Clinical Study Protocol

A single centre, single dose, open-label, randomised, two period crossover study to assess the bioequivalence of an oral azathioprine suspension 10 mg/mL (Jayempi™) versus oral azathioprine tablet 50mg (Imurek®, Aspen Pharma Trading Limited, Dublin, Ireland) in at least 30 healthy adult subjects under fasting conditions.

EudraCT:	2018-004719-28
SPONSOR STUDY NUMBER:	INV691
INVESTIGATIONAL MEDICINAL PRODUCTS:	TEST (A): 1 x 5mL (50 mg) of Jayempi™ Oral Suspension 10mg/mL. *Nova Laboratories Ltd., Leicester, UK.* REFERENCE (B): 1 x Imurek 50mg Tablet. *Marketing Authorisation Holder is Aspen Pharma Trading Limited, Dublin, Ireland.*
DEVELOPMENT PHASE:	Bioequivalence Study (Phase I)
SPONSOR:	Nova Laboratories Ltd.
STUDY CENTRE:	Medicines Evaluation Unit.
REGION OF SUBMISSION:	European Medicines Agency

Dates

Version 3.0: (03 May 2019)

Final

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABPI	Association of the British Pharmaceutical Industry
Adverse event reporting	Adverse events will be documented as such only from the time that the IMP has been administered. Events experienced before that time will be regarded as part of the medical history of the subject.
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical classification
AUC	Area under the plasma concentration versus time curve
$AUC_{(0-t)}$	Area under the plasma concentration versus time curve, from time zero to where t is the time of the last quantifiable concentration
$AUC_{(0-\infty)}$	Area under the plasma concentration versus time data pairs, with extrapolation to infinity
AZA	Azathioprine
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
CDER	Centre for Drug Evaluation and Research
Citrus fruits	Any of numerous fruits of the genus *Citrus* e.g., orange, lemon, lime, grapefruit and tangerine
Clinic day	Time ranging from the start of the profile period until discharge from the clinic
C_{max}	Maximum observed plasma concentration
Concomitant medication	Any medication given in addition to the IMP
eCRF	Electronic Case report form
CTA	Clinical Trial Authorisation
CV%	Coefficient of variation (%)
Discontinuer	Enrolled subject who is withdrawn by the investigator before the clinical phase of the study has been completed
Drop-out	Enrolled subject who withdraws from the study of the subject's own volition before the clinical phase of the study has been completed
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
Enrolled subject	Subject allocated a subject number which confirms formal entry into

	the study
FDA	Food and Drug Administration (United States Department of Health and Human Services)
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase (transpeptidase)
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
ICH E3	ICH Guideline for Structure and Content of Clinical Study Reports
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ISO/IEC	International Organization for Standardization / International Electrotechnical Commission
λ_z	Terminal elimination rate constant
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
n	Number of subjects
Non-qualifier	Subject not included in the study due to ineligibility during the screening period, or an eligible subject who became ineligible before allocation of a subject number (e.g., due to illness and/or use of medication)
Non-smoker	Subject who has not smoked previously and/or has not used nicotine or nicotine-containing products for at least 12 months; subjects who have discontinued smoking or the use of nicotine / nicotine-containing products (including e-cigarettes, snuff and similar products) at least 12 months before the first administration of the IMP
OECD	Organization for Economic Cooperation and Development
PK	Pharmacokinetic(s)
Profile period	Pharmacokinetic blood sampling period, including clinic stay

PT	Prothrombin time
Replacement	Eligible subject who enters the study to replace a drop-out or discontinuer
REC	Independent Research Ethics Committee
SAE	Serious adverse event (collected and reported from consent)
Screening period	Time window during which subjects are evaluated to establish eligibility for enrolment into the study
SOC	System Organ Class
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SST	Serum Separator Tube
Study start	Study start is defined as administering or giving directions for the administration of the IMP to a subject for the purposes of this study
SUSAR	Suspected unexpected serious adverse reaction
t_{max}	Time to maximum observed plasma concentration
TPMT	Thiopurine methyltransferase
Treatment period	Time between the first and last study-related procedures of a period of IMP administration
$t_{½}$	Apparent terminal elimination half-life
UK	United Kingdom
USA	United States of America
Wash-out period	Period between consecutive administrations of IMP

3. ETHICAL AND REGULATORY REVIEW AND APPROVAL

3.1. Mandatory Approvals

Written approval for the final version of the clinical study protocol and any amendments, as well as other applicable documents will be obtained from an independent Research Ethics Committee (REC) and the national Competent Authority (by submission or notification of a CTA according to local regulations) before performance of any study-related procedures.

3.2. Ethical Conduct of the Study

The Ethics Committee will be informed that the study is sponsored by Nova Laboratories Ltd. and financed by Nova Laboratories Ltd.

The Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Principal Investigator will ensure the distribution of these documents to the applicable Ethics Committee.

The opinion of the Ethics Committee should be given in writing. The Principal Investigator should submit the written approval to Sponsor before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study. The Sponsor should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The Sponsor will provide the Competent Authority, Ethics Committee and investigators at the study centres with safety updates and progress reports at least annually and otherwise as appropriate, including informing them of any SUSARs (Suspected Unexpected Serious Adverse Reactions) or urgent safety measures; completion or termination of the study and providing a final report within one year of the end of the study.

The Chief Investigator shall be responsible for ensuring that the clinical study is performed in accordance with the following:

- Declaration of Helsinki (Brazil, 2013)
- ICH Harmonised Tripartite Guideline for Good Clinical Practice.
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No. 1031) and subsequent amendments.
- United States Code of Federal Regulations (CFR) specifically CFR 21 parts 11, 50, 54, 312 and 314.

3.3. Subject Information and Informed Consent

Before commencement of the screening procedures, the subjects will be informed verbally by the investigator and in writing concerning the nature, purpose and risks involved in the screening procedures as well as the purpose, procedures, restrictions, obligations, remuneration, insurance coverage and possible adverse drug reactions relevant to the study.

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date the statement of informed consent summarizing the discussion prior to enrolment. They will be assured that they may withdraw from the study at any time without jeopardizing their medical care. Each subject will be given a signed copy of the subject information sheet and statement of informed consent form. Subjects will be given at least 24 hours to consider participation in the study.

The original as well as any revision of the subject information sheets and statements of informed consent provided to the subjects will be submitted for approval as appropriate.

Representative written information for the subjects and sample consent forms will be kept in the Investigator Site File.

3.3.1. Confidentiality

Study findings will be stored in accordance with local and global data protection laws. Information on confidentiality is also contained in the subject information sheet.

The subjects will be informed that representatives of the sponsor, REC, regulatory authorities or auditors may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. All external communications and documents relevant to subjects in the study will identify each subject only by the subjects' study numbers.

3.3.2. Remuneration of Subjects

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the study. Information on how subjects will be compensated is contained in the subject information sheet.

3.3.3. Indemnity

Insurance cover has been arranged in compliance with the Association of the British Pharmaceutical Industry (ABPI) guidelines to indemnify the subjects in the event of death or any deterioration in health or well-being caused by participation in the study.

The certificate of insurance will be kept in the Investigator Site File.

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator and Study Staff:

Information on the investigators and other persons whose participation will materially affect the conduct of the study is contained in the Investigator Site File.

Principal Investigator: Dr. Naimat Khan

Study Centre:

Medicines Evaluation Unit Ltd.
The Langley Building, Southmoor Road, Wythenshawe,
Manchester, M23 9QZ
Tel: [redacted]

Safety Analytical Laboratory:

The Doctor's Laboratory (TDL)
The Halo Building, 1 Mabledon Place, London,
WC1H 9AX, UK
Tel: [redacted]

Data Management and Statistics:

SQN Clinical
Gostling House, Diss Business Park
Hopper Way, Diss
Norfolk, IP22 4GT, UK
Tel: [redacted]

Pharmacokinetics Analytical Laboratory:

Alderley Analytical Ltd. Alderley Park,
Macclesfield,
Cheshire. SK10 4TG. UK
Tel: [redacted]

Thiopurine methyltransferase (TPMT) phenotyping testing:

Black Country Pathology Services
Clinical Skills Services Building, Royal Wolverhampton Hospitals NHS Trust,
Wednesfield Road,
Wolverhampton, WV10 0QP
Tel: [redacted]

Pharmacovigilance:

Diamond Pharma Services
Suite 2, Ground Floor, Field House, Station Approach,
Harlow, Essex, CM20 2FB, UK
Tel: [redacted]

Sponsor:

Nova Laboratories Ltd.
Martin House, Gloucester Crescent
Wigston, Leicester LE18 4YL
United Kingdom
Tel: [redacted]
Fax: [redacted]

Sponsor Medical Expert:

[redacted]
Consultant Medical Advisor (Boyd Consultants), / Medical Monitor / Research Physician
Boyd Consultants,
Unit M South Cambridge Business Park,
Babraham Road,
Sawston,
Cambridgeshire, CB22 3JH

Tel: [redacted]

Sponsor Contact Person:

[redacted]
Head of Clinical Development
Nova Laboratories Ltd.
Martin House, Gloucester Crescent
Wigston, Leicester LE18 4YL
United Kingdom
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

Monitor:

Information regarding the study monitor will be contained in the Trial Master File.

4.1. STATEMENT AND SIGNATURE: PRINCIPAL INVESTIGATOR

A single centre, single dose, open-label, randomised, two period crossover study to assess the bioequivalence of an oral azathioprine suspension 10 mg/mL (Jayempi™) versus oral azathioprine tablet 50mg (Imurek®, Aspen Pharma Trading Limited, Dublin, Ireland.) in at least 30 healthy adult subjects under fasting conditions.

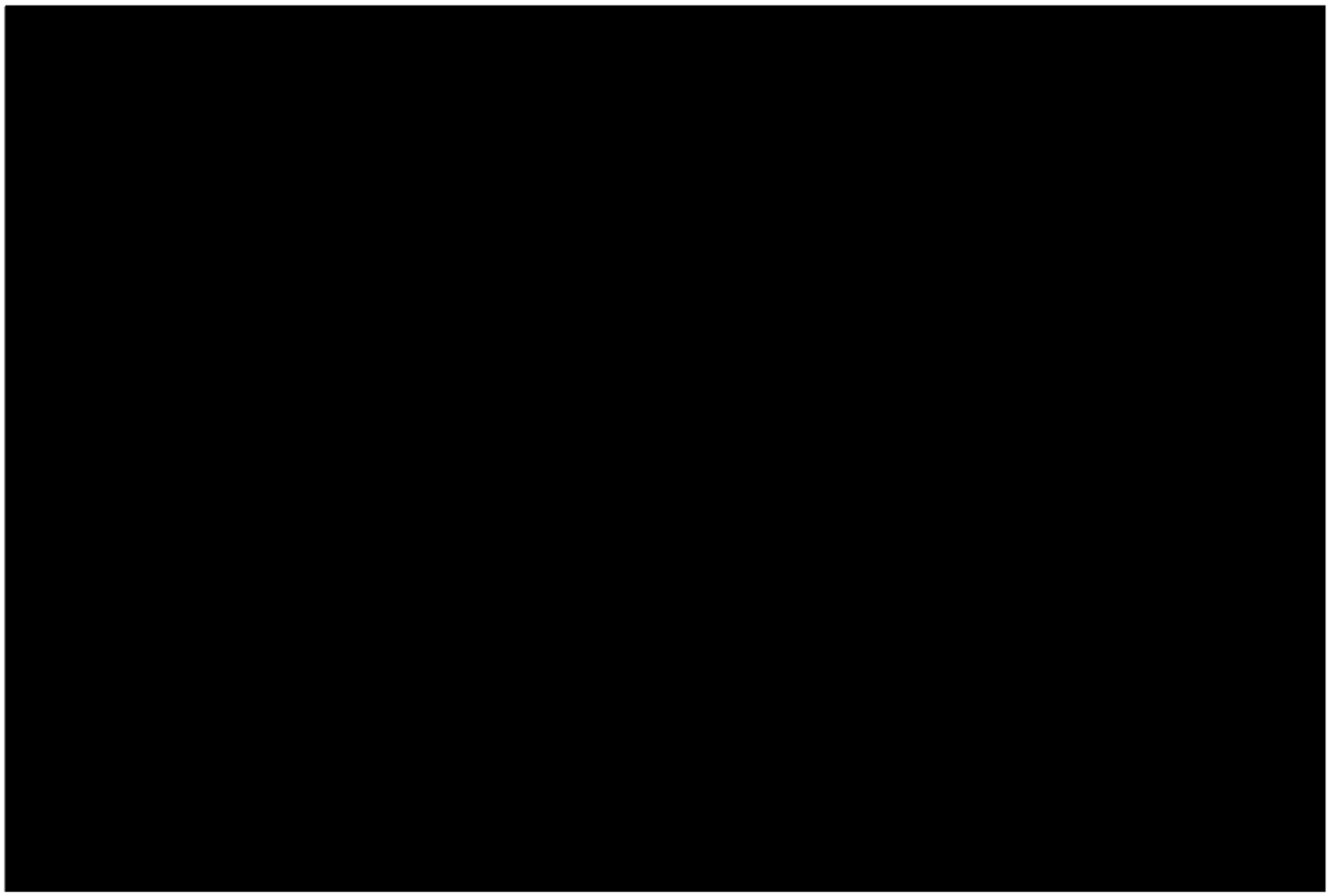
I, the undersigned, verify that, to the best of my abilities and knowledge:

1. I have reviewed this original clinical study protocol and approve its contents.
2. I am familiar with the properties of the investigational medicinal product (IMP) as described in the References. I am qualified by scientific training and experience to conduct the clinical investigational study identified above. My medical education and experience is stated in the curriculum vitae provided.
3. The study centre has adequate staff and appropriate facilities (including laboratories) that will be available for the duration of the study to be conducted in conformance with this clinical study protocol and Good Clinical Practices (including the national Competent Authority guidelines), as assured by an "in-house" quality assurance program.
4. I agree to obtain permission from the sponsor in writing should any changes be required to the clinical study protocol. Should the safety of the study subjects necessitate immediate action, which represents a deviation from the clinical study protocol, the sponsor will be informed as soon as possible.
5. I shall obtain in writing the necessary approval from the REC and national Competent Authority. I shall ensure communication of any modification, amendment or deviation of the clinical study protocol, and also inform the REC and the national Competent Authority (where applicable) in the event of discontinuation of the study and the reasons for discontinuation.
6. I agree to obtain written informed consent from all subjects prior to performance of any study-related activity. Both oral and written subject study information will be provided in the language the subject prefers. Subjects will be given at least 24 hours to consider participation in the study.
7. I shall ensure that electronic case report forms (eCRFs) are completed, signed and archived at the study centre as applicable.
8. I agree to allow the auditor/inspector/any representatives of regulatory authorities access to all relevant documents and be available to discuss any findings/issues.

9. I shall ensure that the confidentiality of all information about subjects is respected by all persons involved, as well as information supplied by the sponsor. Any disclosure of such information will only be made subject to the sponsor's written approval.

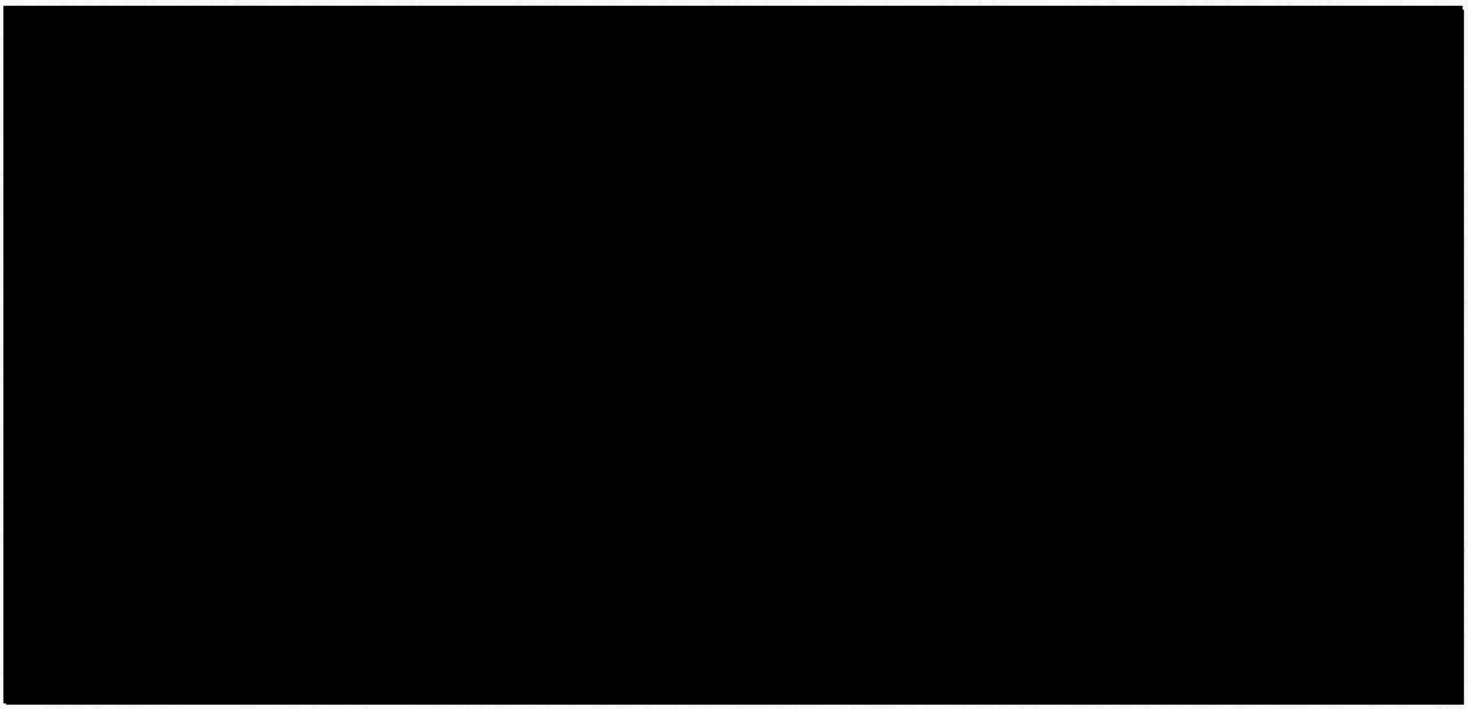
10. I agree to render a clinical study report of my findings at the end of this study, suitable for regulatory purposes, whether or not the study has been completed.

11. In my absence one of the co-investigators, approved for participation in this study, will act as principal investigator for study-related decisions.



4.2. SIGNATURE: SPONSOR SIGNATORY / SIGNATORIES

A single centre, single dose, open-label, randomised, two period crossover study to assess the bioequivalence of an oral azathioprine suspension 10 mg/mL (Jayempi™) versus oral azathioprine tablet 50mg (Imurek®, Aspen Pharma Trading Limited, Dublin, Ireland) in at least 30 healthy adult subjects under fasting conditions.



5. INTRODUCTION

5.1. Background

The drug substance azathioprine is a well-established drug and has been used as an immunosuppressant post-organ transplant and in autoimmune and inflammatory diseases for almost 60 years.

Azathioprine is used alone or in combination with other immunosuppressive therapy to prevent rejection following organ transplantation, and to treat an array of autoimmune diseases, including rheumatoid arthritis, pemphigus, systemic lupus erythematosus, Behçet's disease, and other forms of vasculitis, autoimmune hepatitis, atopic dermatitis, myasthenia gravis, neuromyelitis optica (Devic's disease), restrictive lung disease, and others. It is also an important therapy and steroid-sparing agent for inflammatory bowel disease (such as Crohn's disease and ulcerative colitis) and for multiple sclerosis.

In the European Union, azathioprine (Imurek) is currently approved for use in organ transplantation from human donors, auto-immune diseases such as rheumatoid arthritis and inflammatory bowel disease.

Clinical trial data and evidence collected over the last 50 years demonstrates that azathioprine has an important role as an immunosuppressant for organ transplantation and a variety of autoimmune and inflammatory diseases in both adults and children. Treatment protocols have evolved during this period and necessitate that azathioprine is administered to children at doses related to their body size. However, only 25 and 50mg strength tablets are presently marketed across the EU, making accurate oral dosing difficult to achieve. Although the currently approved tablet formulations can be halved or quartered to derive an intermediate dose, in most cases this still requires rounding doses up or down. Moreover, young children often find taking tablets very difficult. Acceptability of the formulation in children is of paramount importance, especially in post organ transplantation and diseases where adherence can significantly impact on outcomes.

As a consequence, unlicensed liquid formulations, prepared extemporaneously or procured as a ‘Special’ (under the provisions of the UK Medicines Act 1968), are widely prescribed and

dispensed. This unlicensed use potentially exposes children to medication errors and the consequential higher risk of adverse reactions or inadequate efficacy.

Jayempi administered using an oral syringe will allow the dose of azathioprine to be tailored to patient requirements, both accurately and safely. Moreover, improved ease of administration for children will enhance medication acceptability and adherence. Jayempi will also be of benefit to adolescents and adults who find taking tablets difficult.

The applicant is planning to submit a centralised application to the European Medicines Agency: of an alternative formulation to a reference listed drug and as a Hybrid application under Article 10(3) regulation. Hence, a bioequivalence study comparing Jayempi to the reference listed drug, Imurek 50 mg (Aspen Pharma Trading Limited, Ireland) in healthy male and female volunteers is proposed.

Risk/Benefit Analysis

There is no direct benefit to the study subjects.

Healthy volunteer studies of azathioprine have safetly been done before and have resulted in the MHRA granting a marketing authorisation (Public Assessment Report, Azathioprine 50mg Film-coated Tablets, UK/H/934/01/DC, Relonchem Ltd).
Nova Laboratories have safely undertaken a similar heatlthy volunteer study with the primary metabolite of azathioprine, namely mercaptopurine, for which a European Marketing Authorisation has been obtained (European public assessment report (EPAR) for Xaluprine).

The study design reduces the risk to subjects. Specifically:

- Dose and dosing regimen: A low dose will be used on two occasions only, so the immunosuppressive effect of either the investigational medicinal product or the reference medication is unlikely to have any clinically relevant or lasting effect in this population of healthy volunteers.

- Eligibility:

Subjects will be rigorously screened and will be registered on The Over-volunteering Prevention System (TOPS) to prevent over volunteering. Only healthy subjects will be enrolled.

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with Azathioprine. Also it has been reported that decreased TPMT activity increases the risk of secondary leukaemias and myelodysplasia in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics. All subjects who consent to the study will undergo TPMT phenotyping and those with a deficient, low or intermediate TPMT enzyme activity will be excluded from taking part.

Patients with inherited mutated NUDT15 gene are at increased risk of severe azathioprine toxicity with the usual doses of thiopurine therapy, such as early leukopenia and alopecia. These patients generally require dose reduction, particularly those being NUDT15 variant homozygotes . The frequency of NUDT15 c.415C>T has an ethnic variability of approximately 10% in East Asians, 4% in Hispanics, 0.2% in Europeans and 0% in Africans. In any case, close monitoring of blood counts is necessary. In this study, subjects of East Asian and Hispanic ethnicity will be excluded.

- Reproductive Risks: Animal studies have revealed malformations due to azathioprine. In embryo-toxicity studies, azathioprine showed teratogenic (affecting the development) or lethal effects on embryos in various animal species. In humans, however, there are contradictory findings about the teratogenic potential of azathioprine. There have been reports of intrauterine growth retardation, prematurity and low birth weight over azathioprine, especially in combination with corticosteroids. There are also reports of spontaneous abortions after both maternal and paternal exposure. Therefore, the following risk mitigation strategies have been put into place:
    - Male and female subjects at reproductive age should use a condom plus one highly effective contraceptive measures during the administration of azathioprine and at least 6 months after the end of treatment.
    - Subjects who plan to procreate within 6 months after IMP administration will not be included in the study.

- Male subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study and for 6 months after their final dose.
- Male subjects will be instructed not to donate sperm until 6 months after the last dose.
- Females who are currently pregnant will be excluded
- Females of child bearing potential will have a pregnancy test carried out at screening, at each admission to the clinic prior to dosing and at the follow up visit.
- Should any pregnancies occur (for a female subject or female partner of a male subject, they must be reported immediately and should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications. Pregnancy outcomes must be collected for all female volunteers and the female partners of any males who took the IMP. Consent to report information regarding these pregnancy outcomes would be obtained from the mother.
- In addition to the above, to prevent exposure of any partner (male or female) a condom must be used throughout the study and for 6 months after the final dose of study drug.

5.2. Clinical Pharmacokinetics

Absorption

Azathioprine is absorbed incompletely and variably. The median (range) absolute bioavailability of 6- MP after administration of azathioprine 50 mg is 47% (27 – 80%). Although there are no food effect studies with azathioprine, pharmacokinetic studies with 6-MP have been conducted that are relevant to azathioprine. The mean relative bioavailability of 6-MP was approximately 26% lower following administration with food and milk compared to an overnight fast. 6-MP is not stable in milk due to the presence of xanthine oxidase (30% degradation within 30 minutes). Azathioprine should be administered at least 1 hour before or 3 hours after food or milk.

There is no correlation between the plasma levels of azathioprine and 6-mercaptopurine and the therapeutic efficacy or toxicity of azathioprine.

Distribution

The volume of distribution at steady state (Vdss) of azathioprine is unknown. The mean (± SD) apparent Vdss of 6-MP is 0.9 (±0.8) L/kg, although this may be an underestimate because 6-MP is cleared throughout the body (and not just in the liver).

Concentrations of 6-MP in cerebrospinal fluid (CSF) are low or negligible after IV or oral administration of 6-MP.

Azathioprine is rapidly distributed in the body. Only 30% of the substance is bound to plasma proteins.

Biotransformation

Azathioprine is rapidly broken down in vivo by glutathione-S-transferase into 6-MP and a methylnitroimidazole moiety. The 6-MP readily crosses cell membranes and is extensively metabolised by many multi-step pathways to active and inactive metabolites, with no one enzyme predominating. Because of the complex metabolism, inhibition of one enzyme does not explain all cases of lack of efficacy and/or pronounced myelosuppression. The predominant enzymes responsible for the metabolism of 6-MP or its downstream metabolites are: the polymorphic enzyme thiopurine S-methyltransferase (TPMT), xanthine oxidase, inosine monophosphate dehydrogenase (IMPDH), and hypoxanthine guanine phosphribosyltransferase (HPRT). Additional enzymes involved in the formation of active and inactive metabolites are: guanosine monophosphate synthetase (GMPS, which form TGNs) and inosine triphosphate pyrophosphatase (ITPase). Azathioprine itself is also metabolised by aldehyde oxidase to form 8-hydroxy azathioprine, which may be active.

There are also multiple inactive metabolites formed via other pathways.

There is evidence that polymorphisms in the genes encoding the different enzyme systems involved with metabolism of azathioprine may predict adverse drug reactions to azathioprine therapy.

Thiopurine methyltransferase (TPMT)

TPMT activity is inversely related to red blood cell 6-MP derived thioguanine nucleotide concentration, with higher thioguanine nucleotide concentrations resulting in greater reductions in white blood cell and neutrophil counts. Individuals with TPMT deficiency develop very high cytotoxic thioguanine nucleotide concentrations.

Genotypic testing can determine the allelic pattern of a patient. Currently, 3 alleles—TPMT*2, TPMT*3A and TPMT*3C—account for about 95% of individuals with reduced levels of TPMT activity. Approximately 0.3% (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10%

of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90% of individuals have normal TPMT activity with two functional alleles. There may also be a group of approximately 2% who have very high TPMT activity. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in red blood cells and can also be informative.

Limited liver function

In hepatic impairment, the metabolism of azathioprine is altered. The conversion into the active metabolites is limited. Most importantly, degradation to metabolites is reduced.

Elimination

After oral administration of 100mg ^{35}S-azathioprine, 50% of the radioactivity was excreted in the urine and 12% in the faeces after 24 hours. In the urine, the major compound was the inactive oxidised metabolite thiouric acid. Less than 2% was excreted in the urine as azathioprine or 6-MP. Azathioprine has a high extraction ratio with a total clearance greater than 3L/min in normal volunteers. The plasma half-life of azathioprine is 3 to 5 hours. The renal clearance of 6-MP and the half-life of 6-MP are 191 mL/min/m^2 and 0.9 hr respectively.

6-MP (metabolite of azathioprine) has been detected in colostrum and in breast milk by women treated with azathioprine (6MP is excreted in breast milk at concentrations of 3.4 ng / ml to 18 ng / ml).

For more information see Investigators Brochure.

5.3. Adverse Events, Contraindications and Warnings

Refer to the Summaries of Product Characteristics. As with any medication, the list of adverse events will never be exhaustive, and unexpected or very rare adverse events not listed could potentially occur.

5.4. Rationale for the Study

The sponsor has developed a new formulation (test product) of an existing medication (reference product) which is intended for marketing authorization (see REGION OF SUBMISSION).

The proposed study in healthy volunteers is designed to establish a PK profile under fasting conditions for the orally administered test and reference products to evaluate bioequivalence in

accordance with the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) and the United States Department of Health and Human Services, Food and Drug Administration (FDA) Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. Centre for Drug Evaluation and Research (CDER) March 2003 BP.

6. STUDY OBJECTIVES

Primary Objectives

- The primary objective of this study is to assess whether Nova's oral azathioprine suspension (Jayempi™) and a marketed tablet formulation (Imurek®) are bioequivalent.

Secondary Objectives

- To assess the safety and tolerability of the test product, azathioprine oral 10 mg/ mL suspension.
- To determine the plasma concentrations and pharmacokinetics of the metabolite mercaptopurine

7. INVESTIGATIONAL PLAN

7.1. Overall Study Plan and Design

7.1.1. Study Design

This will be a single-dose, open-label, randomised, two-period crossover study with orally administered 1 x 5mL (50 mg) of Jayempi™ Oral Suspension 10mg/mL versus oral azathioprine tablet 50mg (Imurek®, Aspen Pharma Trading Limited, Dublin, Ireland) on two separate occasions conducted under fasting conditions in healthy male and female subjects at a single study centre.

The study will comprise:

- Thiopurine methyltransferase (TPMT) testing;
- Screening period of maximum 28 days
- Two treatment periods (each of which will include a PK profile period of 12 hours) separated by a wash-out period of at least 3 calendar days (minimum number of days based on half-life of the analyte) and maximum of 14 calendar days between consecutive administrations of the IMP
- A post-study visit 7-10 days after the last dose of the last treatment period of the study.

Subjects will be randomly assigned to treatment sequence, prior to the first administration of IMP.

7.1.2. Thiopurine Methyltransferase Testing

A thiopurine methyltransferase (TPMT) phenotyping test will be performed to confirm if the subject is eligible.

Subjects must consent to having this test done. The test will be performed at:

Black County Pathology Services

Clinical Skills Services Building, Royal Wolverhampton Hospitals NHS Trust,

Wednesfield Road,

Wolverhampton, WV10 0QP

The results of the test will be discussed appropriately with the subject.

7.1.3 Schedule of Study Assessments:

The timing of assessments is displayed in Table 7-1.

The time of dosing commencement may vary for logistical reasons. Actual clock times will vary between subjects, in relation to actual dosing times.

Table 7-1 Schedule of Study Assessments

Assessment	Screening*	Admission 1 Day -1**	Treatment period 1	Admission 2 Day -1**	Treatment period 2***	Post-study Visit[1]
Informed consent	X					
Demographic and anthropometric data[2]	X					
Alcohol and tobacco consumption and drug use	X					
Medical history[3] and prior medication	X	X				
Adverse events and concomitant medication		X[$]	X	X	X	X
Physical examination[4]	X					X
Vital signs[5]	X		X		X	X
12-Lead ECG[6]	X					X
Haematology[7]	X	X		X		X
Clinical chemistry[8]	X	X		X		X
Blood coagulation[9]	X	X		X		X
Serology tests[10]	X					
Urinalysis[11]	X					
Urine screen for drugs of abuse[12]	X	X		X		
Urine screen for tobacco use[13]	X	X		X		
Pregnancy Test[14]	X	X		X		X
Eligibility Assessment	X	X		X		
Randomization			X			
IMP administration			X		X	
PK profile[15]			X		X	
Palatability questionnaire[16]			X		X	
Alcohol breath test[17]	X	X		X		
Study specific screening test[18]	X					

IMP = investigational medicinal product; ECG = electrocardiogram; PK = pharmacokinetic

* Screening procedures can be performed over more than one visit

** Day -1 Safety Labs can be performed within 7 days of dosing. If screening is performed within 7 days of dosing (for treatment period 1 only) safety labs do not need to be repeated. Subject will return to the unit in the afternoon/ evening of Day -1 for admission and remaining admission tests.

***Treatment Period 2 to be carried out 3 to 14 days days of Treatment Period 1.

[$] Concomitant Medications only at admission, as only treatment emergent adverse events will be recorded.

1. Seven (7) to ten (10) days after the last dose of the last period of the study or, in the case of discontinuers or drop-outs who took the IMP, within 72 hours of withdrawal/withdrawing from the study.
2. Gender, race, date of birth, age, height, weight and BMI.
3. The recorded medical history will be updated if necessary on pre-profile nights (Day -1 of Admission 1).
4. A full physical examination will include the following: ear/nose/throat, ophthalmological, dermatological, cardiovascular, respiratory, gastrointestinal, central nervous system, lymph nodes and musculoskeletal.; other evaluations may be performed as deemed necessary by the investigator. Any other evaluations undertaken will be included in the clinical study report, if applicable. The post-study physical examination will only be brief but will include vital signs.
5. Supine and standing systolic and diastolic blood pressure, pulse and body temperature (tympanic) at screening (supine vital signs measured following 5 mins rest in supine position, standing vital signs measured following 2 mins in standing position). Supine blood pressure, pulse and body temperature will be recorded before administration of IMP; in addition, supine blood pressure and pulse will be recorded at 2, 4 and 6 hours (+/- 10 mins) post-dose and at post study visit.
6. Standard 12-lead ECG will be performed at screening and post-study following 5 mins rest in supine position.
7. Haematology (Ethylenediaminetetraacetic acid [EDTA tubes]): leucocytes, erythrocytes, haemoglobin, hematocrit, platelets, basophils, monocytes, neutrophils, eosinophils and lymphocytes (absolute count and percentages).
8. Screening and post-study: Clinical chemistry (Serum separator tubes [SST]): potassium, sodium, urea, creatinine, uric acid, calcium, protein, albumin, total bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and glucose. The clinical chemistry performed during admission of treatment periods 1, 2 and at post treatment will only include the liver function tests GGT, ALP AST and ALT.
9. Blood coagulation tests (citrated tubes): Prothrombin time (PT), activated partial thromboplastin time (aPTT) and International Normalised Ratio (INR).

10. Tests for human immunodeficiency virus (HIV) and Hepatitis B and C, performed. Pre- and post-test counselling will be provided as appropriate.
11. Urinalysis (dipstick): protein, bilirubin, blood and urobilinogen.
12. Using a single urine sample: amphetamines, cannabinoids, cocaine, barbiturates, benzodiazepines, opiates, methadone.
13. Cotinine testing.
14. Serum pregnancy testing at screening (where applicable). Urine pregnancy testing at admission 1, 2 and Post-Study Visit for women of child bearing potential only.
15. Blood collections will be made pre-dose within 30 minutes before administration and at 15 mins (±2 mins), 30 mins (±2 mins), 45 mins(±2 mins), 1hr(±2 mins), 1 hr 20mins(±2 mins), 1 hr 40mins (±2 mins), 2hrs(±5 mins), 2hrs 20 mins(±5 mins), 2hrs 40 mins (±5 mins), 3hrs(±5 mins), 4hrs(±5 mins), 5hrs(±5 mins), 6hrs(±5 mins), 8hrs(±5 mins) and 12hrs(±5 mins)) after study drug administration. The PK sample should be taken on the scheduled timepoint and other procedures due at the same time scheduled around using the applicable windows.
16. A short palatability questionnaire will be completed after dosing on the day that the subject is given oral liquid only.
17. Alcohol breath test using a portable breath alcohol measuring device will be performed at screening, on admission to the research centre of each treatment period and at random, at any time during the study, if deemed necessary by the principal investigator or designee, to detect the presence of alcohol. If any of these tests are positive, subjects will not be allowed further participation in the study.
18. Study-specific screening tests: Thiopurine methyltransferase (TPMT) testing (EDTA tubes) (see Appendix 15.1).

7.1.4 Safety and Data Monitoring Committees:

Not applicable.

7.2 Discussion of Study Design

Bias is prevented by strict adherence to the inclusion and exclusion criteria. All measurements and procedures are clearly defined in advance and will consistently and precisely be applied.

7.2.1 Pre-study Evaluation (Screening)

Within 28 days prior to the first administration of IMP and after written informed consent is obtained, screening procedures will be performed on each subject (see Table 7-1). Subjects who meet the inclusion criteria (Section 7.3.1) will be considered eligible to participate in the study. Subjects who meet one or more of the exclusion criteria (Section 7.3.2) will not be considered eligible to participate in the study. The total screening period will be approximately 28 days.

At the discretion of the investigator screening procedures may be repeated

7.2.2 Expected Duration of Study

The duration of this study is expected to be approximately 2 months per subject (excluding the screening period). The actual overall study duration or subject recruitment may vary.

7.2.3 Treatment Periods (1 and 2)

Each treatment period will include a PK profile period of 12 hours, which will commence with morning dosing of IMP on a 12-hour clinic stay at the study centre.

During all treatment periods subjects will have safety laboratory tests performed within 7 days prior to dosing (if screening is performed within 7 days of dosing (for treatment period 1 only), safety labs do not need to be repeated). They will be admitted to the study centre on the afternoon/ evening of Day -1 for remaining admission tests. An overnight fast of at least 10 hours (a food and beverage-free period with the exception of water) will be observed.

Before dosing on day 1, an indwelling venous cannula may be inserted. A member of the clinical team will decide when to remove or replace the venous cannula based on the time (since insertion of the cannula) or if clotting occurs. If the cannula is removed, the subsequent blood samples will be collected by venepuncture or the cannula will be replaced.

The IMP will be administered in the sitting position with the volume of water specified in section 8.6. Thereafter subjects will be required to refrain from lying down (except when required for clinical procedures e.g. PK sampling) for 4 hours after dosing.

Food and beverages on clinic days will be according to Section 7.2.7.1.

A short palatability questionnaire will be given to the subjects on the day that oral liquid is given and will comprise:

1. What did you think of the taste of the liquid medicine you were given in the study?
2. Was there an aftertaste to the liquid medicine you were given in the study?
3. What did you think of the smell of the liquid medicine you were given in the study?
4. What did you think of the texture of the liquid medicine in the mouth?
5. If you had to, how easy would it be for you to take the liquid medicine regularly, every day?

Subjects will be allowed to leave the study centre on the treatment days after the last assessments have been made.

7.2.4 Post-study Evaluations

See Table 7-1.

If a subject is withdrawn or chooses to withdraw from the study, the investigator will make every effort to perform all evaluations described for the post-study visit.

Post study laboratory investigations with variables outside the reference ranges will not necessarily be repeated to establish if and when those variables returned to within the reference ranges. The variables will be reviewed against the clinical background, other relevant investigations and their relevance to the administered IMP, before a decision will be taken to repeat the investigations in question. At the discretion of the investigator, the investigations of certain variables outside the reference ranges may be repeated until the variables return to within the reference range for the particular laboratory test, or until the investigator considers the repeated variable to be at an acceptable level in relation to the reference range. If the investigator has made every effort to contact the subject and the subject remains unavailable to attend the clinic for repeat of applicable laboratory investigations, the investigator may declare the subject lost to follow-up.

In cases where results of post-study evaluations are reported after the database has been locked, the applicable clinical laboratory reports will be presented in the appendices to the clinical study report.

All evaluations described for the post-study visit will be performed on all subjects who completed the study.

7.2.5 Sampling, Interim Handling and Storage

7.2.5.1 Safety Blood and Urine Samples

Refer to Table 7-1.

Before starting the study, the investigator (or designee) will supply the sponsor with the reference ranges and units of measurement for the laboratory safety variables to be used during the study. If

the reference ranges change during the course of the study, the investigator (or designee) must provide the sponsor with a list of the new reference ranges and the effective dates.

The TPMT deficiency test will be performed by Black County Pathology Services.

All safety blood and urine sampling will be performed by the study centre, according to their local standard operating procedures (SOPs).

The principal investigator or designee will ensure that all biological fluids collected during the study will not be used for purposes other than as directed by the clinical study protocol. All collected biological fluids used for safety investigations will be destroyed within 3 months after the clinical execution of the study has been completed. All biological fluids used for the TPMT deficiency tests performed at Black County Pathology Services will be destroyed there after the clinical execution of the tests required have been completed.

7.2.5.2 Pharmacokinetic Blood Samples

Pharmacokinetic blood samples will be collected at the following times: Blood collections will be made pre-dose within 30 minutes before administration and at 15 mins (±2 mins), 30 mins (±2 mins), 45 mins(±2 mins), 1hr(±2 mins), 1 hr 20mins(±2 mins), 1 hr 40mins (±2 mins), 2hrs(±5 mins), 2hrs 20 mins(±5 mins), 2hrs 40 (±5 mins), 3hrs(±5 mins), 4hrs(±5 mins), 5hrs(±5 mins), 6hrs(±5 mins), 8hrs(±5 mins), and 12hrs(±5 mins) after study drug administration. The total number of blood collections will be 32, 16 samples per period. The total volume of blood taken (including safety bloods) will be approximately 356.3 ml. The actual blood sampling times will be recorded in the eCRFs. The PK sample should be taken on the scheduled timepoint and other procedures due at the same time scheduled around using the applicable windows.

Venous blood samples, up to 10 mL each, for the determination of azathioprine concentrations will be collected. Full details on PK collection, sampling, processing and storage will be provided in a study specific lab manual

Blood samples taken for drug concentration measurements will be analysed by Alderley Analytical according to applicable SOPs.

Unused duplicate plasma PK samples will be stored at Alderley Analytical for up to 1 year after completion of the study (defined as last subject last visit). The sponsor will be required to indicate whether additional storage is needed or whether the samples may be discarded.

7.2.6 Blood Volume

The total blood volume to be collected from each subject during the study is indicated in Table 7-2.

The total volume of blood to be collected from each subject during the study (approximately 230 mL) is considered acceptable.

Table 7-2 Total Blood Volume to be Collected during the Study

Procedure	Visit	No. Samples	Blood Volume per Sample (mL)	No. Treatment Periods	Blood Volume (mL)
Clinical chemistry	Screening[1]	1	5	N/A	5
	Admission	1	2.5	2	5
	Post-study	1	2.5	N/A	2.5
Full blood count	Screening[1]	1	2	N/A	2
	Admission	1	2	2	4
	Post-study	1	2	N/A	2
Blood coagulation	Screening[1]	1	2.7	N/A	2.7
	Admission	1	2.7	2	5.4
	Post-study	1	2.7	N/A	2.7
Azathioprine [2]	Treatment Period	16	~10	2	320
Study specific screening	Screening	1	5ml (EDTA)	N/A	5
Total Blood Volume					**356.3**

[1] From the screening biochemistry blood samples, virology screen will be conducted.
[2] Note that there will be 1ml waste collected for each post dose timepoint

7.2.7 General and Dietary Restrictions

7.2.7.1 Diet

Consumption of grapefruit, grapefruit juice, Seville oranges or orange marmalade, cruciferous vegetables (e.g., cabbage, broccoli, sprouts), liquorice, peppermint-containing products, char-grilled foods, poppy seeds or cranberry juice will not be allowed from 7 days before the start of the study until after completion of the study.

The ingestion of food and beverages containing pineapple and all other fruit juices will not be allowed for 72 hours before the administration of IMP and until the last PK blood sample is collected per treatment period.

The ingestion of food and beverages containing methylxanthines e.g., caffeine (coffee, tea, chocolate, energy drinks and cola) will not be allowed for 72 hours before the administration of IMP and until the last PK blood sample is collected per treatment period. Decaffeinated alternatives are permitted.

The ingestion of food and beverages containing alcohol will not be allowed for 72 hours prior to any safety laboratory samples and for 72 hours before screening and then from 72 hours before the first administration of IMP (treatment period 1) until the last PK blood sample (treatment period 2) is collected.

Food and beverage intake during the clinic stay will be as per clinical unit standard practice

No fluids (apart from water taken with dose) are allowed from 1 h prior to dosing until 1 h afterwards. Water is then allowed ad libitum.

While resident in the clinic, volunteers will follow a standard meal schedule. After a snack on the evening of admission they will be fasted overnight until lunchtime on Study Day 1

Lunch: Approx 4.5 hours post dosing

Snack: Approx 7.5 hours post dosing

Dinner: Approx 10 hours post dosing

Food and beverage intake will be allowed *ad libitum*, unless restrictions apply, after the subjects have been discharged from the clinic.

7.2.7.2 Physical Activity

Strenuous physical activity will not be allowed for 72 hours before the first dose of either treatment period until after discharge.

7.2.7.3 Contraception

To prevent pregnancy female subjects of child bearing potential and male subjects and their female partner must use a condom plus 1 highly effective form of contraception i.e.,

- Condom + Established use of combined hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Condom + Established use of progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Condom + Intrauterine device (IUD).
- Condom + intrauterine hormone-releasing system (IUS).
- Vasectomised partner, provided that partner is the sole sexual partner of the female trial subject and that the vasectomised partner has received medical assessment of the surgical success and this documented evidence is available.
- True abstinence, only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments and up to 6 months after. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and

the preferred and usual lifestyle of the subject. *[Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception]*.

The chosen contraception method(s) must be followed from the first dose until at least 6 months after the last dose of IMP.

To prevent exposure of any partner (male or female) a condom must be used throughout the study and for 6 months after the final dose of study drug

Male subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study and for 6 months after their final dose.

Contraception advice will be documented in the informed consent form.

7.2.7.4 Sperm and Oocyte Donation

Subjects must not donate sperm or oocytes from the first dose and for at least 6 months after the last dose of IMP.

7.2.7.5 Receipt of Live Vaccination

Subjects must not receive live vaccinations 4 weeks prior to first dose and for at least 3 months after the last dose of IMP.

7.3 Selection of Study Population

The criteria are set to ensure a homogeneous subject population without accompanying diseases interfering with the conduct and scientific evaluation of the study. Additionally, the criteria have been selected to minimize risk to the subjects' well-being.

7.3.1 Inclusion Criteria

1. Healthy male and female subjects, 18 years to 55 years inclusive at time of signing the informed consent document
2. Females child Bearing potential with a negative pregnancy test at screening and willing to use a condom plus 1 highly effective method of contraception from first dose until 6 months after last dose of IMP (please see section 7.2.7.3 for contraception details).
3. Females of Non child Bearing potential defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries.(A urine pregnancy test will be required for subjects without Medical documentation to support non child bearing status) or Post-menopausal females defined as being at least 45 years of age with history of amenorrhoea for 12 months without an

alternative medical reason. A confirmatory follicle-stimulating hormone (FSH) may be performed at the discretion of the site Investigator to confirm postmenopausal status.

4. Male subject willing to use 2 highly effective methods of contraception from first dose until 6 months after last dose of IMP (please see section 7.2.7.3 for contraception details).
5. Body Mass Index (BMI) between 18 and 33 kg/m^2.
6. Body weight not less than 50 kg.
7. Subject with no clinically significant abnormal serum biochemistry, haematology and urine examination values within 28 days before the first dose of IMP.
8. Medical history, physical examination, standard 12-lead electrocardiogram (ECG) and vital signs investigations: Findings clinically acceptable or within reference ranges, unless the investigator considers the deviation to be irrelevant for the purpose of the study.
9. Non-smokers (subjects using nicotine containing products within 1 year of start of study should not be included).
10. Written informed consent given for the participation in the study.

7.3.2 Exclusion Criteria

1. Evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to limit the validity of consent to participate in the study or limit the ability to comply with protocol requirements.
2. Current alcohol use > 21 units of alcohol per week for males and >14 units of alcohol per week for females.
3. Regular exposure to substances of abuse (other than alcohol) within the past year.
4. Use of any medication, prescribed or over-the-counter or herbal remedies, within 2 weeks prior to the first administration of IMP except if this will not affect the outcome of the study in the opinion of the investigator.
5. Participation in a new chemical entity clinical study within the previous 3 months or a marketed drug clinical study within the 30 days before first dose of IMP and until the study is complete (i.e. the subject has undergone their post study visit). (*Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study*).
6. A major illness during the 3 months before commencement of the screening period.

7. History of hypersensitivity or allergy to the IMP or its excipients or any related medication (please refer to azathioprine Oral suspension IMPD and Imurek® SmPC for list of excipients).
8. History of bronchial asthma or any other bronchospastic disease, history of epilepsy, history of porphyria, history of rheumatoid arthritis, history of pancreatitis, history of any liver disease or any other medical condition that in the opinion of the investigator may interfere with the study outcome measures or impact upon the safety of the subject.
9. Clinically relevant abnormalities in the coagulation status.
10. Clinically diagnosed peptic ulceration within the past 5 years.
11. History of bleeding disorders.
12. History of any of the following: seizures, diabetes, migraine, cardiovascular (including hypertension and hypotension), pulmonary, neurological, hepatic, renal or gastrointestinal conditions, hematopoietic abnormalities, blood disorders, gout, leg ulcers, lactose intolerance or ongoing infectious diseases at the discretion of the investigator.
13. Subjects with a deficient, low or intermediate TPMT enzyme activity by means of phenotyping.
14. Since subjects with inherited mutated NUDT15 gene are at increased risk of severe azathioprine toxicity with the usual doses of thiopurine therapy this protocol will exclude subjects of East Asian or Hispanic ethnicity (in whom the NUDT15 mutant alleles are most common).
15. Subjects who participated in previous thiopurine studies within six months.
16. Relevant history or laboratory or clinical findings indicative of acute or chronic disease, likely to influence study outcome.
17. Donation or loss of blood equal to or exceeding 450 mL during the 3 months before the first administration of IMP.
18. Subjects with a supine systolic blood pressure >150 mmHg and diastolic BP >90 mmHg.
19. Orthostatic hypotension (fall in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic when standing).
20. Resting supine pulse of >110 beats per minute or <40 beats per minute.
21. Positive testing for HIV and/or Hepatitis B and/or Hepatitis C.
22. Positive urine screen for drugs of abuse.
23. Positive urine screen for tobacco use.
24. Subjects who plan to procreate within 6 months after IMP administration.

25. Subject with known fertility problems still wanting to procreate.
26. Immunization using a live organism vaccine within 4 weeks prior to the first dosing of IMP.
27. Any specific IMP safety concern.
28. Female subjects who are currently breastfeeding.

7.3.3 Withdrawal Criteria

Subjects have the right to withdraw from the study at any time, irrespective of the reason, without detriment to their medical care.

The following are pre-defined incidents that may lead to withdrawal:

1. Adverse events as a result of the IMP, at the discretion of the investigator.
2. Intercurrent illness requiring medication. The decision whether or not to withdraw the subject will be at the discretion of the investigator and will depend on the nature of the illness and medication used.
3. Protocol violation by subjects, at the discretion of the investigator. Protocol violation is defined as the wilful disobeying of protocol instructions which have been communicated to the subjects verbally and in writing.
4. Pathologically raised body temperature.
5. Positive testing for drugs of abuse.
6. Positive testing for cotinine.
7. Positive alcohol breath test.

The primary reason for treatment discontinuation will be documented.

If the investigator withdraws a subject from treatment or if a subject declines further participation, a post-study visit will be completed for subjects who were exposed to IMP, within 72 hours of withdrawal/withdrawing from the study.

If a subject's reason for discontinuation is an adverse event, this must be reported in accordance with the procedures detailed in Section 12. The investigator must make every effort to contact a subject before he can be regarded as lost to follow-up.

7.3.4 Replacement of Subjects

Subjects who withdraw or are withdrawn from the study may be replaced, if fewer complete the study than the estimated number of evaluable subjects (see Section 11.2). Replacements will be randomised to treatment.

Subject screening numbers will be allocated at screening.

7.3.5 Premature Termination of the Study

The sponsor or the principal investigator has the right to terminate the study at any time for medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

If the study is prematurely terminated for any reason, the investigator will promptly inform the subjects and will ensure appropriate therapy and follow-up for the subjects. The REC and the MHRA will be informed as soon as possible after the decision has been made to terminate the study and the reasons for termination.

Should the study be prematurely terminated, the completed and partially completed eCRFs and remaining IMP must be returned to the sponsor.

Medicines Evaluation Unit standard operating procedures (SOPs) governing these actions will be followed.

8 INVESTIGATIONAL MEDICINAL PRODUCTS

8.2 Products to be administered

Subjects will receive either the test or reference product, according to the randomization schedule, under fasting conditions. Subjects will receive each product once.

8.3 Identity of Investigational Medicinal Products

Test Product* (A)

Generic name	:	Azathioprine
Trade name	:	(Jayempi™) 10 mg/ mL Oral solution
Dosage form	:	Oral suspension containing 10 mg/mL Azathioprine
Dose	:	1 x 5mL (50 mg) of Jayempi™ Oral Suspension 10mg/mL per treatment period under fasting conditions
Mode of administration	:	Orally
Manufacturer	:	Nova Laboratories Ltd.
Country of origin	:	Leicester, UK

Reference Product (B)

Generic name	:	Azathioprine
Trade name	:	Imurek® 50mg tablet
Dosage form	:	Tablet containing 50 mg azathioprine
Dose	:	1 x Imurek 50mg Tablet per treatment period under fasting conditions
Mode of administration	:	Orally
Manufacturer	:	Aspen Pharma Trading Limited, Dublin, Ireland
Country of origin	:	Ireland

8.3.1 Supply and Storage

The sponsor will supply sufficient quantities of test and reference products bulk supply packed, labelled and released according to Good Manufacturing Practice (GMP) Annex 13 requirements. The principal investigator or designee will ensure that the IMPs are stored in a limited access area according to the storage instructions of the label, the information in the literature or instructions supplied by the sponsor.

The pharmacy department, as designee of the principal investigator, will dose from the bulk supply according to MEU SOPs and also according to the randomization list provided by SQN. Any additional packaging or labelling requirements required at site will be according to Good Manufacturing Practice (GMP) Annex 13 requirements. Accountability records will be prepared and maintained and monitored by the sponsor.

Investigational medicinal product to be administered at the study centre on clinic days will be retained in separate containers for each product.

8.3.2 Investigational Medicinal Product Accountability

Medicines Evaluation Unit is fully responsible for Investigational Product accountability according to their SOPs. This must include accurate records for dates and amounts of Investigational Products received, dispensed (subject by subject accounting) and that the IMP will not be used for purposes other than as directed by the clinical study protocol. Test product accountability will be performed for the liquid by volume of administration being checked and witnessed by two members of staff at administration, and for the tablet by tablet count by two members of staff.

Once the clinical phase of the study has been completed or prematurely terminated, and after drug accountability has been performed, used and unused IMPs will be handled in accordance with requirements of the Regulatory Authority. If incinerated, the certificate of incineration will be filed in the Investigator Site File.

8.3.3 Retention Samples

The sponsor will retain a sufficient quantity for re-testing of the test product and reference product.

8.4 Randomization Schedule

The randomisation will be produced by SQN. The treatment will be allocated by staff at the site using the randomisation list provided.

Subjects who withdraw or are withdrawn from the study may be replaced, if fewer complete the study than the estimated number of evaluable subjects (see Section 11.2). Replacements will be randomised to treatment.

8.5 Selection of Doses in the Study

In compliance with bioequivalence guidelines, the dosage in this study will include a single 50 mg oral dose of azathioprine, on each of two separate occasions with a washout period of at least 3 calendar days, under fasting conditions. Azathioprine is used in various indications, but the starting dosage is usually 1-3mg/kg/body weight/day and adjusted according to the clinical response (which may not be evident for weeks or months) and haematological tolerance Thus, in an adult male weighing 70 kg the typical dose will typically be between 70 and 200 mg/day. In this study, volunteers will be given a single 1 x 50 mg dose of 6-MP (as an oral suspension or tablet) at each of the two dosing visits with a washout period of at least 3 days between visits. The relatively low dose and the dosing schedule minimises the risk of any short or long term toxicity from two doses of azathioprine.

See Section 5.

8.6 Administration of Investigational Medicinal Products

After an overnight fast of at least 10 hours, subjects will receive either the reference or test product according to the randomization schedule. The reference IMPs will be administered with 240 mL of water.

In the case of the solution (Test product), 5 mL of the solution will be prepared by drawing up into syringe for oral administration according to the instructions provided by the Sponsor. The syringe will be placed directly into the mouth of the subject and the contents gently released. The syringe will then be rinsed with 5 mL water immediately after dosing, which the subject will swallow. Subjects will then be asked to drink an additional 235 mL of water. See also Section 5 and Section 7.2.3.

IMP administration instructions will be provided.

8.7 Blinding

The study is open-label. However, as stated in the EMA guidelines on investigation of bioavailability and bioequivalence [6], analysis of the samples should be conducted without information on treatment, therefore the laboratory staff responsible for drug concentration analysis will be blinded to the treatment.

8.8 Prior and Concomitant Medication

Subjects must refrain from using any medication, other than oral contraception, prescribed or over-the-counter (including herbal remedies, St. John's wort [*Hypericum perforatum*]), for 2 weeks before the first administration of IMP and for the duration of the study. Occasional use of paracetamol ≤2 g/day and/or ibuprofen (≤1200 mg/day) is allowed for pain

The administration of concomitant medication will be handled on a case-by-case basis at the discretion of the investigator. If any medication is required during the course of the study, it must immediately be reported to the investigator. Where medication is taken or needs to be taken, a decision whether to continue or discontinue the subject's participation in the study will be based on subject safety, the time of medication administration and the possible influence of the ingested medication on the PK of the IMP and interference with the assay method.

8.9 Treatment Compliance

To ensure treatment compliance, the IMP will be administered by the principal investigator or designee. A mouth check will be performed by the principal investigator or designee to ensure that the subjects have swallowed the IMP.

9 PHARMACOKINETIC AND SAFETY VARIABLES

9.2 Pharmacokinetic and Safety Measurements

Refer to Section 7.1.2.

9.3 Appropriateness of Measurements

Standard measures to assess PK and safety apply during the study.

9.4 Primary Pharmacokinetic Variables

Refer to Section 11.4.

9.5 Pharmacokinetic Drug Assays

Alderley Analytical has been inspected by the MHRA GCP Inspectorate and is included in the United Kingdom GLP Compliance Program. The analyses are conducted and reported in accordance with the Good Practice regulations and guidelines. Additionally, the Safety Clinical Laboratory, The Doctors Laboratory in London, is accredited according to the requirements of the GCP, GLP and CPA inspectorate. Analytical methods are validated according to internationally accepted standards. The quality and integrity of the analytical work generated in this study will be evaluated according to the acceptance criteria, as described in the SOPs of Alderley Analytical.

Quantitative analysis of azathioprine in the collected plasma samples will be performed by Alderley Analytical using liquid chromatography with mass spectrometry (LC-MS/MS).

All the samples received at Alderley Analytical including samples from drop-outs and discontinuers, will be analysed. Bioanalytical data will be processed according to the relevant SOPs of Alderley Analytical.

Complete method validation and bioanalytical reports will be provided.

10 DATA QUALITY ASSURANCE AND DATA MANAGEMENT

A study initiation meeting chaired by the Sponsor or designee will be held prior to study commencement. The Principal Investigator or designee will be in attendance at the study initiation meeting.

10.2 Quality Control and Source Data Verification

Source data verification will be conducted with due regard to subject confidentiality.

The site will allow the study monitor and sponsor representatives direct access to all study documents, medical files, and source documents to enable verification of the study data, whilst maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the study centre.

10.3 Audit/Inspections

The investigator site, facilities and all data and documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The investigator must allow the auditor/inspector/any representatives of regulatory authorities access to all relevant documents and be available to discuss any findings/issues. An audit certificate will be included in the clinical study report if an audit was performed.

10.4 Study Monitoring

The conduct of the study will be monitored by a representative of the sponsor to ensure compliance with applicable regulatory requirements and GCP. The summary documentation of the monitoring visits will form part of the study documentation and will be archived as such.

10.5 Data Collection

Data Management will design an eCRF to capture all data generated during the study.

The study centre’s paper source records will be used to capture certain safety data - this will be indicated on the Source Document Agreement.

Designated investigator staff will enter the data required by the protocol into the electronic CRFs (eCRFs) using fully validated software that conforms to 21 CFR Part 11 requirements. Staff will not be given access to the eCRF until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the Biometrics group. The Investigator must certify that the data entered into the eCRF are complete and accurate.

Source data will be defined as such in the Source Document Agreement. The responsible study monitor will check data at the monitoring visits to the clinical study centre (see Section 10.3).

All clinical work conducted under this clinical study protocol is subjected to GCP regulations. This includes an inspection by the sponsor and Regulatory Authority representatives at any time. The investigator will agree to the inspection of study-related records by Regulatory Authority representatives and the audits of the sponsor or third parties named by the sponsor (also see Section 10.2).

11 STATISTICAL METHODS

11.2 Statistical Methodology

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made.

Any deviations from the statistical methods described in this document, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the clinical study report.

11.2.1 Pharmacokinetic Population

All subjects who complete the study and for whom primary PK variables can be calculated for all treatments will be included in the statistical PK analysis for the study.

In case of events such as vomiting, diarrhoea and use of concomitant medication, which could render the plasma concentration-time profile unreliable, such subjects may be excluded from the PK population after review of the severity of the event and the start and stop time in relation to dosing. When vomiting occurs within 2x the calculated median t_{max} of the reference product, data from all treatments being compared will be excluded from PK and statistical evaluation. Subjects with pre-dose azathioprine concentrations ≥ 5% of C_{max} will be excluded from all statistical PK analysis (including descriptive statistics). The available concentration data of the above subjects and those who do not complete the study will only be listed, not presented in descriptive statistics or included in PK or formal statistical analysis.

11.2.2 Safety Population

All subjects who received at least one dose of IMP will be included in the safety analysis for the study.

11.3 Sample Size

Thirty (30) subjects will be randomised, to allow for dropouts or subjects who otherwise fail to complete the study with at least 28 evaluable subjects. The sample size for this study has been selected without any formal statistical considerations. However, similar bioequivalence studies (AT/H/0270/001-002/DC, UK/H/2846/004/DC and UK/H/934/01/DC) for azathioprine have recruited between 24-30 subjects. This figure has been determined adequate to meet the study objectives.

11.4 Protocol Deviations and Changes to Planned Analyses

Permission from the sponsor in writing will be obtained should any changes be required to the clinical study protocol. Should the safety of the study subjects necessitate immediate action, which represents a deviation from the clinical study protocol, the sponsor will be informed as soon as possible.

Protocol deviations and changes to planned analyses will be described in the clinical study report.

For protocol amendments, see Section 3.1.

11.5 Pharmacokinetic Variables

The following PK variables will be calculated for azathioprine and the metabolite mercaptopurine for each subject and treatment using non-compartmental analysis and using the actual sampling time intervals (relative to IMP administration):

11.5.1 Primary Variables

- Maximum observed plasma concentration (C_{max})
- AUC Area under the plasma concentration curve from zero to time of the last quantifiable concentration (AUC_{0-t})
- Area under the plasma concentration curve from zero extrapolated to infinity ($AUC_{0-\infty}$).

11.5.2 Secondary Variables

- Time to maximum observed plasma concentration (t_{max})
- Terminal elimination rate constant (λ_z)
- Apparent terminal elimination half-life ($t_{½}$).

Calculation of the PK variables will be made with Phoenix WinNonlin 6.3. AUCs will be calculated using the linear trapezoidal rule. The version of the software applied will be documented in the clinical study report.

11.6 Presentation of Data, Descriptive Statistics and PK Assessment

The actual blood sampling times and deviations will be listed for each subject dosed, product and scheduled sampling time. A listing reflecting summary statistics (n, arithmetic mean, geometric mean, median, coefficient of variation, standard deviation, minimum and maximum) per product will be provided for plasma concentrations of azathioprine.

Concentrations below LLOQ will be indicated as below the lower limit of quantification (BLQ). These BLQ concentrations will be handled as follows:

- For PK summaries and analyses , all BLQ values in the absorption phase, prior to the first reported concentration, will be substituted by zeros. The BLQ values between evaluable concentrations will be substituted by ½LLOQ, before the calculation of the PK variables. The terminal BLQ values will be set to missing. These measures are taken to prevent an over-estimation of AUC. Values reported as 'NS' (no sample) will be set to "missing".

For PK calculations, missing concentrations will be deleted, resulting in an interpolation between the nearest two concentration values.

A table reflecting summary statistics (n, arithmetic mean, geometric mean, median, coefficient of variation, standard deviation, minimum and maximum) per product will be provided for PK variables of azathioprine, including the number of points used to calculate λz (λz will, however, not be summarised).
A listing reflecting summary statistics (n, arithmetic mean, geometric mean, median, coefficient of variation, standard deviation, minimum and maximum) will be provided for the ratios (%test/reference) of the primary PK variables and for the difference (test – reference) of t_{max}.

The individual plasma concentration versus actual time profiles of azathioprine for each subject and product, as well as the mean plasma (arithmetic and geometric) plasma concentration versus scheduled time profiles of azathioprine for each product, will be presented graphically on a linear-linear and log-linear scale. Individual plasma concentrations will be presented using actual, rather than planned, sampling times. Combined individual concentration versus time graphs per product will also be presented on a linear-linear scale, together with the geometric mean values. The individual log-linear graphs from WinNonlin will be presented.

The data listings, descriptive statistics, statistical analysis and graphs of this study will be generated using SAS® version 9.4 or later.

11.7 Analysis of Bioequivalence

The test product (azathioprine only) will be compared to the reference products by means of statistical analysis with respect to the primary PK variables using an analysis of variance (ANOVA) with sequence, subject(sequence), product and period effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "test/reference" geometric mean ratios of these variables will be tabulated.

Bioequivalence of the test and reference products will be assessed on the basis of the 90% confidence intervals for the primary PK variables of azathioprine in relation to the conventional bioequivalence range of 80.00% to 125.00%.

In case of outliers present in the data regarding the primary PK parameters, the analyses will be performed on both the complete data and on the data excluding the outliers. Bioequivalence will however be assessed on the complete data.

Analysis of t_{max} will be done using Wilcoxon's Signed Rank test.

The median t_{max} of the test and reference will be tabulated together with the p-value from Wilcoxon's Test.

11.8 Analysis of Safety Data

Demographic and anthropometric variables will be listed for all subjects in the safety population. Demographic variables will also be tabulated (n, arithmetic mean, median, standard deviation, minimum and maximum of continuous variables, and frequency counts and percentages of categorical variables, as applicable). Subject disposition will also be listed and summarised

Haematology, clinical chemistry and urinalysis values will be listed. For the full blood count, clinical chemistry values and urinalysis, only the abnormal values will be listed and flagged in the listings as "L" (for values lower than the lower limit of the reference range) and "H" (for values higher than the upper limit of the reference range). Clinical chemistry and haematology will be summarised.

Vital signs and ECGs will be listed for all subjects in the safety population.

Adverse events reflecting the System Organ Class (SOC) and preferred term for each AE, concomitant medication reflecting Anatomical-Therapeutic-Chemical classification (ATC) will be listed. Adverse events will be summarised as per the following:

- by treatment
- by treatment, SOC and preferred term
- by treatment, SOC, preferred term time and relationship.
- by treatment, SOC, preferred term and severity.

12 ADVERSE EVENTS

Each subject will be carefully monitored by the investigator for AEs. In addition, information on AEs will be obtained from the subjects by regular questioning of each subject by the study staff, although no leading questions will be asked. When an AE occurs, the investigator will decide whether to withdraw the subject from the study and/or initiate appropriate treatment. After withdrawal from the study, it will be ensured that the subject is given appropriate medical care, if needed, which may take the form of referral to a physician.

In the case of any event requiring medical intervention occurring during the clinic stay, the investigator will institute general supportive measures including, where necessary, respiratory assistance and cardiopulmonary resuscitation.

12.2 Definitions

12.2.1 Adverse Events (or Adverse Experiences)

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. It can be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product.

12.2.2 Adverse Drug Reaction

A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.

12.2.3 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the SPC (or other applicable product information such as the Investigator's Brochure for the test product). This includes class-related reactions that are mentioned in the SPC but which are not specifically described as occurring with this product.

12.2.4 Serious Adverse Events

Serious adverse event (SAE) means an adverse reaction which:

- Results in death;

- Is life-threatening*
- Requires in-patient hospitalization or
- Prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly or birth defect.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission *via* a medicinal product of an infectious agent is also considered a serious adverse reaction.

Please note SAEs must be reported within 24 h of knowledge of the event by submitting an initial SAE report via email or fax to *Diamond PV Ltd*:

[redacted]

Diamond PV Ltd will notify the Sponsor and Sponsor's Responsible Physician of the SAE via e mail within 24 h of receipt of the initial SAE report.

12.3 Classification of Adverse Events

Adverse events have to be recorded on an AE form in the subject's eCRF and graded as mild, moderate, or severe according to the following definitions:

- **Mild:** Causing no limitation of usual activities; the subject may experience slight discomfort.
- **Moderate:** Causing some limitation of usual activities, the subject may experience annoying discomfort.
- **Severe:** Causing inability to carry out usual activities, the subject may experience intolerable discomfort or pain.

* Life threatening in this context refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

12.4 Definition of Adverse Events Relationship.

The investigator will determine the relationship of any adverse event to the IMP according to the following criteria:

- **Certain:** A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which concurrent disease or other drugs or chemicals cannot explain and response to withdrawal plausible, and reappearance of the reaction on repeated exposure.
- **Probable/Likely:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a reasonable response on withdrawal (de-challenge).
- **Possible:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Unlikely:** A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanation.
- **Not related:** A clinical event, including laboratory test abnormality, which can be explained by any reason excluding the administered drug.
- **Conditional/Unclassified:** A clinical event, including laboratory test abnormality, which can / cannot be judged because more data for proper assessment needed or additional data under examination.
- **Not assessable/Unclassified:** A report suggesting an adverse event that cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

12.5 Adverse Events Documentation

The recording of every single AE/ SAE has to be in line with ICH Topic E2B (M) and has to meet the following requirements:

- Detailed subject data
- Exact documentation of the event
- Exact description of temporal sequence to the therapy course
- Documentation of severity

- Documentation of the results of diagnostic and therapeutic measurements
- Results of a repeated exposure (re-exposure) if possible
- Details of the development and outcome including medical judgment
- As much data as possible have to be obtained which are important for judgment concerning the relationship of the AE/SAE to IMP
- Critical examination of the relationship to IMP.

All AEs have to be charted according to this scheme when spontaneously reported by the subject, observed by the principal investigator or designee or elicited by general questioning.

12.6 Reporting Procedures of Adverse Events/Serious Adverse Events

The principal investigator or designee is responsible for recording in the eCRF **all** AEs which have occurred during the study (including clinically important deviations of laboratory values from the reference ranges), regardless of their relationship to the IMP. Any AE or SAE reported to site by the subject after the end of the study within a reasonable time period and considered to have been caused by the IMP must also be recorded. All recorded AEs will be summarised and reported on in the clinical study report.

All suspected adverse reactions that occur in the concerned study, and that are both unexpected and serious are subject to expedited reporting. A suspected unexpected serious adverse reaction (SUSAR) which is fatal or life-threatening will be reported as soon as possible to the authority.

Occurrence of **any** SAEs (including death, irrespective of the reason) has to be notified **immediately** (within 24 hours) after becoming aware of the event, to the monitor, sponsor, and the Competent Authority (where appropriate i.e. a SUSAR). The notification must be followed by a written report within 48 hours of the initial notification, or at latest on the following working day. The first report should contain a detailed description of the observed symptoms and the concomitant therapy. The investigator has to judge the possible causal relationship between the event and the IMP and should arrange additional examinations at his/her discretion to clarify if the event is connected with the IMP. He/She should consult a specialist if necessary.

All AEs and SAEs have to be followed up until an outcome is known. In the event of an SAE, the outcome has to be reported in the eCRF and to the principal investigator, sponsor, monitor, the REC and the Competent Authority (where appropriate i.e. a SUSAR)**.**

12.7 Pregnancy

Pregnancies must be reported to Diamond PV Ltd immediately (within 24 hours) and should be followed up to determine outcome, including spontaneous or voluntary termination, details of the

birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications.

Pregnancy outcomes must be collected for all female volunteers and the female partners of any males who took the IMP. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

13 LEGAL AND ADMINISTRATIVE ASPECTS

13.2 Documentation

The Investigator site file and associated study documentation will be archived for at least 5 years after the end of the study (last subject last visit) as per The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (No. 1928) The study documentation may be transferred to an offsite storage facility during this period but will remain under the control of MEU.

The Sponsor has delegated the set up and maintenance of the Sponsor trial master file (TMF) to MEU. The TMF will checked by the Sponsor's monitor at monitoring visits and will be returned to the Sponsor at the end of the study, who will archive it for at least 25 years after the end of the study.

13.3 Publication of Results

If a publication based on the results of this study is envisaged, approval from the sponsor will be obtained and a draft manuscript will be submitted to the sponsor for scrutiny and comment. The choice of scientific journal will be mutually agreed on by the principal investigator and the sponsor.

13.4 Sponsor's Obligation

The onus rests with the sponsor to ensure that this clinical study protocol complies with all their requirements.

13.5 Clinical Study Report

An integrated clinical study report (CSR) will be prepared in accordance with the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). The CSR will be signed by the investigator in accordance with Annex I of the Directive 2001/83/EC as amended. Copies will be provided to the REC in accordance with regulatory requirements and MEU SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

14 REFERENCES

EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) and the United States Department of Health and Human Services, Food and Drug Administration (FDA) Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. Centre for Drug Evaluation and Research (CDER) March 2003 BP.

Public Assessment Report, Azathioprine 50mg Film-coated Tablets, UK/H/934/01/DC, Relonchem Ltd at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con014182.pdf Accessed 11 Jan 2019.

European public assessment report (EPAR) for Xaluprine, Nova Laboratories Ltd. https://www.ema.europa.eu/en/medicines/human/EPAR/xaluprine-previously-mercaptopurine-nova-laboratories. Accessed 11 Jan 2019

In accordance with ICH E3, only articles from the literature pertinent to the evaluation of the study were cited and will be attached to the appendices of the CSR.