 week	then 30 ml BD for 1 week then stop

These doses are within the recommendations in the Summary of Product Characteristics (SPC) (Syprol, Rosemount: “2-12 years 20 mg TDS, 12 -18 years 40 mg TDS”) and the Medicines for Children and BNF C (both as for SPC)

Pizotifen tablet (500 microgram)

Youngest children 5 to 7 years old (80% weigh 15-35 kg)
Titration

week 1	1 tab a.m. (placebo)	1 tab p.m. (500 microgram p.m.)
week 2	2 tab a.m. (placebo)	2 tab p.m. (1 mg p.m.)

Maintenance

week 3-14	3 tab a.m. (placebo)	3 tab p.m. (1.5 mg p.m.)

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses 14 to 100 microgram/kg/day for 80% of the population this age
Tail week 15-16

if was on 1 tab BD	reduce to ½ tab BD for 1 week then stop	
if was on 2 tab BD	reduce to 1 tab BD for 1 week then stop	
if was on 3 tab BD	reduce to 2 tab BD for 1 week	then 1 tab BD for 1 week then stop

Middle children aged 8 to 11 years old (80% weigh 20-55 kg)
Titration

week 1	2 tab a.m. (placebo)	2 tab p.m. (1 mg p.m.)
week 2	3 tab a.m. (placebo)	3 tab p.m. (1.5 mg p.m.)

Maintenance

week 3-14	4 tab a.m. (placebo)	4 tab p.m. (2 mg p.m.)

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses 18 to 100 microgram/kg/day for 80% of the population this age
Tail week 15-16

if was on 2 tab BD	reduce to 1 tab BD for 1 week then stop	
if was on 3 tab BD	reduce to 2 tab BD for 1 week	then 1 tab BD for 1 week then stop
if was on 4 tab BD	reduce to 3 tab BD for 1 week	then 2 tab BD for 1 week then stop

Older children aged 12 to 16 years old (80% weigh 30-85 kg)

Titration

week 1	3 tab a.m. (placebo)	3 tab p.m. (1.5 mg p.m.)
week 2	4 tab a.m. (placebo)	4 tab p.m. (2 mg p.m.)

Maintenance

week 3-14	6 tab a.m. (placebo)	6 tab p.m. (3 mg p.m.)

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses 18 to 100 microgram/kg/day for 80% of the population this age
Tail week 15-16

if was on 3 tab BD	reduce to 2 tab BD for 1 week	then 1 tab BD for 1 week then stop
if was on 4 tab BD	reduce to 3 tab BD for 1 week	then 2 tab BD for 1 week then stop
if was on 6 tab BD	reduce to 4 tab BD for 1 week	then 3 tab BD for 1 week then stop

Pizotifen liquid (500 microgram / 10 ml)

Youngest children 5 to 7 years old (80% weigh 15-35 kg)
Titration

week 1	10 ml a.m. (placebo)	10 ml p.m. (500 microgram p.m.)
week 2	20 ml a.m. (placebo)	20 ml p.m. (1 mg p.m.) or max 1ml/kg BD

Maintenance

week 3-14	up to 30 ml a.m. (placebo)	30 ml p.m. (1.5 mg pm.) or max 1 ml/kg BD

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses 14 to 50 microgram/kg/day for 80% of the population this age
Tail week 15-16

if was on 10 ml BD	reduce to 5 ml BD for 1 week then stop	
if was on 20 ml BD	reduce to 10 ml BD for 1 week then stop	
if was on 30 ml BD	reduce to 20 ml BD for 1 week	then 10 ml BD for 1 week then stop

Tail week 15-16
Middle children aged 8 to 11 years old (80% weigh 20-55 kg)
Titration

week 1	20 ml a.m. (placebo)	20 ml p.m. (1 mg p.m.)
week 2	30 ml a.m. (placebo)	30 ml p.m. (1.5 mg p.m.) or max 1 ml/kg BD

Maintenance

wk 3-14	up to 40 ml a.m. (placebo)	40 ml p.m.(2 mg p.m.) or max. 1 ml/kg BD

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses 18 to 50 microgram/kg/day for 80% of the population this age
Tail week 15-16

if was on 20 ml BD	reduce to 10 ml BD for 1 week then stop	
if was on 30 ml BD	reduce to 20 ml BD for 1 week	then 10 ml BD for 1 week then stop
if was on 40 ml BD	reduce to 30 ml BD for 1 week	then 20 ml BD for 1 week then stop

Older children aged 12 to 16 years old (80% weigh 30-85 kg)
Titration

week 1	30 ml a.m. (placebo)	30 ml p.m. (1.5 mg p.m.)
week 2	40 ml a.m. (placebo)	40 ml p.m. (2 mg p.m.) or max 1 ml/kg BD

Maintenance

wk 3-14	up to 60 ml a.m. (placebo)	60 ml p.m.(3 mg p.m.) or max. 1 ml/kg BD

(reduce dose one step if possible or probable dose related adverse events)

This corresponds to doses 18 to 50 micrograms/kg/day for 80% of the population this age
Tail week 15-16

if was on 30 ml BD	reduce to 20 ml BD for 1 week	then 10 ml BD for 1 week then stop
if was on 40 ml BD	reduce to 30 ml BD for 1 week	then 20 ml BD for 1 week then stop
if was on 60 ml BD	reduce to 40 ml BD for 1 week	then 30 ml BD for 1 week then stop

Table 2: Doses

Age group	Treatment arm	Week	Morning	Evening	Tail (week 15-16)
Youngest children aged 5 to 7 years old (80% weigh 15-35 kg)	PLACEBO PROPRANOLOL PIZOTIFEN	1	10 ml or 1 tab	10 ml or 1 tab	5ml or ½ tab for 1 week then stop
		2	20 ml to maximum 1ml/kg or 2 tab	20 ml to maximum 1ml/kg or 2 tab	10 ml or 1 tab for 1 week then stop
		3-14	Up to 30ml to max 1ml/kg or 3 tab	30 ml to maximum 1ml/kg or 3 tab	20 ml or 2 tab for 1 week then 10 ml or 1 tab for 1 week then stop
Middle children aged 8 to 11 years old (80% weigh 20-55 kg)	PLACEBO PROPRANOLOL PIZOTIFEN	1	20 ml or 2 tab	20 ml or 2 tab	10 ml or 1 tab for 1 week then stop
		2	30 ml to maximum 1ml/kg or 3 tab	30 ml to maximum 1ml/kg or 3 tab	20 ml or 2 tab for 1 week then 10 ml or 1 tab for 1 week then stop
		3-14	Up to 40 ml to max 1ml/kg or 4 tab	40 ml to maximum 1ml/kg or 4 tab	30 ml or 3 tab for 1 week then 20 ml or 2 tab for 1 week then stop
Older children aged 12 to 16 years old (80% weigh 30-85 kg)	PLACEBO PROPRANOLOL PIZOTIFEN	1	30 ml or 3 tab	30 ml or 3 tab	20 ml or 2 tab for 1 week then 10 ml or 1 tab for 1 week then stop
		2	40 ml to maximum 1ml/kg or 4 tab	40 ml to maximum 1ml/kg or 4 tab	30 ml or 3 tab for 1 week then 20 ml or 2 tab for 1 week then stop
		3-14	Up to 60 ml to max 1ml/kg or 6 tab	60 ml to maximum 1ml/kg or 6 tab	40 ml or 4 tab for 1 week then 30 ml or 3 tab for 1 week then stop
If necessary, because of a possible or probable dose related adverse event, reduce dose by one titration step					
Propranolol (10 mg / 10 ml or 10 mg tab) These doses are within the recommendations in the Summary of Product Characteristics (SPC) (Sytrol, Rosemount: "2-12 years 20 mg TDS, 12 -18 years 40 mg TDS") and the Medicines for Children and BNF C (both as for SPC) and corresponds to doses of 0.6 to 2 mg/kg/day (liquid) to 4 mg/kg/day (tab) for 80% of children this age					
Pizotifen (500 microgram / 10 ml or 500 microgram tab) These doses are close to the recommendations in the SPC (Sanomigran, Novartis: "2-12 years up to 1.5 mg/day, up to 1 mg as single dose at night; 12-18 years up to 4.5 mg/day, up to 3 mg as single bedtime dose") and the Medicines for Children and BNF C (both as for SPC) and corresponds to doses from 0.014 to 0.05 mg/kg/day (liquid) to 0.1 mg/kg/day (tab) for 80% of children this age					

CONCOMITANT THERAPY

Permitted medications

Any other regular medication (apart from Propranolol or other beta blocker or Pizotifen or Cyproheptidine in the last 3 months)

Other migraine preventative medication should normally be withdrawn first, e.g. an antiepileptic drug or antidepressant, but it may be continued (apart from Propranolol or other beta blocker or Pizotifen or Cyproheptidine in the last 3 months) as long as the dose does not change during the 12 week assessment.

Rescue medication and additional treatment(s)

There are no antidote treatments for the study medications in the trial. If any participant develops breathing difficulties they should seek medical advice, e.g. the usual bronchodilator treatments would be appropriate for bronchospasm. This is unlikely to occur as patients with a recent history of asthma will be excluded from the trial.

All participants will be given an individual rescue treatment plan for migraine headaches, depending on their and their paediatrician's experience and preference. A default example plan, based on the British Association for the Study of Headache (BASH) management guideline[14] will be provided to investigators but they are not bound by it. All rescue treatments used and their doses and effects will be recorded in the diary during the 4 weeks baseline assessment block 1 and the assessment blocks 2, 3 and 4 (weeks 11-14, 25-28, 37-40).

Default rescue medication plan for migraine attacks

A suggested plan is outlined in Appendix A, based on the BASH guideline13.

Restrictions

Rizatriptan should be avoided by the trial participants while taking the trial treatments and for 5 days after stopping the trial treatments, as a lower dose is recommended with concomitant Propranolol, because of a drug interaction.

Different non-steroidal anti-inflammatory drugs (NSAIDs) should not be used together, e.g. Ibuprofen can be combined with Paracetamol or Sumatriptan but not with Diclofenac. Aspirin should be avoided in children under 16 years. Parents / guardians and young participants will be asked to check the contents of any over-the-counter remedies, e.g. with the research nurse.

Compliance

Compliance will be assessed in 2 ways:
1) by verbally questioning the participant and parent / guardian at visits: "What do you do when you forget a dose, roughly how often a week does that happen?" The % of missed doses will be recorded. The % compliance is defined as 100 - % missed doses.

2) by examination of returned medication bottles, and measurement of the observed residual tablet numbers or residual liquid volumes. Missed doses by tablet number or volume will be expressed as:.

$$\% \text{ Compliance} = 100 \times \frac{(S - R)}{P}$$

Where S = amount supplied, R = amount returned and P = amount planned to be taken, all measured either as number of tablets or ml as applicable calculated from the dose prescribed, taking into account any lowering of dose due to adverse events, breakages and spillages.

The level of acceptable compliance with study medication will be set at > 50% on both measures for the main outcome assessment period (weeks 11-14).

Accountability for drugs & placebos

Drug supplies must be kept in a secure, limited access storage area under the storage conditions specified by pharmacy.

The investigator and / or local site pharmacist must maintain records of the study drug's delivery to the trial site, the inventory at the site, the distribution to each participant, and the return to the trial drug distribution centre or alternative disposition of unused study drugs. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (patient medication kit numbers) assigned to the study medication. Investigators and /or local site pharmacists will maintain records that document adequately that the participants were provided with the correct study medication. These records will be part of each patient's Case Report Form (CRF). All study medication bottles received by the site must be accounted for. Study medication bottles lost by participants or not returned by participants or their parents / guardian to the study site must be documented.

Participants and their parents / guardian will be instructed to return all study medication bottles, including full, partially full, and empty bottles. Usually this will be facilitated by the local research nurse who will deliver the new supply (at visits 3, 4, 5) and pick up the old bottles (at home visits 4, 5, 6) during the 16 week trial treatment phase (weeks 1 to 16 inclusive). The local research nurse will measure and document the numbers of tablets and volume of study medicine remaining in the bottles returned, and if any bottles are lost, and the reasons why. The investigator must verify that all study medication bottles returned by participants or sent to the site by the trial drug distribution centre and not dispensed, have been returned as directed by the trial drug distribution centre, and that no remaining bottles are in the investigator's possession.

Written and verbal instructions on the home storage of study medication bottles will be given to participants and their parents / guardians by the doctor or research nurse and reviewed at all visits and contacts.

Management of study drug overdose

Propranolol

The symptoms of over dosage for Propranolol may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock (see Investigators Brochure for more details).

Pizotifen

The symptoms of over dosage for Pizotifen may include drowsiness, dizziness, hypotension, dryness of mouth, confusion, excitatory states (in children), ataxia, nausea, vomiting, dyspnoea, cyanosis, convulsions (particularly in children), coma and respiratory paralysis.

Treatment: Administration of activated charcoal is recommended; in case of very recent intake, gastric lavage may be considered. Severe hypotension must be corrected (CAVE: adrenaline may produce paradoxical effects). If necessary, symptomatic treatment including monitoring of the cardiovascular and respiratory systems. Excitory states or convulsions may be treated with short acting benzodiazepines.

Criteria for terminating trial

The study may be stopped as a whole because of a regulatory authority decision, change in opinion of the REC or overwhelming evidence of efficacy / inefficacy, safety concerns or issues with trial conduct at the discretion of the Sponsor.

Recruitment at a centre may be stopped particularly for reasons of low recruitment, protocol violation or inadequate data recording.

STATISTICS

Sample size and justification

This study consists of two separate trials, one of Propranolol vs Propranolol Placebo and the other of Pizotifen vs Pizotifen Placebo, although from the participant's perspective, for all practical purposes, it will seem a 3 arm study.

The Poisson assumption for the number of attacks per month is unsafe and allowance must be made for over-dispersion in the sample size estimate and in the analysis. A similar allowance will be made for the total number of adverse events per participant.

The value assumed in the placebo arm for the primary response variable (frequency of attacks in the last month of treatment) is based on attack rate data summarised in the review of Victor & Ryan (2003)[2]. This review showed that even placebo arm attack rates had declined by the end of treatment, although standard deviations appeared relatively stable.

The sample size for the primary endpoint was estimated using formula 9.13 on page 176 of Machin et al[20], assuming a 33% reduction in the attack rate in the active arms. A mean attack rate per month of 3 episodes with variance of 4 was assumed for the placebo arms. The formula gives the total number of attacks that must be observed, and this was divided by 2.5 (average number of attacks per person) to give the total number of participants in each study.

The over-dispersion in comparison with a Poisson distribution was allowed for by multiplying the required number of participants based on the standard formula by a factor of 1.33.

The sample size estimate for each trial assumes a power of 80%, and 5% two-sided significance, and allows for the 2:1 allocation of active:placebo treatment within each trial.

On these assumptions the required sample size is 226 evaluable participants for each trial, i.e. 452 in total, to detect a reduction in mean attack rate in both arms from 3 to 2 per month.

Secondary endpoints. The Committee for Proprietary Medicinal Products (CPMP) note for guidance on clinical investigation of medicinal products for the treatment of migraine[21] 2004, notes that a secondary outcome might include the proportion of responders. A simulation showed that the reduction in attack rate would correspond to about a 17 percentage point increase in responders in the active treatment arm, which is consistent with the proposal of Van der Kuy & Lohman[3] that further studies on migraine prophylaxis are justifiable if the percentage of responders is more than 35-40% compared with a placebo response rate of 23%. Assuming a trial-specific power of 80% and 5% two-sided significance level and a difference in response rates of 17 percentage points, assuming a 23% response rate in controls, standard sample size calculations [22] indicate that 294 participants per trial (98 on placebo, 196 on active) would be needed.

Headache intensity at the end of the treatment is measured on a four point scale (no headache; mild headache (headache but full activity); moderate (headache and reduced activity); severe (headache and cannot do anything just lies down / sleeps). As migraine has to be severe or moderate (and have additional features), we aim to detect a shift of one category on this scale from severe to moderate or less, and from moderate to mild or less. We will not analyse mild headaches. At a worst case (assuming a uniform distribution of scores) this would correspond to a shift of 0.89 standard deviations, for which only 45 participants would be needed / trial, so this secondary endpoint would most certainly be covered by our planned sample size.

With a target of 600 evaluable participants in total there is ample power for both the primary and the above secondary endpoints, although it would be unreasonable to expect adequate power for every conceivable secondary endpoint.

The target of 600 for recruitment also leaves a margin for drop out of up to 25% (=1-452/600) for the primary outcome but only 2% (=1-588/600) for the proportion of responders outcome.

Assessment of efficacy

Primary efficacy analysis

The primary endpoint for each participant is the number of attacks during weeks 11 to 14 (see Table 1). The 1st dose of trial treatment will be as close to the date of randomisation as practicable, usually within a few days, e.g. the following Monday, and no more than 2 weeks after (see Table 1). The primary efficacy parameter will be the relative attack rate between the two treatment arms and their placebo arms, estimated by a Poisson regression model. The model will include terms to account for treatment arm, stratification variables and other covariates (baseline frequency of attacks, prior Triptan use and whether treatment naïve). The anticipated over- dispersion will be accounted for by estimation of robust standard errors.

The analysis will be performed on the full analysis set (following the intention to treat principle). Consideration will be given to using a Complier Average Causal Effect (CACE) analysis. If it is decided to use CACE, this will be detailed in the Analysis Plan.

For the primary efficacy analysis the statistical test will be two-sided at a nominal 5% two-sided significance level (see sample size justification).

Secondary efficacy analyses

The number of attacks during weeks 11 to 14 will also be analysed using the per protocol set to test the robustness of the result.

All secondary endpoints will be analysed using analysis of covariance, logistic regression or Poisson regression as appropriate. Secondary analyses will include a repeated measures analysis of the attack frequency at different time points (11-14 weeks; 25-28 weeks; 37-40 weeks from randomisation). Headache frequency during weeks 11-14 will also be analysed with respect to the mean mg/kg/day dose for the active treatments for each participant during this period.

Again, terms to account for treatment arm, stratification variables and covariates will be included in the model with allowance for over-dispersion of binary / count data. Time to event data will be handled by survival regression. All secondary endpoints will be analysed only in the full analysis set.

An additional analysis will consist of a direct comparison of the two active treatment arms for the primary outcome variable and the responder outcome.

For the secondary analyses (excluding cost analyses), tests and confidence intervals will also be two-sided and performed at the 5% significance level. No adjustment for multiple testing will be performed.

Interim analyses

No interim analyses for efficacy are planned by the TMG. However the DMC may assess efficacy, as well as safety, during the trial in accordance with their charter, e.g. at 1 and 2 years from the start of recruitment.

For these "administrative" analyses, informal Haybittle-Peto type boundaries [17, 18] of +/- 3 standard errors will be adopted as guidance for efficacy to permit the DMC to break the blind if it wishes, with negligible effect on the properties of the final analysis. In other words for the primary efficacy interim analyses, results may be declared statistically significant if the two-sided P-value at an interim analysis is less than 0.0027.

Interim analyses will be presented to the DMC blinded or unblinded as specified by the DMC.

Analyses undertaken on behalf of the DMC will be performed by an independent statistician, unconnected otherwise with the study team. Further details will be specified in a separate Interim Statistical Analysis Plan, to be completed and approved before the first interim analysis data extract.

Assessment of safety

Safety analyses will be performed on the safety set. Participants who turned out to be ineligible, those classified in the wrong stratum, and those given a treatment that was not allocation will be analysed as treated.

All adverse events will be listed. Treatment-emergent AEs (defined as AEs which first develop or which worsen after the start of trial treatment) will be summarised by treatment, severity and relationship to treatment.

In addition the frequency (number of AEs and number of patients experiencing an AE) of treatment-emergent AEs will be summarised using the Medical Dictionary for Regulatory Activities[16] (MedDRA v 9.1 or later) by primary body system and preferred term.

Physical and neurological findings at baseline and any changes occurring during treatment will be listed.

Vital signs will be listed and summarised, together with changes from baseline.

Procedures for missing, unused and spurious data

A major goal of this study is to obtain virtually complete follow-up. The research nurses will ensure this as far as possible by home visits and close telephone / texting / email contact. No missing values are expected for the key baseline covariates because these data must be submitted prior to randomisation.

Missing covariate and response values will be handled by multiple imputation using chained equations, by means of the ice Stata add-in module[19]. In particular the imputation for missing response data during the final 4 weeks will incorporate information on earlier response data and other variables thought likely to account for the missing data. A sensitivity analysis in which missing outcome data are assumed to be missing not at random will also be performed for the primary outcome and for response.

Definition of populations analysed

The participant population sets are defined as follows:

Safety set: All randomised participants who receive at least one dose of the trial treatments.

Full Analysis set: All randomised participants, who have at least one post-baseline assessment of the primary endpoint or for whom the primary endpoint has been imputed successfully.

Per protocol set: All participants in the Full Analysis set who are deemed to have no protocol violations that could interfere with the objectives of the study.

Listings will indicate the allocation of participants by set, and the number of participants per analysis set will be recorded in the study report.

Planned analyses

General

Continuous variables will be summarised by descriptive statistics (mean, standard deviation, minimum, median and maximum) and frequency tables will be provided for categorical data, stratified by treatment arm in all cases. Details additional to those below will be given in a separate Final Statistical Analysis Plan to be completed and approved before data lock.

Disposition of Patients

This will be summarised, based on the CONSORT[15] flow chart, in terms of the number of patients screened for entry, number excluded prior to randomisation by major reason (and overall), the number of patients randomised and the numbers entering and completing each phase of the study by treatment group and overall.

Demographic and other baseline variables

Demographic data, medical history and concomitant medication will be summarised by descriptive statistics or frequency tables as appropriate, stratified by treatment.

Treatment compliance

Treatment compliance will be summarised by treatment group and time interval since randomisation. Compliance for each week is defined as >50% compliance on both measures (see section 2.5).

Success of blinding

This will be assessed in participants, parents / guardian and investigators by a two-part question at the final on-treatment visit. The first part will ask whether the participant was believed to have received an active treatment or placebo. The second question will be asked only if the answer to the first question was "active", and will ask which active treatment was thought to have been given. Responses to both questions will include a "don't know" category, and the analysis will correct for guessing (see Analysis Plan).

ADVERSE EVENTS

All AEs, including inter-current illnesses, occurring during the trial will be reported and documented as described below in terms of seriousness, severity and causality.

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product, it does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavourable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
For the purpose of this study an AE does include:
1. any study drug related event as listed in appendix B
2. any condition detected or diagnosed after medicinal product has been administered and has a possible, probable or definite causal relationship with the study drug.

Exempted adverse events that will <u>not</u> be classed as trial AEs and do not require reporting are listed in appendix C

An AE does not include a / an:
1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.
2. pre-existing disease or conditions present or detected at the start of the study.
3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. disease or disorder being studied or sign or symptom associated with the disease or disorder (see appendix C) unless more severe than expected for the participant's condition.
5. overdose of either study drugs or concurrent medication without any signs or symptoms.

Seriousness

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, while on the Trial treatments at any dose, or not, that results in any of the following outcomes:
1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation
4. A disability / incapacity
5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an

Emergency Department, blood dyscrasias, or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

Severity

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see below) whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious. For example drowsiness may be severe but not necessarily a serious AE. A stroke eventually resulting in little or no disability may be a mild stroke but would be considered a SAE.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:
Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction. The attribution of cause may be informed by:
1. The known pharmacology of the trial treatments
2. Previous observation or reports of a similar AE with this trial treatment or class of drug
3. The temporal relationship to trial treatment ingestion, remission with trial treatment withdrawal (dechallenge), or relapse on rechallenge

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Clarifications:
Occurring "at any dose" does not imply that the participant is receiving a trial treatment. Life-threatening means that the participant was, in the view of the Principal Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form, might have caused death.

Hospitalisation for elective treatment for a pre-existing condition that did not worsen during the trial is not considered an AE.

Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation, the event is an SAE.

"Inpatient" hospitalisation means the participant has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at an Emergency Department ("Casualty", "A&E", or "Emergency Room").

With regard to the criteria above, medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in that situation.

Adverse Event reporting procedures

The investigator must report all SAEs immediately to the TCC in accordance with the procedures detailed below: "Prompt Reporting of SAEs to the TCC." The CI and sponsor have a legal responsibility to notify both the R&D departments and MHRA, and REC, about the safety of the drugs under clinical investigation. Prompt notification of SAEs by the Principal Investigator to the TCC is essential so that legal obligations and ethical responsibilities towards the safety of other participants are met.

The Principal Investigator must also comply with any applicable local regulatory requirements related to the reporting of SAEs to the local R&D departments.
The TCC will coordinate the reporting to all R&D departments, the REC, the MHRA when appropriate, and will inform all Principal Investigators, the DMC (see below) and TSC.

Prompt Reporting of SAEs to the TCC

SAEs must be reported to the TCC immediately as described in the following table once the investigator determines that the event meets the protocol definition of an SAE.

Time-frames for Submitting SAE Reports to the TCC

	Initial SAE Reports		Additional Information on a Previously Reported SAE	
Type of SAE	Time Frame	Documents	Time Frame	Documents
Death or Life-Threatening Event	Immediately when aware of event	"SAE" CRF pages	48 hrs from being aware of event	Updated "SAE" CRF pages
Other SAEs	Immediately when aware of event	"SAE" CRF pages	48 hrs from being aware of event	Updated "SAE" CRF pages

Role of the Data Monitoring Committee (DMC)

The DMC will receive reports on a regular basis, as determined by the DMC, of all SAEs and non-serious AEs leading to temporary or permanent discontinuation of study medication. The DMC can request and obtain any data if deemed necessary. This will:

- Provide optimal oversight of the safety aspects of the study
- Ensure the overall safety of the participants
- Ensure the early detection of any problems
- At any time, should the DMC have any concerns that the incidence and / or the severity of the reported AEs outweigh the potential benefits of the trial, these concerns along with any recommendations will be communicated to the TSC and to the CTU.

Reporting of non-serious adverse events

Non-serious AEs which lead to temporary or permanent discontinuation of the trial treatment will be recorded on the AE page of the CRF.

Reporting of serious adverse events

The Principal Investigator will be responsible for reporting to the TCC, all outcome events and all SAEs which occur for participants enrolled in this trial. This is regardless of whether:

- the events are considered “related” or “unrelated” to study medication
- the events are considered “expected” or “unexpected”.
- The Principal Investigator and study staff will question participants and parents / guardians about the possible occurrence of SAEs at every clinical contact.
- If a suspected SAE occurs:
- The Principal Investigator will determine if this is an SAE.
- If the event is an SAE, the investigator must assess the relationship to the trial treatment (causality), and should review the list of **Expected Adverse Events For Study Drugs** in Appendix B and **Exempted Adverse Events** in Appendix C. Events considered unrelated to the trial treatment include those due to progression of an existing disease, development of new diseases, treatments, procedures or hospitalisation for these diseases, or known adverse effects of concomitant therapies, other than the trial treatment, received by the participants.
- If the event is judged by the investigator in conjunction with the chief investigator to be related to one or more of the trial treatments (see section on causality above), then the Serious Adverse Event form must be completed and faxed immediately along with any necessary supporting documentation to the TCC. The SAE form should not be delayed until more complete information is available. All fields must be completed for drug-related SAEs. If some fields cannot be completed because the information is not yet available, the fields can be left blank and the information provided at a later date.
- For any SAE that is judged to be related to the trial treatment (including all SUSARs), it is required that the investigator indicates clearly which study drug or drugs are judged to be related. Note that non-serious adverse events which occur concomitantly with a SUSAR should also be entered on the SAE form.

- If the investigator in conjunction with the chief investigator judges that the event is **not** related to the trial treatment, then only the SAE form must be completed, signed and dated by the investigator. This SAE form should be faxed immediately (within 24 hours) to the TCC.

- Refer to FIGURE 2: Flow Diagram for reporting of Serious Adverse Events.

Figure 2: Responsibility of investigator at study site for reporting SAEs

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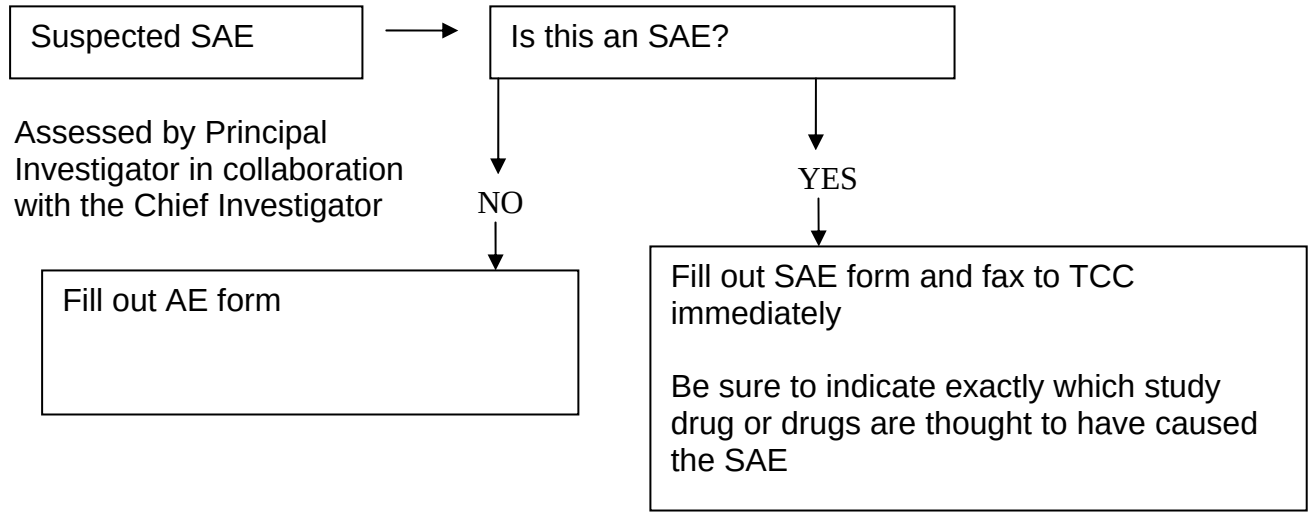
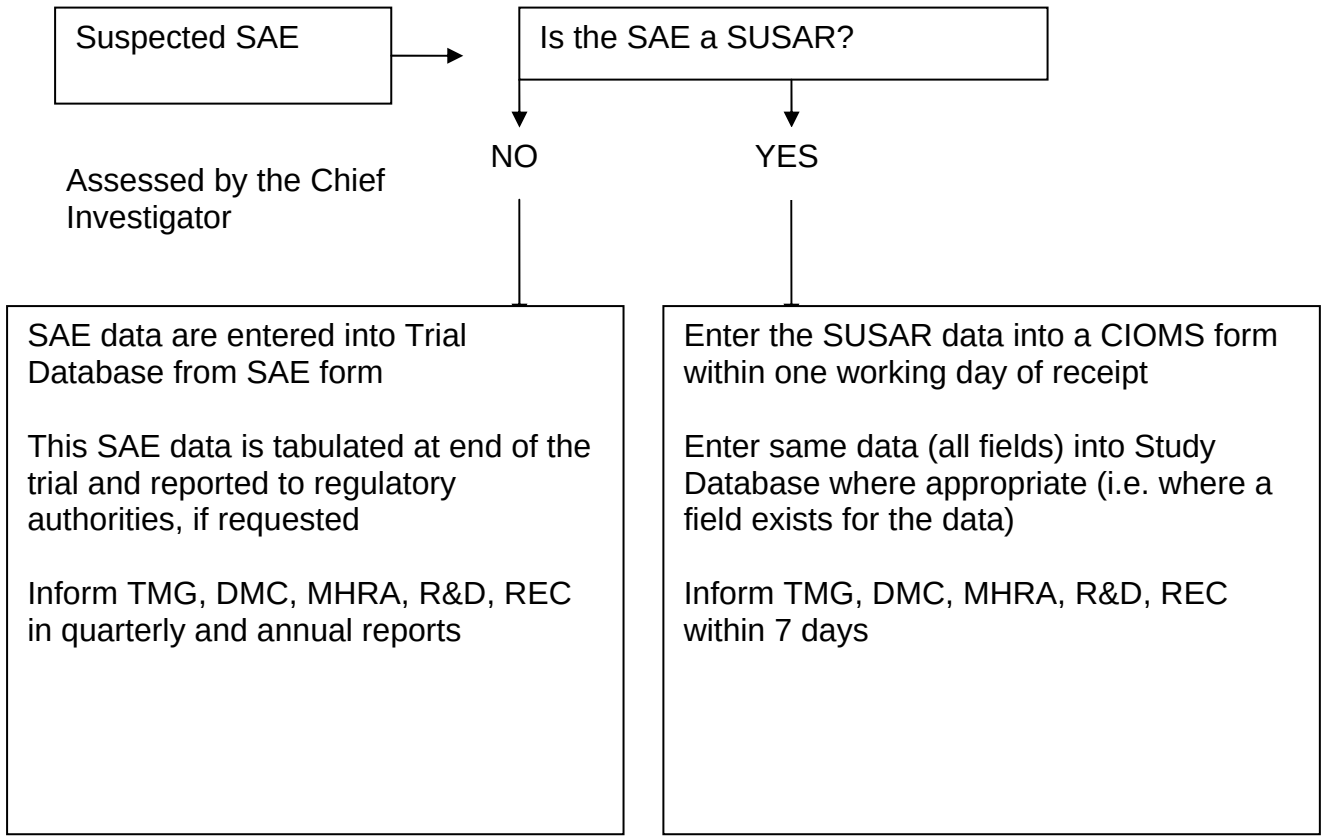


Figure 3: Responsibility of Chief Investigator at trial coordinating centre



SUSARs

A serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- Within seven days, complete the CIOMS form and send to the MHRA.
- Inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event
- Within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

Unblinding of participants

Unblinding of a participant for an investigator can be performed by the TCC (Nottingham CTU), if it is deemed necessary to determine the proper medical treatment and management of the participant. However, for the vast majority of cases unblinding will not be required because there is no antidote to the investigational treatments, and the medical care and usually the management of the patient would not be any different even if the treatment group assignment of the patient were known.

The trial treatment may be stopped at any time by the Principal Investigator or treating physician in the event of an SAE or outcome event, if deemed advisable, and appropriate medical treatment initiated. If unblinding is judged absolutely necessary, the Principal Investigator can discuss the case with the Chief Investigator or the staff of the TCC. Out of hours the Chief Investigator or his nominee will carry a pager. If there is no time and in exceptional circumstances the trial pharmacist (Queens Medical Centre Nottingham) or local pharmacist on call has online access to the treatment codes and can break the blind. In all cases of intentional unblinding an automatic audit trail will be generated at the TCC. Participants who are unblinded or whose medical team are unblinded should continue with the trial protocol and the unblinding will be managed as a protocol violation. Participants who are withdrawn from a trial treatment should continue with the trial follow-up.

RULES FOR AMENDING PROTOCOL

All amendments must be documented, dated and signed by all signatories (or their successors) of the original protocol. The trial coordinator will ensure revisions are disseminated to Principal Investigators and that they know what to do with them. Old versions will be retained for inspection.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated at any centre before the protocol, informed consent forms and participant and parent / guardian information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) departments. Should a protocol amendment be made that needs REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and parent / guardian information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or assent and parent / guardian informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Site File. A copy of each will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent / assent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Drug accountability

Drug supplies will be kept in a secure, limited access storage area under the storage conditions specified by Pharmacy.

The investigator and the local site pharmacist shall maintain records of the study drug's delivery to the pharmacy, an inventory at the site, the distribution to each participant, and the return to the pharmacy or alternative disposition of unused study drugs. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (participant trial number) assigned to the trial participant. Investigators and / or the local site pharmacists will maintain records that document adequately that the participants were provided with the correct study medication. These records will be part of each patient's Case Report Form (CRF). All study medication bottles received by the pharmacy shall be accounted for.

Case Report Forms

Access to the online eCRF will be provided by the TCC (Nottingham Clinical Trials Unit) and paper case report forms (CRFs) will be provided to sites where online access is not available. All paper CRF pages which have entries will be transcribed to the online eCRF, and any changes on the paper CRF must also be made online, where all data will be stored in a secure dedicated server with access restricted by use to appropriate identified password holders. Original paper CRF, were utilised, will remain with the investigator as a permanent record. The Principal Investigator at each centre must ensure that their CRFs are kept in a secure location (i.e. in a locked cabinet or cupboard, or a locked room). Completion and access to the CRFs must be restricted to those personnel approved by the Principal Investigator and recorded on the trial's 'Site Responsibility Delegation Log.' The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up is required.

CRFs are used to record clinical trial data and are an integral part of the trial and subsequent reports. The CRFs, therefore, must be legible and complete. All paper forms must be filled in using black ballpoint pen. Errors must be lined out but not obliterated by using correction fluid but the correction inserted, initialled and dated.

The investigator must sign a declaration ensuring accuracy of data recorded in the CRF.

Each participant will be assigned a participant trial number, allocated at randomisation, for use on CRFs other trial documents and the electronic database. The documents and database will use a sequential site number (starting from 1), sequential participant number (starting from 1) at each site giving a concatenated participant trial number with 2 digits for site and three digits for the participant and also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

Source documents

Source documents provide evidence for the existence of the participant and permit verification of the data collected. Source documents are filed at the investigator's site and may include (but are not limited to) participant diaries, current medical records, laboratory results and pharmacy records. Data reported on the CRFs that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

Source documents must therefore be available. The following data to be reported on the CRF should be included and derived from the source documents:
1. Subject identification (name, hospital record number or NHS number, gender, date of birth, address).
2. Participation in the trial identified by Participant Trial Number and date the informed consent was obtained.
3. Date of each clinic or home or telephone visit for the study, who performed the visit, and date of end of trial visit / participation.
4. Inclusion and exclusion criteria
5. Serious adverse events (SAEs)

For all other data the CRF may serve as its own source document. This includes but is not limited to the following: medical history, medication history, concomitant medications, and non-serious adverse events as specified in the protocol.

The CRF may completely serve as its own source data if the investigator completes a Note to File stating this intention, and the staff members are delegated this responsibility on the Trial Staff List.

Direct access to source data / documents

The principal investigators and their institutions will provide direct access when required to the CRF and all source documents and other trial documentation e.g. signed consent forms, for the purpose of trial monitoring and audit and other lawful regulatory inspection.

The CRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the trial coordinator, sponsor's designee and inspection by relevant health authorities (e.g., R&D]). The accuracy of the data will be verified by reviewing the documents described in the source data section above.

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act. The CRF will only collect the minimum required information for the purposes of the trial and the electronic CRF will not hold information that makes the participant easily identifiable. Where used paper CRFs will be held by local Principal Investigators securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities on request (see above). Computer held data including the trial data base will be held securely and password protected. All data will be stored on a secure dedicated server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Electronic transfer of data will encryption using SSL 128 bit encryption (as used in on-line banking) . All data communications to and from the web server will be done via a secure https connection.

Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.

The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

CONFLICT OF INTEREST

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee sanctioned management plan that has been reviewed and approved by the University of Nottingham prior to participation in this study. All University of Nottingham investigators will follow the University conflict of interest policy (http://www.nottingham.ac.uk/staff-handbook/section-3/conflicts-of-interest.htm).

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures and essential document maintenance. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10%) will be checked on a regular basis for verification. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail.

Trial data and evidence of monitoring will be made available for inspection by the regulatory authority as required.

Whether for trial monitoring, sponsor audit or regulatory inspection, sufficient time, facilities and access to source documents will be allocated by the investigator at each site. The quality assurance auditor will have access to the investigator's trial related files and correspondence, and the relevant informed consent documentation. MHRA inspectors will have access to any document on request, facility, record or personnel considered relevant to the trial.

Data quality will be evaluated in terms of:
Data quality control
Data management

All data will be entered using a web-based single data entry system, which has an overwrite function and is fully audit trailed to document all changes. Data entry screens when deemed applicable will include consistency, range and plausibility checks for obvious errors and these will automatically generate queries for resolution by the investigator. The database will be hosted on a Windows server/IIS platform running ASP that utilizes MS Access and MySQL databases.

When patient diaries are used a 100% check of a 10% sample capped at 50 patient's worth of diary data will be checked, Diary vs. database.

A 100% check of all primary outcome data, Adverse events and withdrawals will be checked for errors, CRF vs. database.

Coding
The following standard coding dictionaries will be used to verify verbatim term integrity and to assist any statistical reporting of, there after:
MedDRA (version 9 or later), for Adverse events.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct, the Chief Investigator and local Principal Investigators will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The decision would only be made upon recommendation by the Trial Steering Committee and Data Monitoring Committee.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC and R&D departments and other regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Publication Committee

The publication committee will be set up by the TMG with the approval of the TSC and comprise the TMG and the TSC chair, in accordance with the Consolidated Standards of Reporting Trials14 (CONSORT) guidance. The publication policy for this study will cover publications and presentations involving results from this study. The Publication policy is presented in Appendix D.

USER AND PUBLIC INVOLVEMENT

The trial was commissioned by the HTA for the Department of Health in the UK with a requirement for consumer involvement.

The pre-protocol focus group

A pilot service user focus group was held in Nottingham12/10/2005. Many families sent apologies and a few expressed an interest in being involved in the future.

Only one family came comprising 2 brothers aged 13 and their mother participated. The group was not conducive to engaging the 2 young men, however it was a useful meeting:

1. the family wanted to know more about the proposed trial and treatments for migraine.
2. they raised interesting questions needing consideration, e.g. would trial participants have to stop other regular (migraine) treatment or not?
3. they explored ways we might overcome swallowing difficulties, e.g. with a syringe.
4. explored their views of some of the outcome measures, e.g. attack frequency, and % responder (the latter was preferred). The young people felt even a statistically significant reduction in migraine frequency would be of little value to them if it was less than a 50% reduction. Hence we have powered the study with the responder rate, secondary outcome measure in mind.
5. they did not mind being double blinded or possibly getting placebo
   they did want to have a lay summary of the findings in due course, and not to have to ask for it.
6. they wanted to know which drug they were on, after the trial.
7. they suggested missing part of a lesson as well as a half day or more at school should be measured.
8. they suggested measuring other migraine symptoms such as nausea and sleepiness as well as headache.
9. they suggested a headache diary that could be a sheet of paper stuck on the kitchen wall.
10. they suggested an incentive to participants such as a gift of a pair of cinema tickets.
11. they offered to help again.

Other focus groups

Funding has been secured for focus group meetings of children and their parents / guardians with migraine and young people with migraine to discuss the trial and its protocol and outcome measures, parent / guardian and participant information sheets, recruitment, the conduct of trials and this trial in particular, feedback and future studies.

Opinions and experience from the Medicines for Children Research Network (MCRN) consumer involvement meetings (2007) and the Trent Local Children's Research Network's open day (2006) have been taken into account.

The pre-protocol survey

A small survey of unselected Nottingham children and young people with migraine and their families was undertaken in April and May 2005:
39 sets of parents / guardians and their 40 children affected with migraine were identified from the CI's personal clinic by word search in electronic set of recent clinic letters.

The Chief Investigator wrote and asked if one parent / guardian and the affected child or young person could fill in a very brief questionnaire on one side of A4 and return it in a S.A.E. 12 parents of 12 children (8 female, aged 7 -17 years, with migraine for 2 to 10 years, (median 3 years) responded. Results were analysed blind:

- 7/12 children had taken regular preventative treatments
- 6/12 believed some worked
- 11/12 agreed there should be more scientific trials of preventative treatments in children
- 10/12 wanted treatments compared with each other and
- 3/12 wanted treatments compared with placebo (2/12 said not but 7/12 responded "don't know")
- 11/12 said participants should be informed of the results
- 11/12 wanted more information about the proposed trial and
- 8/12 said they wanted to help with the trial.

This simple and quick and inexpensive survey only had a 0.3 response rate and engagement of the community of children and young people with migraine and their families is a challenge (see above). There is evidence of user opinion in favour of more controlled scientific studies with user involvement and feedback.

Trial Steering Committee

The TSC has a full (voting) lay member, who is experienced in representing public and patient perspectives to health professionals and health service providers and has collaborated in clinical research. Mrs Trudie Lobban is Chief Executive and founder of a well established patient information and support group: Syncope Trust And Reflex anoxic Seizures ("STARS")[25]. This provides support and advice to patients and families with severe often convulsive syncope (fainting). She is also a founder of the UK Arrhythmia Alliance.

Website

The trial coordinator and trial data manager will establish a trial website with public and separate investigator areas, for answering questions, conversations, getting information and the tools and forms of the trial, and updates and date and agendas and minutes of meetings etc.

Newsletter

The trial coordinator and trial data manager will produce a small newsletter with sections aimed at service users and trial participants and their families and sections aimed at investigators and their local colleagues. There will be service user contributions.

STUDY FINANCES

Funding source

This study is funded by the Health Technology Assessment programme (HTA) of the Department of Health.

Participant stipends and payments

Participants and their parents / guardians will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care (in excess of one every 3 months).

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Chair of TSC: (name) _____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

Trial Pharmacist: (name)_____

Signature:_____

Date: _____

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APPENDICES

APPENDIX A - DEFAULT RESCUE MEDICATION PLAN FOR MIGRAINE ATTACKS

Use no more than on 2 days / week

Step 1 simple oral analgesic with or without antiemetic

Paracetamol 250-500 mg 5-11 years; 500 mg-1 g 12-16 years; or 20 mg/kg; 4 hourly; maximum 90 mg/kg/day and 4 g/day *AND* / *OR*

Ibuprofen 100 mg 5-7 years; 200 mg 8-16 years; 3-/day; max.30 mg/kg/day and 2.4 g/day with or without

Prochlorperazine buccal prep. 1.5-3 mg 5-11 years; 3-6 mg 12-16 years; max. two doses/day *OR*

Metoclopramide 2.5 mg 5-8 years; 5 mg 9-16 years; max. 3 doses/day and 500 micrograms/kg/day

Step 2 parenteral analgesic with or without antiemetic

Diclofenac suppositories 0.3-1 mg/kg (as 12.5 mg, 25 mg, 50 mg, 100 mg); max. 3 doses/ day and 150 mg/day with or without

Domperidone suppositories 15-30 mg 5-11 years; 30-60 mg 12-16 years; max. 2 doses/day

Step 3 triptans with or without antiemetic

Sumatriptan oral 25 mg 5-9 years; 50 mg 10-11 years; 50-100 mg 12-16 years; max. 2 doses/day OR
Sumatriptan nasal 10 mg 8-11 years; 10-20 mg 12-16 years; max. 2 doses/day OR
Sumatriptan s.c. 6 mg 10-16 years; max. 2 doses/day;

Step 4 combinations

Combine step 1 and step 3 treatments OR
Combine step 2 and step 3 treatments.

APPENDIX B - EXPECTED (LISTED) ADVERSE EVENTS FOR STUDY DRUGS

The list below will be used in this trial to determine the “expectedness” of reported SAEs, for all participating centres. This list will be used to determine if an SAE which is considered “related” to study medication will be classified as ICH Category I (serious, related, unexpected) or ICH Category II (serious, related, expected), for purposes of expedited reporting and regulatory compliance.

For pizotifen:

- drowsiness
- increased appetite
- increased body weight
- dizziness
- dry mouth
- nausea
- constipation
- hallucinations
- paraesthesiae
- sleep disorders
- depression and other mood disturbance such as anxiety & aggression
- CNS stimulation
- hypersensitivity reactions such as rash, facial oedema and urticaria

For propanolol:

- bradycardia
- dizziness and/or fainting
- cold extremities
- mood changes
- nightmares
- hallucinations
- sleep disturbance
- hypoglycaemia
- gastrointestinal disturbance
- dry eyes
- paraesthesiae
- bronchospasm
- visual disturbance
- fatigue, tiredness, lassitude

APPENDIX C - EXEMPTED ADVERSE EVENTS RELATING TO DISEASE

The following list of adverse events include those due to the underlying disease, development of new disease processes, treatments, procedures, or hospitalisation for these diseases, or potentially events associated with concomitant therapies. They are potentially expected in the present study population and initially considered not related to the study drugs. However, the individual investigator may decide in specific cases to report them as related to study drug, in which case the Event Monitor would classify them as either ICH Category I or ICH Category II. This would result in expedited reporting by the trial coordinating centre to regulatory authorities: the MHRA and R&D departments and REC.

Exempted Adverse Events:

- abdominal discomfort
- migraine / headache
- anorexia / nausea / vomiting
- photophobia / phonophobia
- transient neurological impairment e.g. hemiplegia, hemianopia, of less than 24 hours duration
- sleepiness
- lack of concentration

APPENDIX D - PUBLICATION POLICY

The publication policy for this study will cover publications and / or presentations involving results from this study.
The purpose of the policy is to:
Facilitate the production of timely, high quality abstracts, slides and manuscripts
Avoid inconsistencies and redundancies in the presentation of results from the trial
Protect against premature publication and other potential violations of the scientific integrity of the data.
Provide the opportunity for all investigators to participate in, and receive publication credit for, the presentation of this study's data and results.
Provide authorship guidelines
Assist in the analysis and reporting of data
Protect intellectual property rights which may arise out of this study.

Policy administration
The policy will be administered by the Publication Committee which includes the TMG and chair of the TSC
The TSC has final decision on approving primary and secondary publications. Abstracts and slides need only approval by the Publication Committee.

Key features of the policy
No unpublished pooled data from any source (e.g., progress reports, reports at annual meetings) can be published in any format without approval of the Publication Committee, with the exception of data published in internal UoN publications.
Neutral or negative results will not constitute a reasonable justification to delay publication.

Publication Committee Membership and Responsibilities
The Publication Committee comprises:

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The Publication Committee has overall responsibility for acceptance of projects and final approval of publications, but may delegate responsibilities to ad hoc publications Sub-committee(s) as may be needed for specific projects.

APPENDIX E - DIAGNOSTIC CRITERIA

Migraine Attack
Each headache must fulfil at least 2 of the following 3 criteria to be classed as a Migraine Attack:

1. Headache lasting 1 to 72 hours.

2. With 2 or more of:
   - Unilateral location (left or right), or bilateral (left and right)
   - Pulsating quality (throbbing)
   - Moderate or severe intensity (inhibits or prohibits daily activities)
   - Aggravated by exertion (e.g. walking up stairs).

3. During the headache 1 or more of:
   - Nausea and or vomiting
   - Photophobia and or phonophobia (symptoms can be inferred from behaviour).

Migraine Disease Category

1 Migraine without aura (MO)

A. 5 or more attacks fulfilling B-D:

B. Headache lasting 1 to 72 hours.

C. With 2 or more of:
Unilateral location (left or right), or bilateral (left and right)
Pulsating quality (throbbing)
Moderate or severe intensity (inhibits or prohibits daily activities)
Aggravated by exertion (e.g. walking up stairs).

D. 1 or more during headache:
Nausea and or vomiting
Photophobia and or phonophobia (symptoms can be inferred from behaviour).

E. Not attributable to another disorder (clinically).

2 Migraine with aura (MA)

A. 2 or more attacks fulfilling B-D:

B. Aura consisting of 1 or more of the following:

- Fully reversible visual symptoms
  including positive features (e.g. flickering lights, spots or lines)
  and / or negative features (e.g. loss of vision).

- Fully reversible sensory symptoms
  including positive features (e.g. pins and needles)
  and /or negative features (e.g. numbness).

- Fully reversible dysphasic speech.

C. 2 or more of the following:

- Homonymous visual symptoms and /or unilateral sensory symptoms.
- 1 or more aura symptom develops over 5 minutes or more and /
  or different aura symptoms occur in succession over at least 5 minutes.

Each symptom lasts at least 5 minutes and not more than 60 minutes.

D. Headache fulfilling criteria B-E for migraine without aura (MO) begins during the aura or follows aura within 60 minutes.

3 Probable migraine (PM)
Attacks fulfilling all but one of criteria A-D for 1 migraine without aura (MO) and not attributable to another disorder (clinically).

Participants may have other types of headache in addition.