Summary of Trial

EudraCT Number: 2014-004958-34

Sponsor's Protocol Code Number: UNOLE0457

National Competent Authority: UK - MHRA

Clinical Trial Type: EEA CTA

Trial Status: Completed

Date on which this record was first entered in the EudraCT database: 2015-01-29

A. Protocol Information

- Member State Concerned: UK - MHRA
- EudraCT number ; 2014-004958-34
- Full title of the trial: Midazolam Measurement and Modelling using Matrix Samplers
- Title of the trial for lay people, in easily understood, i.e. non-technical, language: Measurement and Prediction of Blood Midazolam levels in Children
- Name or abbreviated title of the trial where available: The 4Ms study
- Sponsor's protocol code number UNOLE0457
- Trial is part of a Paediatric Investigation Plan No

B. Sponsor Information

- Sponsor: 1
- Name of Sponsor: University of Leicester
- Country : United Kingdom
- Status of the sponsor Non-Commercial
- Source(s) of Monetary or Material Support for the clinical trial:
    1. Name of organisation providing support : GlaxoSmithKline PLC
       Country: United Kingdom
    2. Name of organisation providing support Phenomenex Inc
       Country: United Kingdom

C. IMP Identification

- IMP: 1
- IMP Role : Test
- Status of the IMP to be used in the clinical trial
    - IMP to be used in the trial has a marketing authorisation: Yes
    - The IMP has been designated in this indication as an orphan drug in the Community: No
- Description of the IMP
    - Product name: Midazolam
    - Pharmaceutical form: Solution for injection/infusion
    - Specific paediatric formulation: No
    - Routes of administration for this IMP Intravenous use: Intravenous drip use, Intravenous bolus use
    - IMP Identification Details (Active Substances)
    - INN - Proposed INN MIDAZOLAM
    - CAS number 59467-96-8
    - EV Substance Code SUB08950MIG
    - Strength: Concentration unit mg/ml milligram(s)/millilitre
    - Concentration type: equal
    - Concentration number 5mg to 1 ml
- The IMP contains an:
    - Active substance of chemical origin: Yes
    - Active substance of biological/ biotechnological origin (other than Advanced Therapy IMP (ATIMP): No
    - The IMP is a:
        - Advanced Therapy IMP (ATIMP) No
        - Somatic cell therapy medicinal product No
        - Gene therapy medical product No
    - Tissue Engineered Product : No
    - Combination ATIMP (i.e. one involving a medical device) No
    - Committee on Advanced therapies (CAT) has issued a classification for this product: No
    - Combination product that includes a device, but does not involve an Advanced Therapy: No
    - Radiopharmaceutical medicinal product : No
    - Immunological medicinal product (such as vaccine, allergen, immune serum): No
    - Plasma derived medicinal product No

- Extractive medicinal product : No
- Recombinant medicinal product No
- Medicinal product containing genetically modified organisms : No
- Herbal medicinal product: No
- Homeopathic medicinal product: No
- Another type of medicinal product: No

D. General Information on the Trial

- Medical condition or disease under investigation
  - Medical condition(s) being investigated: Not applicable
  - Medical condition in easily understood language: Not applicable
  - Condition being studied is a rare disease: No

- Objectives of the trial
  - Main objective of the trial: To determine whether critically ill children metabolise midazolam differently to otherwise healthy children undergoing routine surgery.
  - Secondary objective of the trial: To determine whether blood midazolam level measurements made from microvolume samples of dried blood are equivalent to blood midazolam measurements made using wet blood samples.
- Trial contains a sub-study: No
- General Information on the Trial

  - Principal inclusion criteria
    I. Children aged between 1 month (corrected gestational age) and less than 16 years admitted to hospital either to Paediatric Intensive Care or for planned surgical procedures requiring general anaesthesia.
    II. Children commenced on intravenous (IV) midazolam therapy by the direct care team.
    III. Parents or legal guardians of children willing to provide written consent for their child to take part in the study.
    IV. Where appropriate, children provided written assent to take part in the study.

- Principal exclusion criteria
    I. Children who refused assent and children whose parents or legal guardian refused consent were excluded from the study.
    II. Any significant disease or disorder which, in the opinion of the direct care team, may either put the participant at risk because of study participation or adversely affect the participant's ability to participate in the study.
    III. Any significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of study participation, or, influence the result of the study, or, adversely affect the participant's ability to participate in the study.

- End points

    I. Primary end point(s): To determine midazolam pharmacokinetic (PK) parameters (clearance, volume of distribution and half-life) in critically ill children and in otherwise healthy children undergoing surgery. The PK parameters modelled on study data will be used to test whether midazolam pharmacokinetics are significantly different in these two populations.
    II. Secondary end point(s): To determine whether measurement of midazolam levels using microvolume samples of dried blood is equivalent to midazolam measurements made using wet blood samples.

    - Scope of the trial

- Scope of the trial
- Diagnosis : No
- Prophylaxis : No
- Therapy : No
- Safety : No
- Efficacy : No
- Pharmacokinetic : Yes
- Pharmacodynamic: No
- Bioequivalence : No
- Dose response : No
- Pharmacogenetic : No

- Pharmacogenomic: No
- Pharmacoeconomic: No
- Others: No

- Trial type and phase
  - Human pharmacology (Phase I): No
  - First administration to humans: No
  - Bioequivalence study: No
  - Other : No
  - Other trial type description
  - Therapeutic exploratory (Phase II) : No
  - Therapeutic confirmatory (Phase III) : No
  - Therapeutic use (Phase IV): Yes
  - Design of the trial: Controlled No
  - Randomised: No
  - The trial involves single site in the Member State concerned: Yes
  - The trial involves multiple sites in the Member State concerned: No
  - The trial involves multiple Member States: No
  - Trial involving sites outside the EEA
  - Trial being conducted both within and outside the EEA : No
  - Trial being conducted completely outside of the EEA: No
  - Trial has a data monitoring committee : No

- Population of Trial Subjects
  - Age Range

    Trial has subjects under 18: Yes

    In Utero: No

    Preterm newborn infants (up to gestational age < 37 weeks): No

    Newborns (0-27 days): No

    Infants and toddlers (28 days-23 months): Yes

    Children (2-11years): Yes

    Adolescents (12-17 years): Yes

    Adults (18-64 years): No

    Elderly (>=65 years): No
  - Gender

    Female: Yes

    Male Yes
  - Group of trial subjects

    Healthy volunteers: No

    Patients: Yes

Specific vulnerable populations: No

Women of childbearing potential not using contraception: No

Women of child-bearing potential using contraception: No

Pregnant women: No

Nursing women: No

Emergency situation: No

- Plans for treatment or care after the subject has ended the participation in the trial (if it is different from the expected normal treatment of that condition): None required

- Date of Competent Authority Decision: 2015-01-30
  - Ethics Committee Opinion of the trial application Favourable
  - Date of Ethics Committee Opinion : 2014-12-16

- End of Trial
  - End of Trial Status Completed
  - Date of the global end of the trial: 2016-10-09

E. Study results

I. Abstract

Rationale: Critical illness may adversely alter midazolam pharmacokinetics (PK) and, thereby, predispose already sick children to drug accumulation and adverse drug reactions. Optimizing midazolam dosing in critically-ill children requires a better understanding of its PK. However, repeated and relatively large blood volume samples are major barriers to performing PK studies in children. A new dried blood collection platform (VAMS™ tips) to capture a precise volume (10 µl) of blood offers a potential solution to quantitative and accurate drug bioanalysis for PK studies in children.

Objectives: To a) determine midazolam PK parameters in critically ill (= PICU group) and well children undergoing elective surgery (=ES group) and administered IV drug, and b) compare concentrations of midazolam and 1-OH midazolam (main metabolite) in 'wet' and 'VAMS' tips.

Methods: From 100 children (64=PICU group, 36=ES group) aged 1 month to 15 years, 355 paired blood sample time points (wet and VAMS) were obtained (228 =PICU, 127=ES). Bioanalyses was performed using HPLC/ MS.

II. Summary of Results

- 100 children took part in the 4Ms study between April 2015 and October 2016. 36 of those children were well children attending the hospital for elective surgical procedures and remaining 64 were critically ill children admitted to children's ICU.
- 355 blood samples were obtained from these children(= 228 PICU group, 127=ES group)
- None of the children who were recruited into the study withdrew or discontinued from the trial.
- Demographic details, underlying diagnoses and midazolam & 1-OH Midazolam concentrations data of children recruited into the study are summarised below**.** (Figure 1 , Tables 1-4)

- ***Total numbers recruited***: 100

- **Numbers recruited in** PICU group 64 (36 Male, 28 Female)
  Elective Surgical group 36 (24 Male, 12 Female)

- **Pharmacokinetic blood samples**: Total 355
  PICU group: 228
  Average BSTP/subject in PICU group: 3.6
  Elective Surgical Group: 127
  Average BSTP/subject in PICU group: 3.5

- **Average total blood volumes obtained per patient**:
  Wet samples: 681 µL (Range 200 µL -1000 µL)
  VAMS tips: 103 µL (Range 30 µL -150 µL)

Table 1: Age, weight, BMI and blood sample time points of the 4MS study

Characteristics of Patients Recruited	**Median**	**Range**
Age in months	22	1-191
Weight in Kilogram	13.70	2.9-78.4
No of blood samples time points obtained	3.37	1-5

Table 2 Ethnicity of children recruited into the study

Ethnicity of children recruited	**Number**
Caucasian	81
Asian	14
Afro Caribbean	2
Mixed ethnicity	3

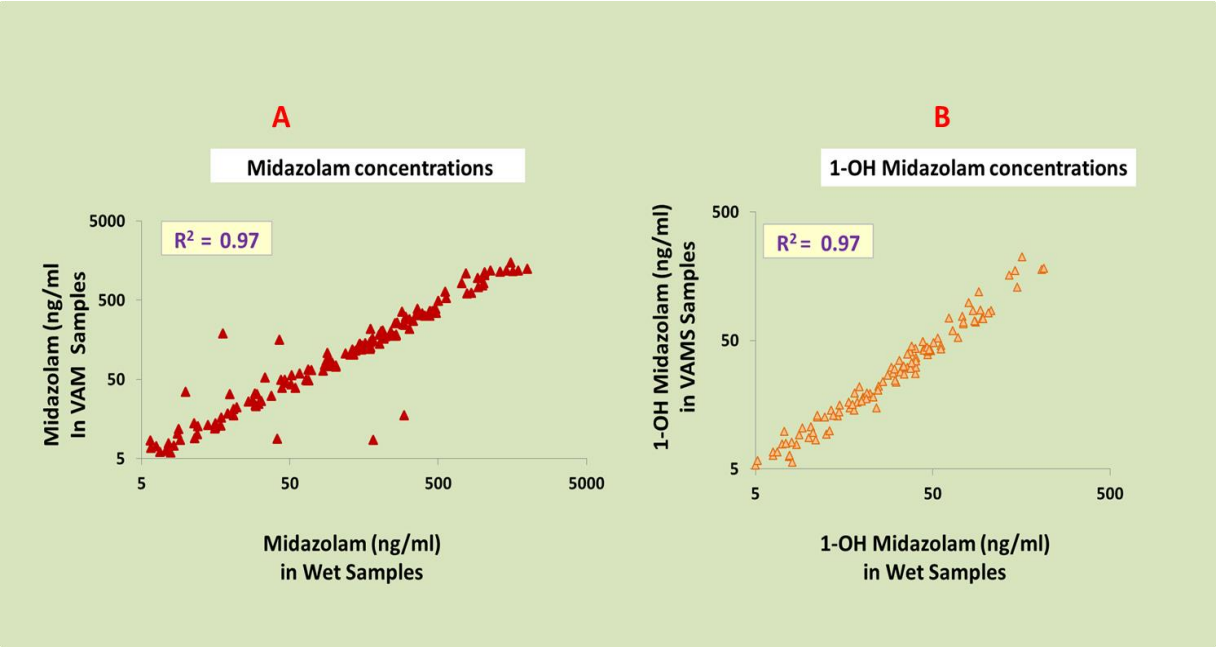
Table 3: Diagnoses of children recruited into the study

PICU Group (n=64)	Total Number (Post-surgical procedure n=34)	Elective Surgical Group (n=36)	Total Number
Respiratory	13	Urology	13
Cardiac	27 (25)	ENT	19
Neurology	3	Gastroenterology	2
Gastroenterology	5 (7)	Other	2
ENT	1		
Other	15 (2)		

Table 4: Midazolam and 1-OH Midazolam concentrations in the study children

	Mean Midazolam concentrations (ng/ml) (Range)	Mean 1-OH midazolam concentrations (ng/ml) (Range)
Elective Surgical Group	28 (5-356)	9 (5-64)
PICU Group	332 (5-1987)	56 (5-1507)

Figure 2: Relationship between (A) Midazolam and (B) 1-OH Midazolam concentrations determined from wet blood samples and VAMS tips



7. Discussion:

- Our results showed significant between patient variability in plasma midazolam concentrations: over 300-fold and 30 fold in midazolam and 1-OH midazolam concentrations respectively. Also significantly higher concentration of midazolam and 1-OH midazolam was observed in the PICU group compared to the ESW group: 10 fold and 6 fold higher, respectively.

- PK modelling of the data is currently in progress.
- In relation to the new dried blood collection platform, concentrations of midazolam and 1-OH midazolam observed using wet blood samples and VAMS tips were closely correlated (Figure 2). Our experience of the VAMS blood collection platform was generally positive. The study team required minimal training to collect blood onto VAMS tips. We found that collecting blood samples using VAMS tips was easy and simple. The storage requirements for VAMS samplers were minimal. No VAMS samples were rejected for bioanalysis due to collection problems.