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CANCER RESEARCH UK
Centre for Drug Development

# A Cancer Research UK Phase I/II study to compare [$^{124}$I]*m*IBG PET/CT to [$^{123}$I]*m*IBG imaging in patients with metastatic neuroblastoma

Sponsor protocol number: CRUKD/12/002

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# PARTICIPATING PRINCIPAL INVESTIGATORS AND INVESTIGATIONAL SITES

Details of Principal Investigators and Investigational Sites are recorded on the Participating Investigators and Centres list in the Sponsor's Trial Master File.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | Abbreviation | Definition |
|---|---|---|
| **A** | ABPI | Association of the British Pharmaceutical Industry |
| | AE | adverse event |
| | ALP | alkaline phosphatase |
| | ALT | alanine aminotransferase |
| | ANC | absolute neutrophil count |
| | AST | aspartate aminotransferase |
| **B** | BP | blood pressure |
| **C** | CECT | contrast-enhanced CT |
| | CDD | Centre for Drug Development |
| | CR | complete response |
| | CRA | Clinical Research Associate |
| | eCRF | electronic case report form |
| | CSM | Clinical Study Manager |
| | CT | computerised tomography |
| | CTA | clinical trial authorisation |
| | CTCAE | Common Terminology Criteria for Adverse Events |
| | CV | coefficient of variation |
| **D** | 3D | 3-dimensional |
| | Day | calendar day |
| | DCE-MRI | Dynamic Contrast Enhanced- Magnetic Resonance Imaging |
| **E** | EANM | European Association of Nuclear Medicine |
| | EDC | electronic data capture |
| | EFS | event free survival |
| | EU | European Union |
| **F** | FDA | U.S. Food and Drug Administration |
| | [$^{18}$F]FDG | Fluorine-18 radiolabelled fluorodeoxyglucose |
| **G** | GCP | Good Clinical Practice |
| | G-CSF | granulocyte-colony stimulating factor |
| | eGFR | estimated Glomerular Filtration Rate |
| | GMP | Good Manufacturing Practice |
| | GP | General Practitioner |
| **H** | HCG | human chorionic gonadotrophin |
| | HIV | human immunodeficiency virus |
| | HRA | Health Research Authority |
| **I** | [$^{123}$I] | Iodine-123 (radioactive isotope of iodine) |
| | [$^{124}$I] | Iodine-124 (radioactive isotope of iodine) |
| | ICH GCP | International Conference on Harmonisation of Good Clinical Practice |
| | ICRP | International Commission on Radiological Protection |
| | IMP | investigational medicinal product |
| | INSS | International Neuroblastoma Staging System |
| | ITF | Investigator Trial File |
| | IUD | Intra-uterine device |
| **M** | MBq | megabecquerel |
| | MHRA | Medicines and Healthcare products Regulatory Agency |
| | *m*IBG | *meta*-Iodobenzylguanidine |
| | MIP | maximum intensity projection |
| | MRI | magnetic resonance imaging |
| | mSv | milliSieverts (unit of ionising radiation) |
| | MUP-PET | multi-wire proportional chamber position emission tomography |
| | *MYCN* | v-myc myelocytomatosis viral-related oncogene |
| **N** | NAT | noradrenaline transporter |

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | Abbreviation | Definition |
|---|---|---|
| | NaI | Sodium iodide |
| | NCI | National Cancer Institute |
| | NCRI CCLG | National Cancer Research Institute Children's Cancer and Leukaemia Clinical Studies Group |
| | NHS | National Health Service |
| **P** | PET | positron emission tomography |
| | PET/CT | positron emission tomography/computerised tomography |
| | PI | Principal Investigator |
| | PSRB | Protocol Safety and Review Board |
| **Q** | QP | Qualified Person |
| **R** | REC | Research Ethics Committee |
| | $R_2^*$ | transverse MRI relaxation rate (measure of intrinsic susceptibility MRI) |
| **S** | SAE | serious adverse event |
| | SD | standard deviation |
| | SDV | source data verification |
| | SIOPEN | International Society of Paediatric Oncology Europe Neuroblastoma |
| | SOP | standard operating procedure |
| | SPC | Summary of Product Characteristics |
| | SPECT | single-photon emission computed tomography |
| | SUSAR | suspected unexpected serious adverse (drug) reaction |
| | SUV (max/mean) | Standardized Uptake Value (maximum/mean) |
| **T** | TAC | time-activity curves |
| **U** | UCLH | University College London Hospital |
| | UHR | Ultra-high risk (group) |
| | UK | United Kingdom |
| | ULN | upper limit of normal |
| | µg | microgram |
| | µmol | micromole |
| | USA | United Sates of America |
| | USM | urgent safety measure |
| **W** | WBC | white blood cell |
| | WHO | World Health Organisation |
| | WMIC | Wolfson Molecular Imaging Centre |

# PROTOCOL SIGNATURES

**Investigator Signature:**

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK (United Kingdom) Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki (Appendix 1), the applicable regulations of the relevant NHS Trusts and the study protocol. I agree to conduct the study according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study, and ensure that all staff members are aware of their clinical study responsibilities.

INVESTIGATOR'S NAME: _____

SIGNATURE: _____

DATE: _____

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

2 ICH Harmonised Guideline Integrated Addendum to ICH E6: Guideline for Good Clinical Practice E6(R2) Step 4 dated 09 November 2016.

# PROTOCOL SIGNATURES

**Sponsor Signature:**

The Sponsor has read and agrees to the protocol, as detailed in this document. I am aware of my responsibilities as the Sponsor under the UK (United Kingdom) Clinical Trials Regulations[3], the guidelines of Good Clinical Practice (GCP)[4], the Declaration of Helsinki (Appendix 1), the applicable regulations of the UK law and the study protocol. The Sponsor agrees to conduct the study according to these regulations and guidelines and to appropriately direct and assist sponsor's staff who will be involved in the study and ensure that all staff members are aware of their clinical study responsibilities.

Signed by the Director of the Sponsor's Centre for Drug Development at Cancer Research UK:

NAME:

DIRECTOR OF DRUG DEVELOPMENT

SIGNATURE:

DATE:

3 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

4 ICH Harmonised Guideline Integrated Addendum to ICH E6: Guideline for Good Clinical Practice E6(R2) Step 4 dated 09 November 2016.

# 1 PROTOCOL SYNOPSIS

**Full Title:** A Cancer Research UK Phase I/II study to compare [$^{124}$I]*meta*-Iodobenzylguanidine (*m*IBG) positron emission tomography/computerised tomography (PET/CT) to [$^{123}$I]*m*IBG imaging in patients with metastatic neuroblastoma.

**Short Title:** A Phase I/II study of [$^{124}$I]*m*IBG PET/CT in neuroblastoma.

## 1.1 CLINICAL STUDY OBJECTIVES AND ENDPOINTS

| Primary objective | Endpoint |
|---|---|
| 1. To show that [$^{124}$I]*m*IBG PET/CT can detect an equal or greater number of neuroblastoma lesions compared to conventional [$^{123}$I]*m*IBG planar scintigraphy. | 1. Comparison of the percentage of lesions detected as positive by [$^{123}$I]*m*IBG planar scintigraphy which are also considered positive with [$^{124}$I]*m*IBG PET/CT. |

| Secondary objectives | Endpoints |
|---|---|
| 1. To show that [$^{124}$I]*m*IBG PET/CT can detect an equal or greater number of neuroblastoma lesions compared to conventional [$^{123}$I]*m*IBG scintigraphy with 3D imaging by SPECT (single photon emission computerised tomography). | 1. Comparison of the percentage of lesions detected as positive by [$^{123}$I]*m*IBG SPECT which are also considered positive with [$^{124}$I]*m*IBG PET/CT. |
| 2. Assessing the safety and toxicity profile of a single intravenous administration of [$^{124}$I]*m*IBG. | 2. Determining the causality of each adverse event to [$^{124}$I]*m*IBG and grading severity according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.02. |

| Tertiary objectives | Endpoints |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

| Tertiary objectives | Endpoints |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |

## 1.2 STUDY DESIGN

This is a multi-centre, non-therapeutic Phase I/II study directly comparing [$^{124}$I]*m*IBG PET/CT and conventional [$^{123}$I]*m*IBG imaging in patients with newly diagnosed, relapsed or refractory metastatic neuroblastoma. A minimum of 9 (if stopped after interim analysis) or 33 evaluable patients will be scanned at two centres in the UK.

Patients will be those who require routine conventional [$^{123}$I]*m*IBG planar scintigraphy as a means of assessing response to their ongoing treatment or for staging of their disease. The majority of patients will also be planned to undergo 3D imaging by SPECT where this is available. Eligible patients will undergo the planned routine [$^{123}$I]*m*IBG imaging as part of this study. These routine [$^{123}$I]*m*IBG planar scintigraphy findings will be reported by a Nuclear Medicine physician at the investigational site and will be used to confirm suitability for the subsequent novel [$^{124}$I]*m*IBG PET/CT imaging prior to administration of the novel [$^{124}$I]*m*IBG Solution for Injection.

The [$^{124}$I]*m*IBG PET/CT imaging will take place approximately 3-21 days after routine [$^{123}$I]*m*IBG imaging and before the commencement of any new anti-cancer therapy. Patients who fulfil the clinical criteria for [$^{124}$I]*m*IBG imaging in Section 4.1.3 will receive one injection of [$^{124}$I]*m*IBG and undergo imaging with [$^{124}$I]*m*IBG PET/CT the following day. Patients who do not fulfil these criteria will be withdrawn from the study. [$^{124}$I]*m*IBG PET/CT imaging undertaken as part of the clinical study will not affect the management or delay the commencement of new anti-cancer therapy of patients recruited to this study.

[$^{124}$I]*m*IBG PET/CT imaging data from the first patient will be analysed immediately by the Investigators to assess whether the scanning equipment specifications and scanning methodology are effective. The methodology will be adapted as required to ensure the quality of subsequent imaging data. Adaptations may also be made to resolve any practical and logistical issues with the events schedule for the next patient. Recruitment to the study will be competitive between centres. There is no minimum time interval required between patients.

The interim analysis will be performed after a minimum of 50 lesions have been identified by [$^{123}$I]*m*IBG planar scintigraphy from a minimum of 9 evaluable patients. If the number of lesions which were also identified using [$^{124}$I]*m*IBG PET/CT is less than 45 out of 50 the trial will be stopped early for futility. If all lesions (e.g. 50 out of 50) were also identified using [$^{124}$I]*m*IBG PET/CT the trial may be stopped early for efficacy. Otherwise recruitment will continue until a minimum of 100 lesions have been identified by [$^{123}$I]*m*IBG planar scintigraphy from a minimum of 33 evaluable patients.

All patients will be monitored for safety reporting from the time the patient / parent or guardian (as applicable) provides informed consent until their Off-Study assessment performed during a clinic visit or by telephone on Day 3 to 7 before the start of subsequent anti-cancer therapy. If there are any reported events considered to be related (highly probably, probably or possibly) to [$^{123}$I]*m*IBG and/or [$^{124}$I]*m*IBG still present at the Off-Study assessment, the patient will be followed by their Oncologist

until resolution, recovery to baseline, or stabilisation of these events, unless the patient starts another anti-cancer therapy.

**Interpretation of imaging**

The imaging review will be performed separately by an agreed number of observers who are Nuclear Medicine physicians experienced in the assessment of neuroblastoma. Two observers will be study Investigators and all others will be independent from the study to prevent subjective bias in the interpretation of the nuclear medicine *m*IBG scans. Lesions will be identified and scored by each observer using a diagnostic confidence level. The observers will review the lesions identified and where there is a difference in their separate scores they will return to the imaging in order to reach a consensus score. The number of lesions identified as positive by this scoring will be used to meet the primary objective of comparison of the novel [$^{124}$I]*m*IBG PET/CT modality with the recommended standard *m*IBG imaging modality for neuroblastoma which is [$^{123}$I]*m*IBG planar scintigraphy (see Section 9.1).

The majority of patients treated for neuroblastoma will have [$^{123}$I]*m*IBG scintigraphy using 3D SPECT over the chest and abdomen in addition to planar scintigraphy of the full body. The imaging review performed for the assessment of the primary objective will be repeated to read and score lesions identified by the available [$^{123}$I]*m*IBG SPECT. The number of positive lesions identified by SPECT will be used to meet the secondary objective of comparison of [$^{124}$I]*m*IBG PET/CT with [$^{123}$I]*m*IBG scintigraphy with 3D SPECT.

The imaging review will then be repeated to read and score all the available conventional imaging taken together including [$^{123}$I]*m*IBG planar and SPECT scintigraphy and cross sectional imaging with CT and MRI.

[redacted]

[redacted]

[redacted]

## 1.3 ADMINISTRATION SCHEDULE

Patients will receive one intravenous injection of [$^{123}$I]*m*IBG administered as per standard clinical practice and according to the SPC one day before the planned conventional planar scintigraphy ± SPECT performed on Day -21 to -3 for the routine assessment of neuroblastoma.

Patients who fulfil the clinical criteria for [$^{124}$I]*m*IBG imaging described in section 4.1.3 will receive one intravenous injection on Day 1. All patients will receive a minimum injected dose of 10 MBq and a maximum injected dose of 50 MBq [$^{124}$I]*m*IBG equating to a maximum chemical dose of 10 µg of stable *m*IBG. The maximum activity administered to adult patients will be 50 MBq. This maximum activity, 50 MBq, will be requested for each adult patient as the specified target dose. On occasions that the maximum activity, 50 MBq, is not met, but is still within the required range of 10 to 50 MBq, patient administration will proceed and the scanning time adjusted accordingly. The maximum activity administered to paediatric patients will be scaled according to weight using the European Association of Nuclear Medicine (EANM) paediatric dose card (see section 5.3). This maximum activity will be

requested for each paediatric patient as the specified target dose. With reference to the EANM scheme for paediatric patients, a baseline activity of 3.5 MBq, a minimum activity of 10 MBq and class B scaling factors are deemed appropriate. This will result in administration of an activity between 10 and 50 MBq depending on the patient's weight. On Day 2 patients will undergo a low dose, non-diagnostic CT followed sequentially by PET acquisition. The scanning schedule will take between 30 and 75 minutes, depending on whether the scanning time is to be adjusted to account for administration of lower activity than specified target dose. If the scan schedule is likely to exceed 75 minutes then this should be discussed with the patient prior to the injection of [$^{124}$I]*m*IBG to seek verbal consent. Any discussions should be documented in the patients' medical notes.

## 1.4 PATIENT GROUP

A minimum of 9 (if stopped after interim analysis) or 33 evaluable patients aged over 1 year, with histologically proven neuroblastoma with stage 4 disease (as defined by the International Neuroblastoma Staging System (INSS)), will be entered into the study. A patient must have a minimum of 1 neuroblastoma lesion identified on routine conventional [$^{123}$I]*m*IBG planar scintigraphy to be evaluable for the primary objective.

# 2 INTRODUCTION

## 2.1 BACKGROUND

Neuroblastoma is the most frequent solid extracranial tumour of childhood. More than 1200 new cases per year are diagnosed in the United States of America (USA) and Europe (Maris, Hogarty et al. 2007, Gatta, Zigon et al. 2009). Approximately 50% of the cases are considered high risk (i.e. metastatic or harbouring v-myc myelocytomatosis viral-related oncogene (*MYCN)* amplification) and for those, outcome after multimodal treatment (chemotherapy, surgery, high-dose chemotherapy with haemopoietic stem cell rescue, radiotherapy and minimal residual disease therapy) is still poor. Five-year overall survival has remained below 40% in larger multicentre trials (Matthay 2008, Pearson, Pinkerton et al. 2008). Despite initial promise, the long-term beneficial effect of immunotherapy on overall survival is still unknown (Yu, Gilman et al. 2010). Hence, more than 60% of patients with high risk neuroblastoma experience relapse or progression and in this setting outcome is extremely poor with long-term survival below 10% (London, Castel et al. 2011). There is therefore an unmet need to develop new imaging modalities for these poor prognosis patients.

Accurate staging using imaging is critical to the risk stratification of patients with neuroblastoma, and functional imaging plays a crucial role in both the diagnostic evaluation of primary tumours and the identification and quantification of metastatic disease. Further along the treatment pathway, the high sensitivity offered by functional scans is essential to the detection of small volume residual disease, which results in changes to therapy. Scan findings are therefore crucial in guiding type, intensity and timing of treatment. The mainstay of functional imaging of staging and response to therapy investigations is scintigraphy using [$^{123}$I]*m*IBG (*meta*-Iodobenzylguanidine), an analogue of catecholamine precursors which is taken up specifically by tumour cells (Hadley and Rabe 1986, Lumbroso, Guermazi et al. 1988, Brodeur, Pritchard et al. 1993, Leung, Shapiro et al. 1997, Hero, Hunneman et al. 2001).

There is a strong rationale for research aimed at improved imaging modalities employing *m*IBG, which is the only sensitive and specific tumour imaging biomarker available for neuroblastoma. There are currently a number of initiatives to rationalise the evaluations involved in staging neuroblastoma and identifying response to therapy, and *m*IBG scanning is pivotal and essential to these. Although other imaging modalities have been investigated as possible alternatives to *m*IBG scanning including technetium-99m bone scintigraphy, SPECT, [$^{18}$F]FDG PET/CT and others, these have failed to achieve a significant overall improvement in neuroblastoma imaging. Although superior to planar scintigraphy, SPECT has several disadvantages which are that resolution still remains relatively poor and the quantification of uptake is difficult. SPECT or SPECT/CT imaging is also time-consuming, with a single body region taking up to 30 minutes; which is a particular problem in children as they are less able to comply with lying still for extended periods of time than adults.

For other tumours apart from neuroblastoma, [$^{18}$F]FDG (fluorine-18 radiolabelled fluorodeoxyglucose) PET/CT's unique ability to synthesise structural and metabolic information has established its routine use for staging and post treatment assessment. It is also very rapid, with the entire body being imaged in 20 minutes in the latest scanners. However, [$^{18}$F]FDG, unlike *m*IBG, is not a tumour-specific biomarker and suffers from poor specificity in neuroblastoma as a result. Iodine-124, as a positron emitting radiotracer with a long half-life, offers the potential to take full advantage of the high sensitivity and specificity of *m*IBG in conjunction with the excellent spatial and anatomical resolution offered by PET/CT.

Iodine-124 is cyclotron generated, with a relatively long half-life of 4.18 days. Early work was carried out at the Royal Marsden in 1992 on its possible use as a PET tracer in radioiodine therapy planning for neuroblastoma using an early multi-wire proportional chamber position emission tomography (MUP-PET) positron camera (Ott, Tait et al. 1992). Since that time iodine-124 has been virtually ignored by researchers until its favourable radiochemical properties and long half-life focused renewed interest on its use in the imaging of antibodies using PET. There is currently increasing interest in this radioisotope as a potential imaging tool in thyroid cancer, which has led to iodine-124 (as sodium iodide) having been successfully applied to radioiodine dosimetry in that setting (Freudenberg, Jentzen et al. 2007, Jentzen, Weise et al. 2008, Hobbs, Wahl et al. 2009). Optimal acquisition

settings for iodine-124 detection by PET in the clinical setting have now been published (Freudenberg, Antoch et al. 2008, Lubberink, Abdul Fatah et al. 2008, Phan, Jager et al. 2008, Capoccetti, Criscuoli et al. 2009, Gregory, Hooker et al. 2009) and [$^{124}$I]*m*IBG has already been manufactured in the USA and Manchester for use in a number of *in vitro* gene expression studies (Lee, Hall et al. 2001, Robinson, Julyan et al. 2004, Keen, Dekker et al. 2005, Dekker, Keen et al. 2005a, Dekker, Keen et al. 2005b, Williams, Julyan et al. 2007), but there are no published data in the clinical context of children with neuroblastoma to date.

## 2.2 INVESTIGATIONAL MEDICINAL PRODUCTS

### 2.2.1 [$^{123}$I]*m*IBG

Administration of [$^{123}$I]*m*IBG for planar scintigraphy imaging is routine standard of care for the group of patients eligible for this study. However, as this assessment will form part of this clinical trial as a comparator imaging modality, [$^{123}$I]*m*IBG is classified as an IMP. Clinical supplies will be obtained through the Radiopharmacy at each investigational site through routine supply mechanisms.

The active substance [$^{123}$I]*m*IBG, also known as Iodine-123 ($^{123}$I) Iobenguane, is licensed in the UK for use as a diagnostic imaging agent for the localisation of tumours originating in tissue that embryologically stems from the neural crest (e.g. pheochromocytomas, paragangliomas, chemodectomas and ganglioneuromas) and for the detection, staging and follow-up of therapy of neuroblastoma. It is marketed by multiple suppliers in the UK. [$^{123}$I]*m*IBG will be identified by active substance in this protocol.

### 2.2.2 [$^{124}$I]*m*IBG Solution for Injection

[$^{124}$I]*m*IBG Solution for Injection will be produced in accordance with European Union (EU) Good Manufacturing Practice (GMP).

The radiosynthetic route for the preparation of the active substance [$^{124}$I]*m*IBG in [$^{124}$I]*m*IBG Solution for Injection will be a based on the method developed by Vaidyanathan *et al.* (Vaidyanathan and Zalutsky 1993) which uses iododesilylation as the mode of iodine-124 incorporation. In brief, [$^{124}$I]NaI is reacted with *meta*-trimethylsilylbenzylguanidine and the resultant [$^{124}$I]*m*IBG is purified and isolated by reverse-phase chromatography. The product is buffered and formulated in an isotonic medium then aseptically filtered to give [$^{124}$I]*m*IBG Solution for Injection suitable for human administration.

[redacted]

## 2.3 MECHANISM OF ACTION

*m*IBG acts as stable radiolabelled mimetic of endogenous noradrenaline. After administration it is taken up by neuroendocrine cells by an active uptake mechanism via the noradrenaline transporter and is stored in the neurosecretory granules, resulting in a specific concentration in contrast to cells of other tissues.

*m*IBG has been used extensively in man primarily radiolabelled with either iodine-123 or iodine-131. *m*IBG radiolabelled with iodine-124 has previously been administered to two patients (Ott, Tait et al. 1992).

## 2.4 PRECLINICAL DATA ON *m*IBG

### 2.4.1 Pharmacology

*m*IBG has a similar chemical structure to noradrenaline and as a result selectively concentrates in tissues with rich adrenergic innervation - such as tumours of neuro-ectodermal origin. Similarly to noradrenaline, *m*IBG is taken up into cells by the noradrenaline transporter (NAT) and is then transferred from intracellular cytoplasm to neurosecretory vesicles. Unlike noradrenaline, *m*IBG is poorly metabolised and is excreted largely as the unchanged parent molecule (Wafelman, Hoefnagel et al. 1994, GE Healthcare Limited 2009). *m*IBG radiolabelled with iodine-123 and iodine-131 has been used extensively as a diagnostic imaging agent in man since the 1980s.

In the proposed study *m*IBG radiolabelled with iodine-124 will be administered at low chemical doses (maximum of 10 µg stable *m*IBG) for diagnostic imaging purposes only. At these low doses *m*IBG is not expected to have any significant pharmacodynamic effect on the patient.

### 2.4.2 Pharmacokinetics and Metabolism

In preclinical models, *m*IBG is rapidly distributed from the blood and accumulates in adrenergically innervated tissues, including the adrenal medulla, salivary glands, heart, spleen and lungs. Accumulation of *m*IBG is predominately via the noradrenaline transporter (NAT), in the adrenergic neurons. Non-neural accumulation is lost in a matter of hours while neural accumulation is retained for much longer (over 24 hours). Prolonged retention is strongly associated with the level of tissue adrenergic innervation (Wafelman, Hoefnagel et al. 1994, GE Healthcare Limited 2009).

Based on studies with [$^{123}$I]*m*IBG, after administration 70 to 90% of the dose of radioactivity is recovered in urine within four days. This radioactivity is predominately unaltered *m*IBG. Metabolites of *m*IBG detected in urine include radiolabelled iodide, *meta*-iodohippuric acid, hydroxy-iodobenzylguanidine and *meta*-iodobenzoic acid, however, these only account for approximately 5 to 15% of the administered dose.

The distribution of intravenously administered *m*IBG includes rapid initial uptake in liver (33% of the administered dose) and much less in lungs (3%), myocardium (0.8%), spleen (0.6%), and salivary glands (0.4%). Uptake in normal adrenals (adrenal medulla) can lead to visualisation with radiolabelled *m*IBG and hyperplastic adrenals show a high uptake(GE Healthcare Limited 2009).

Recent preclinical imaging studies have suggested that in non-clinical species [$^{124}$I]*m*IBG PET does indeed give superior images compared with [$^{123}$I]*m*IBG SPECT (Moroz, Serganova et al. 2007). The superior distribution data obtained by [$^{124}$I]*m*IBG PET, especially at later time points, has also been assessed preclinically as a method to improve dosimetry estimates for [$^{131}$I]*m*IBG radiotherapy (Seo, Gustafson et al. 2012).

### 2.4.3 Toxicology

The toxicity of [$^{124}$I]*m*IBG can be split into two components; that arising from the administered chemical dose of *m*IBG and that arising from the radioactive dose of iodine-124. The former component has been characterised preclinically in studies of *m*IBG toxicity, however, this has largely been superseded by extensive clinical use of radiolabelled *m*IBG both as a diagnostic radiopharmaceutical and as a targeted radiotherapeutic. The dosimetry of [$^{124}$I]*m*IBG has been calculated with reference to published biokinetic data (see Section 2.5.4).

In rats administration of intravenous *m*IBG at 20 to 40 mg/kg/day (120 to 240 mg/m$^2$/day) induces signs of serious toxicity with 20 mg/kg considered to be the maximum tolerated dose. At doses of 5 to

20 mg/kg/day (30 to 120 mg/m$^2$) some acute effects were observed, including respiratory distress, but the only long-term effects documented were a slight increase in weight of the liver and heart.

In dogs intravenous administration of *m*IBG at 20 mg/kg/day (400 mg/m$^2$/day) was a lethal dose. Lower dose levels (14 mg/kg, 280 mg/m$^2$) produced transient toxic cardiac effects. Repeated intravenous administration of *m*IBG to dogs at 2.5 to 10 mg/kg (50 to 200 mg/m$^2$) was also found to induce some cardiovascular effects, including increased blood pressure, increases in heart rate and in cardiac pulse propagation, but all signs were of a transient nature (Smets, Bout et al. 1988, GE Healthcare Limited 2009).

The [$^{124}$I]*m*IBG prepared for this study will have a maximum possible administered chemical dose of 10 µg per patient. This chemical dose will be well within the range of human exposure to *m*IBG and is likely to be lower than that administered during the [$^{123}$I]*m*IBG scan the patient will have received prior to inclusion in this study. As a consequence the safety of *m*IBG can be directly inferred from the extensive and current routine use of [$^{123}$I]*m*IBG and [$^{131}$I]*m*IBG in clinical practice.

## 2.5 CLINICAL EXPERIENCE WITH [$^{124}$I]*m*IBG

### 2.5.1 Pharmacology

*m*IBG was developed in the early 1980s as a noradrenaline mimic to visualise tumours of the adrenal medulla. Diagnostic imaging with radiolabelled *m*IBG is widely used to image tumours of neuroendocrine origin primarily those of the neuro-ectodermal system (phaeochromocytomas, paragangliomas and neuroblastomas); although other neuroendocrine tumours (e.g. carcinoid, medullary thyroid carcinoma) can also be visualised. For clinical diagnostic imaging *m*IBG is usually radiolabelled with iodine-123 or, more rarely, iodine-131 (Bombardieri, Giammarile et al. 2010).

### 2.5.2 Pharmacokinetics and Metabolism

The pharmacokinetics of *m*IBG labelled with iodine-124 are expected to be identical to *m*IBG labelled with iodine-123 or iodine-131, i.e. rapid initial uptake in liver, lungs, myocardium, spleen and salivary glands (GE Healthcare Limited 2009).

After administration of *m*IBG, uptake of radioactivity generally reflects organs and tissues of either rich adrenergic innervation or with a role in catecholamine excretion. High levels of uptake are observed in the liver with lower levels observed in the spleen, lungs, salivary glands, skeletal muscle and myocardium. Myocardial uptake may be particularly high, especially in children under 1 year old (although patients under 1 year old will be excluded from this study). Radioactivity may accumulate to a variable degree in nasal mucosa, lungs, gallbladder, colon and uterus. No skeletal uptake is observed. Uptake in the thyroid was only observed when pre-treatment with non-radioactive iodide to competitively block the thyroid had been omitted. Distribution in patients and healthy subjects was comparable (Nakajo, Shapiro et al. 1983, Shapiro, Copp et al. 1985, Wafelman, Hoefnagel et al. 1994, Shulkin and Shapiro 1998, Bombardieri, Giammarile et al. 2010).

Data has been published on the pharmacokinetics of radioactivity after both diagnostic and radiotherapeutic [$^{131}$I]*m*IBG administration. After intravenous administration of radiolabelled *m*IBG, radioactivity is distributed from the vascular compartment within one hour followed by a slow redistribution from the peripheral compartment into the central compartment. Terminal elimination half-live of radioactivity from blood has been reported to be 9 to 130 h in neuroblastoma patients (Wafelman, Hoefnagel et al. 1994, Vallabhajosula and Nikolopoulou 2011).

The excretion of radioactivity after administration of radiolabelled *m*IBG has been established clinically and the subject of published reviews (Shapiro and Gross 1987, Wafelman, Hoefnagel et al. 1994, Vallabhajosula and Nikolopoulou 2011). Following intravenous administration of radiolabelled *m*IBG radioactivity is rapidly and almost entirely excreted in urine. The importance of renal excretion is confirmed by faecal recoveries of radioactivity of less than 2%. As might be expected glomerular filtration rate (GFR) has a major influence with higher plasma/blood cell distribution ratios observed in renally impaired patients.

The composition of the excreted radioactivity has been investigated clinically. *m*IBG represented 60% to 92% of total radioactivity. Radiolabelled *meta*-iodohippuric acid was the main excreted metabolite together with small amounts of radioiodide (2% to 6%).

### 2.5.3 Safety

The safety of *m*IBG itself has not been clinically addressed while data on radiolabelled *m*IBG has focussed on the use of high radioactive dose [$^{131}$I]*m*IBG for radiotherapy. However, this safety data will be predominately related to the radioactive absorbed dose of iodine-131 and is of limited relevance to this study. Rapid administration of high doses of *m*IBG can lead to pharmacological effects such cardiovascular side-effects, nausea and vomiting; particularly in [$^{131}$I]*m*IBG radiotherapy where high chemical doses (greater than 10 mg) have been administered (Lynn, Shapiro et al. 1984, Barrett, Joyal et al. 2010), 200-fold higher than the proposed maximum chemical dose of 50 µg. However, these adverse effects are very rare when slow injection is used (Bombardieri, Giammarile et al. 2010).

Probably the most relevant safety data comes from a clinical study of AdreView™ (Iobenguane (I 123) injection), the diagnostic [$^{123}$I]*m*IBG produced by GE Healthcare. This study was performed in 251 patients with known or suspected pheochromocytoma or neuroblastoma who were given a single administration of [$^{123}$I]*m*IBG and monitored for adverse reactions over a 24 hour period. The average age was 49 years for adults and 4 years for paediatric patients. Adverse reactions were all mild to moderate in severity and were predominantly isolated occurrences (occurring in no more than two patients) of one of the following reactions: dizziness, rash, pruritus, flushing or injection site haemorrhage.

Hypersensitivity reactions have uncommonly been reported during the post-marketing use of AdreView™ [$^{123}$I]*m*IBG and it is contraindicated in patients with known hypersensitivity to iobenguane or iobenguane sulphate.

In the proposed study [$^{124}$I]*m*IBG will be administered at radioactive doses suitable for diagnostic imaging. The efficacy of *m*IBG in an imaging context is well established. No anti-tumour efficacy of *m*IBG is expected in this study.

### 2.5.4 Dosimetry

Please refer to the current SPC for dosimetry information for [$^{123}$I]*m*IBG.

Absorbed and effective doses have been calculated using *m*IBG biokinetic data from the International Commission on Radiological Protection (ICRP) 53 (ICRP 2007). Effective doses for *m*IBG labelled with the three radionuclides of iodine for all age models are summarised in Table 1. It can be seen from these results that [$^{124}$I]*m*IBG delivers effective doses that are approximately 15 times higher than that of diagnostic [$^{123}$I]*m*IBG and 1.5 times higher than for [$^{131}$I]*m*IBG.

**Table 1 Effective doses (mSv/MBq) for different age models**

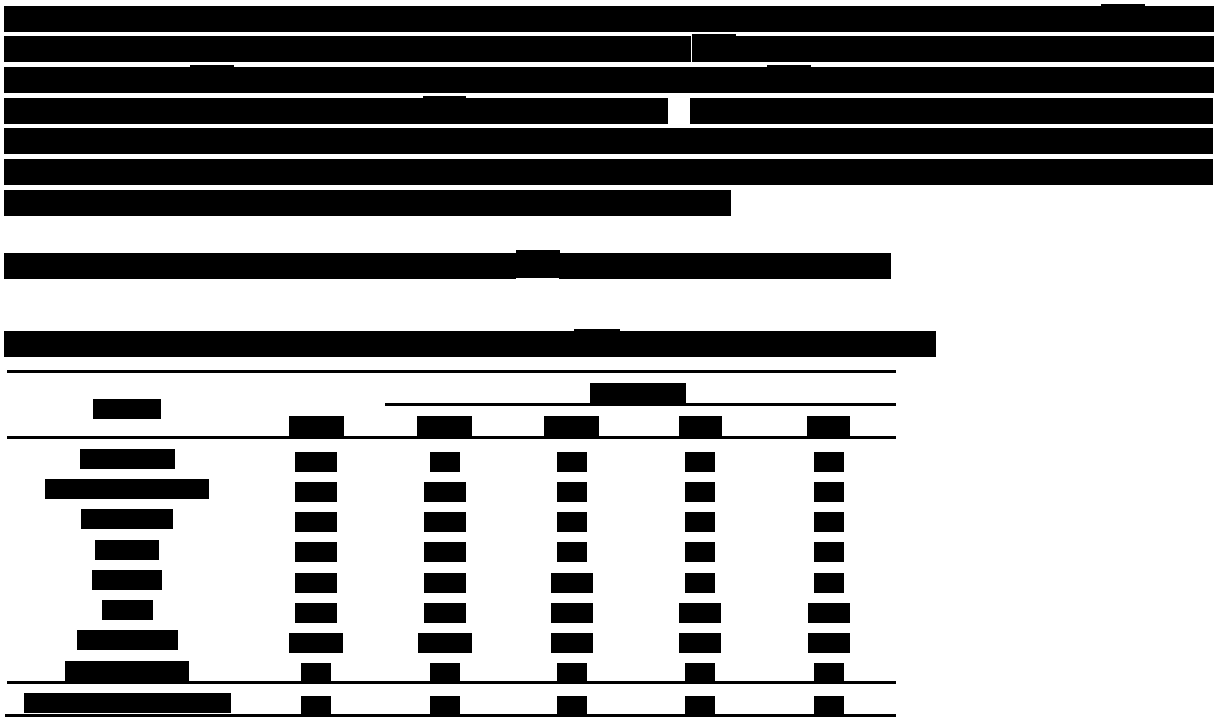
| | [$^{123}$I]*m*IBG | [$^{131}$I]*m*IBG | [$^{124}$I]*m*IBG |
|---|---|---|---|
| Adult | 0.011 | 0.106 | 0.159 |
| 15 Year | 0.014 | 0.143 | 0.207 |
| 10 Year | 0.021 | 0.218 | 0.313 |
| 5 Year | 0.032 | 0.332 | 0.472 |
| 1 Year | 0.059 | 0.637 | 0.872 |

European Association of Nuclear Medicine (EANM) recommendations for administered activities at diagnostic levels are scaled from those recommended for adults (Bombardieri, Giammarile et al. 2010). These recommend a minimum of 80 MBq and a maximum of 400 MBq for [$^{123}$I]*m*IBG, and a minimum of 35 MBq and a maximum of 80 MBq for [$^{131}$I]*m*IBG. The equivalent activities delivering the same effective doses for [$^{124}$I]*m*IBG are shown in Table 2.

**Table 2 Recommended diagnostic activity levels for *m*IBG scans**

Recommended administered dose of radioactivity for [$^{123}$I]*m*IBG and [$^{131}$I]*m*IBG diagnostic scans and the radioactivity dose of [$^{124}$I]*m*IBG which would deliver the equivalent effective dose

| Age | Weight (kg) | [$^{123}$I]*m*IBG (MBq) | Equivalent [$^{124}$I]*m*IBG (MBq) | [$^{131}$I]*m*IBG (MBq) | Equivalent [$^{124}$I]*m*IBG (MBq) |
|---|---|---|---|---|---|
| Adult | 73.70 | 400.0 | 26.7 | 80.0 | 53.3 |
| 15 Year | 56.80 | 336.0 | 22.6 | 67.2 | 46.4 |
| 10 Year | 33.20 | 216.2 | 14.6 | 43.2 | 30.1 |
| 5 Year | 19.80 | 136.1 | 9.2 | 35.0 | 24.6 |
| 1 Year | 9.72 | 80.0 | 5.4 | 35.0 | 25.6 |



EANM recommendations for the timing of diagnostic [$^{123}$I] and [$^{131}$I]*m*IBG scans are at 24 h and 24 h to 48 h respectively. An advantage of iodine-124 is that, due to its relatively long physical half-life and superior imaging quality, high quality scans are possible at both 24 h and 48 h. This study will enable the optimal scan times for [$^{124}$I]*m*IBG PET/CT to be determined and will also provide additional information on the retention as well as the uptake of the radiopharmaceutical. Scans will be performed at 4 h, 24 h, 48 h and 72 h post-administration of [$^{124}$I]*m*IBG in a sub-group of up to six patients. [$^{124}$I]*m*IBG is a biomarker of both the burden of disease and treatment effect.

The absorbed and effective doses used for radiation protection calculations are based on data from ICRP 53. Absorbed doses to some organs, particularly the heart and spleen, are significantly higher than those to other organs, including the adrenals and lungs, due to greater retention. The accuracy of these biokinetic data is marred by the lack of spatial resolution in the case of [$^{131}$I]*m*IBG imaging and by a low half life in the case of [$^{123}$I]*m*IBG. This [$^{124}$I]*m*IBG PET/CT study would update these values and would permit the range of absorbed doses to be determined. This would be of significant benefit to future studies involving [$^{124}$I]*m*IBG.

## 2.6 RATIONALE FOR THE PROPOSED STUDY

A new targeted imaging technique for neuroblastoma is proposed using the positron-emitter [$^{124}$I]*m*IBG as a novel PET radiotracer. Prognostic stratification and treatment decisions for patients with neuroblastoma are critically dependent on accurate imaging, but the current standard modality,

[$^{123}$I]*m*IBG scintigraphy including 3D imaging by SPECT, suffers from significant shortcomings including poor spatial resolution and a lack of ability to accurately quantify results.

This study will demonstrate whether [$^{124}$I]*m*IBG PET/CT is able to detect an equivalent number of *m*IBG avid lesions in neuroblastoma more accurately compared to conventional [$^{123}$I]*m*IBG imaging. Should this study be successful, the role of [$^{124}$I]*m*IBG PET/CT in children with neuroblastoma will be fully evaluated in a large prospective international clinical trial that will study in a homogeneous population, the prognostic and predictive roles of this novel technique. The [$^{124}$I]*m*IBG PET/CT imaging will take place approximately 3-21 days after [$^{123}$I]*m*IBG imaging during a scheduled break in anti-cancer therapy. The metastatic patient population undergoing re-staging has been selected because there is frequently a sufficient time window after their routine scanning to perform additional imaging without causing any delay in the start of subsequent anti-cancer therapy. Patients will have stopped previous anti-cancer therapy at least seven days before the routine [$^{123}$I]*m*IBG scanning used for comparison in this study in order to minimise the effects of this therapy on the residual lesions. The interval from cessation of previous therapy and the time between the *m*IBG modalities will be considered in the interpretation of the imaging data. The results of the novel [$^{124}$I]*m*IBG PET/CT imaging will not be reported to the local oncologist and will not be used to inform the management of patients.

A more accurate technique will have a number of advantages:

1. Currently, 60% of children with high-risk neuroblastoma experience relapse and most of these (>90%) die. New therapeutic approaches are being developed. A more accurate diagnostic tool will help to improve risk stratification and represent a more robust predictive biomarker.
2. All children with high-risk neuroblastoma currently receive the same intensive multimodal therapy. The International Neuroblastoma Risk Group (INRG) and International Neuroblastoma Response Criteria initiatives are now developing a consensus document to define an ultra-high risk group (UHR) of patients based on imaging criteria at diagnosis (*m*IBG score) who will be able to receive novel experimental drugs in the frontline setting with the aim of improving outcome. Whereas non-UHR patients with a better outcome will continue with conventional high-risk therapy. Therefore better risk stratification is likely to lead to earlier access to novel drugs for these poor prognosis children.
3. Yanik *et al*. (Yanik, Parisi et al. 2010, Decarolis, Schneider et al. 2013, Yanik, Parisi et al. 2013) and others have shown that patients who achieve a complete metastatic response (CR) on conventional [$^{123}$I]*m*IBG imaging after induction have a significantly better prognosis than non-CR patients (3-years event free survival (EFS) was 44.9% for those with Curie score 0 to 2 after induction versus EFS 15.4% for those with Curie score >2 after induction (see Appendix 5 for Curie scoring system)). If [$^{124}$I]*m*IBG is better than [$^{123}$I]*m*IBG in detecting metastatic lesions, it will be a more powerful discriminative tool between CR and non-CR patients, therefore guiding therapy after induction.
4. Children with localised neuroblastoma based on [$^{123}$I]*m*IBG scanning currently receive intermediate risk therapy. A more sensitive technique will potentially detect those patients with a low level of metastatic disease who would then receive high-risk therapy that will improve their outcome.
5. In the minimal residual disease setting (after myeloablative therapy or during follow-up), a more sensitive technique will guide therapy (i.e. patients only benefit from immunotherapy if they have cleared their metastatic disease) and also detect early relapses. While early detection of relapses might not translate into an increase in overall survival, it might provide improved access to early clinical trials (patients with better performance).
6. In early clinical trials, the definition of response and identification of the most effective agents will be improved.

A contrast enhanced CT (CECT) scan of diagnostic quality using intravenous and oral contrast is routinely performed as part of a combination of assessments for the staging or restaging of neuroblastoma. Hybrid PET/CT imaging includes a CT of lower ionizing radiation dose than CECT, which provides anatomical localisation and attenuation correction for the PET component of the scan. Access to the new generation of PET/CT scanners is now common at paediatric oncology

departments where patients with neuroblastoma are treated. Thus PET/CT could potentially replace the current two imaging techniques: [$^{123}$I]*m*IBG scanning and CECT.

The long-term objective for this Phase I/II study is that, subject to its being possible to demonstrate a sufficiently high degree of diagnostic accuracy for [$^{124}$I]*m*IBG PET/CT, it would form the basis of further studies to evaluate this technique involving larger series of patients, initially through the National Cancer Research Institute Children's Cancer and Leukaemia Clinical Studies Group (NCRI CCLG) Neuroblastoma Subgroup and then International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN). This would allow a more detailed assessment of its value in the pre-treatment staging and post-treatment assessment of neuroblastoma, and proper evaluation of the potential role of [$^{124}$I]*m*IBG PET/CT as a guide to response-adapted therapy.

Should further research demonstrate [$^{124}$I]*m*IBG PET/CT to be a valuable advance in neuroblastoma imaging, we anticipate that it would be a relatively easy technique to introduce to clinical practice at centres with access to PET/CT. This is because it would require no special adaptation to PET/CT scanners already widely used throughout the UK. [$^{124}$I]*m*IBG has already been manufactured for research use and could be produced in any cyclotron facility. Its long half-life of 4.18 days compares very favourably with the two hour half-life of [$^{18}$F]FDG which would represent a significant advantage from a practical and logistical point of view, allowing the radiotracer to be produced in a single cyclotron in the UK and then realistically transported with ease to other centres. We also anticipate that, should [$^{124}$I]*m*IBG PET/CT become part of routine clinical management of neuroblastoma, tracer production costs would quickly reduce due to greater demand.

Radioiodine therapy with [$^{131}$I]*m*IBG is increasingly a component of trials for high risk neuroblastoma and recent evidence has shown that individualised treatment planning based on absorbed whole-body and tumour doses can be performed to prevent under-treatment or unnecessary toxicity from over-treatment (Gaze, Chang et al. 2005, Buckley, Chittenden et al. 2009). The increased spatial resolution of three dimensional [$^{124}$I]*m*IBG PET/CT imaging over 3D [$^{123}$I]*m*IBG SPECT would improve the accuracy of quantitative imaging on which patient-specific absorbed dose calculations are based.

In summary, the hypothesis of this study is that [$^{124}$I]*m*IBG PET/CT will achieve high sensitivity and specificity in detecting neuroblastoma tumour, deliver the excellent spatial resolution required to precisely localise small disease foci, offer reliable and reproducible quantitative assessment of disease extent, and enable better evaluation of disease response to existing and new therapies for neuroblastoma. In the future it could provide more functional and anatomical data than routine [$^{123}$I]*m*IBG scintigraphy, where full body planar scintigraphy is performed alone or combined with 3D SPECT scintigraphy of the thorax and abdomen, and conventional cross sectional CT or MRI scanning. This would minimise the need to perform two or more scans of different modality.

### 2.6.1 [redacted]

[redacted]

### 2.6.2 [redacted]

[redacted]

[redacted]

### 2.6.3 Anticipated impact of the study on UK clinical practice

If [$^{124}$I]*m*IBG PET/CT is shown to be a significant advance on [$^{123}$I]*m*IBG scintigraphy this would have a major impact on current clinical practice in neuroblastoma in the UK and internationally. The potential clinical benefits of [$^{124}$I]*m*IBG PET/CT to neuroblastoma patients may be summarized as follows:

- It would offer increased sensitivity for predicting outcome and accurately stratifying therapy. Accurate disease staging is particularly critical, because of the very different therapies employed for the various risk groups. Failure to detect even very small disease foci, as currently occurs with [$^{123}$I]*m*IBG planar scintigraphy and 3D SPECT, even in expert hands, may lead to incorrect understaging, leading to insufficient first line therapy and early disease recurrence, with a major reduction in the chance of long term cure. Conversely, inappropriate overstaging leading to unnecessary treatment for high-risk disease may lead to growth reduction, thyroid function disorders, learning difficulties, and a greater risk of secondary cancers in these children.

- A major international strategy to improve the prognosis of high risk disease involves stratification of therapy based on response to indicial induction therapy based on response on [$^{123}$I]*m*IBG scintigraphy. The improved accuracy of [$^{124}$I]*m*IBG PET/CT would substantially strengthen this approach.

- It would replace the visual assessment of disease used in [$^{123}$I]*m*IBG scintigraphy with objective and reproducible quantitative measurement (SUV mean and max). Accurate quantitative assessment of disease extent would enable more rigorous and effective assessment of the efficacy of both existing and novel therapies.

- At least two investigations ([$^{123}$I]*m*IBG scintigraphy and CT scanning, and in some cases also bone scanning and MRI) would be replaced by one. This would speed up the diagnostic pathway and, as these scans often involve general anaesthetics in children, mean that only one rather than two (or more if other imaging techniques such as MRI are employed) general anaesthetics would be required.

# 3 STUDY DESIGN

## 3.1 CLINICAL STUDY OBJECTIVES AND ENDPOINTS

| Primary objective | Endpoint |
|---|---|
| 1. To show that [$^{124}$I]*m*IBG PET/CT can detect an equal or greater number of neuroblastoma lesions compared to conventional [$^{123}$I]*m*IBG planar scintigraphy. | 1. Comparison of the percentage of lesions detected as positive by [$^{123}$I]*m*IBG planar scintigraphy which are also considered positive with [$^{124}$I]*m*IBG PET/CT. |

| Secondary objectives | Endpoints |
|---|---|
| 1. To show that [$^{124}$I]*m*IBG PET/CT can detect an equal or greater number of neuroblastoma lesions compared to conventional [$^{123}$I]*m*IBG scintigraphy with 3D imaging by SPECT. | 1. Comparison of the percentage of lesions detected as positive by [$^{123}$I]*m*IBG SPECT which are also considered positive with [$^{124}$I]*m*IBG PET/CT. |
| 2. Assessing the safety and toxicity profile of a single intravenous administration of [$^{124}$I]*m*IBG. | 2. Determining the causality of each adverse event to [$^{124}$I]*m*IBG and grading severity according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.02. |

| Tertiary objectives | Endpoints |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

| Tertiary objectives | Endpoints |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |

## 3.2 PATIENT EVALUABILITY

To be evaluable for the primary imaging analysis a patient must be eligible for the study, receive [$^{123}$I]*m*IBG and undergo planar scintigraphy, fulfil the clinical criteria for [$^{124}$I]*m*IBG imaging, receive [$^{124}$I]*m*IBG and complete the required PET/CT scanning schedule in accordance with the Study Imaging Manual. Any patient who is not evaluable for the primary imaging analysis will be replaced.

To be evaluable for the assessment of toxicity a patient must have received [$^{124}$I]*m*IBG.

## 3.3 DESIGN OF THE CLINICAL STUDY

This is a multi-centre, non-therapeutic Phase I/II study directly comparing [$^{124}$I]*m*IBG PET/CT and conventional [$^{123}$I]*m*IBG imaging in patients with newly diagnosed, relapsed or refractory metastatic neuroblastoma. A minimum of 9 (if stopped after interim analysis) or 33 evaluable patients will be scanned at two centres in the UK.

Patients will be those who require routine [$^{123}$I]*m*IBG planar scintigraphy as a means of assessing response to their ongoing treatment or for staging of their disease. The majority of patients will also be planned to undergo 3D imaging by SPECT where this is available. Eligible patients will undergo the planned routine [$^{123}$I]*m*IBG imaging as part of this study. These routine [$^{123}$I]*m*IBG planar scintigraphy findings will be reported by a Nuclear Medicine physician at the investigational site and will be used to confirm suitability for the subsequent novel [$^{124}$I]*m*IBG PET/CT imaging prior to administration of the novel [$^{124}$I]*m*IBG Solution for Injection.

Please refer to section 7.9 Schedule of Assessments for a detailed table of the relative timing of the study scans. The [$^{124}$I]*m*IBG PET/CT imaging will take place approximately 3-21 days after routine [$^{123}$I]*m*IBG imaging and before the commencement of any new anti-cancer therapy. Patients who fulfil the clinical criteria for [$^{124}$I]*m*IBG imaging in Section 4.1.3 will receive one injection of [$^{124}$I]*m*IBG and undergo imaging with [$^{124}$I]*m*IBG PET/CT the following day. Patients who do not fulfil these criteria will be withdrawn from the study. [$^{124}$I]*m*IBG PET/CT imaging undertaken as part of the clinical study will not affect the management or delay the treatment of patients recruited to this study.

[$^{124}$I]*m*IBG PET/CT imaging data from the first patient will be analysed immediately by the Investigators to assess whether the scanning equipment specifications and scanning methodology are effective. The methodology will be adapted as required to ensure the quality of subsequent imaging data. Adaptations may also be made to resolve any practical and logistical issues with the events schedule for the next patient. Recruitment to the study will be competitive between centres. There is no minimum time interval required between patients.

The interim analysis will be performed after a minimum of 50 lesions have been identified by [$^{123}$I]*m*IBG planar scintigraphy from a minimum of 9evaluable patients. If the number of lesions which

were also identified using [$^{124}$I]*m*IBG PET/CT is less than 45 out of 50 the trial will be stopped early for futility. If all lesions (e.g. 50 out of 50) were also identified using [$^{124}$I]*m*IBG PET/CT the trial may be stopped early for efficacy. Otherwise recruitment will continue until a minimum of 100 lesions have been identified by [$^{123}$I]*m*IBG planar scintigraphy from a minimum of 33 evaluable patients.

The imaging review will be performed separately by an agreed number of observers who are Nuclear Medicine physicians experienced in the assessment of neuroblastoma. Two observers will be study Investigators and all others will be independent from the study to prevent subjective bias in the interpretation of the nuclear medicine *m*IBG scans. Lesions will be identified and scored by each observer using a diagnostic confidence level. The observers will review the lesions identified and where there is a difference in their separate scores they will return to the imaging in order to reach a consensus score. The number of lesions identified as positive by this scoring will be used to meet the primary objective of comparison of the novel [$^{124}$I]*m*IBG PET/CT modality with the recommended standard *m*IBG imaging modality for neuroblastoma which is [$^{123}$I]*m*IBG planar scintigraphy (see Section 9.1).

The majority of patients treated for neuroblastoma will have [$^{123}$I]*m*IBG scintigraphy using 3D SPECT over the chest and abdomen in addition to planar scintigraphy of the full body. The imaging review performed for the assessment of the primary objective will be repeated to read and score lesions identified by the available [$^{123}$I]*m*IBG SPECT. The number of positive lesions identified by SPECT will be used to meet the secondary objective of comparison of [$^{124}$I]*m*IBG PET/CT with [$^{123}$I]*m*IBG scintigraphy with 3D SPECT.

[redacted]

All patients will be monitored for safety reporting from the time the patient / parent or guardian (as applicable) provides informed consent until the Off-Study assessment on Day 3 (the day after the [$^{124}$I]*m*IBG PET/CT scan) to Day 7. The Off-Study assessment should either take place during a routine clinic visit or by telephone prior to the start of subsequent anti-cancer therapy. If there are any reported events considered to be related (highly probably, probably or possibly) to [$^{123}$I]*m*IBG and/or [$^{124}$I]*m*IBG which are still present at the Off-Study assessment, the patient will be followed by their Paediatric Oncologist until resolution, recovery to baseline, or stabilisation of these events, unless the patient starts another anti-cancer therapy.

### 3.3.1 [redacted]

[redacted]

### 3.3.2 [redacted]

[redacted]

# 4 PATIENT SELECTION

## 4.1 ELIGIBILITY CRITERIA

The patient must fulfil the eligibility criteria presented in Sections 4.1.1 and 4.1.2 prior to enrolment on the clinical trial and the subsequent administration of [$^{123}$I]*m*IBG. [redacted]

Following [$^{123}$I]*m*IBG planar scintigraphy ± SPECT for routine clinical care of neuroblastoma, patients will only continue in the study and undergo [$^{124}$I]*m*IBG imaging if they fulfil the additional clinical criteria outlined in Section 4.1.3.

### 4.1.1 Inclusion Criteria

1. Histologically proven neuroblastoma with stage 4 disease as defined by the International Neuroblastoma Staging System (INSS)
2. Aged ≥ 1 year at the time that written informed consent is given.
3. Planned to undergo conventional [$^{123}$I]*m*IBG planar scintigraphy for routine clinical care of neuroblastoma.
4. Life expectancy of at least 12 weeks.
5. World Health Organisation (WHO) performance status of 0, 1 or 2 (Appendix 2) for patients aged > 12 years old or Lansky play scale score of ≥ 50% (Appendix 3) for patients aged ≤ 12 years old.
6. Written (signed and dated) informed consent from patient ≥ 16 years old and/or parent or legal guardian for patients <16 years old and the patient be capable of co-operating with scanning requirements. (N.B. Written or verbal assent as appropriate should be sought from all patients who are under 16 years old).

#### 4.1.1.1 [redacted]

- [redacted]
- [redacted]

#### 4.1.1.2 [redacted]

- [redacted]
- [redacted]
- [redacted]

### 4.1.2 Exclusion Criteria

1. Treatment with any medications contra-indicated with *m*IBG scanning as listed in Appendix 4. For example, decongestants containing pseudoephedrine, phenylpropalomine and phenylephrine, sympathomimetics, cocaine, antihypertensives, tricyclic antidepressants. These drugs should be stopped before administration as indicated in this list (usually for four biological half-lives to allow almost complete wash-out but refer to list). The Investigator should seek prospective approval of any planned variation from this list from the responsible Nuclear Medicine Consultant, CI and sponsor Medical Advisor.
2. Stage 4S neuroblastoma as defined by the INSS.

3. Any anti-cancer treatment planned between the routine [$^{123}$I]*m*IBG imaging and the [$^{124}$I]*m*IBG PET/CT scan on Day 2. Anti-cancer treatments can be started only after the Off-Study assessment on Day 3 to Day 7, see schedule of assessments in Section 7. N.B. Patients should not be enrolled in the study if their participation will delay their subsequent treatment for neuroblastoma.
4. Female patients who are pregnant or lactating.
5. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.
6. Known to be serologically positive for Hepatitis B, Hepatitis C or Human Immunodeficiency Virus (HIV).
7. Patients with known hypersensitivity to *m*IBG.
8. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical study.

### 4.1.3 Clinical Criteria for [$^{124}$I]*m*IBG imaging

The patient must fulfil the following clinical criteria prior to administration of [$^{124}$I]*m*IBG Solution for Injection due to the limited clinical experience with this novel radiotracer.

1. One or more disease foci observed on conventional [$^{123}$I]*m*IBG planar scintigraphy. Disease foci will initially be identified by a Nuclear Medicine physician at the investigational site.
2. ≥ 3kg at the time of the [$^{124}$I]*m*IBG imaging to agree with the paediatric EANM guidelines.
3. Haematological and biochemical indices within the ranges shown below.

| Laboratory Test | Value required for patients ≤16 years old | Value required for patients >16 years old |
|---|---|---|
| Haemoglobin | ≥ 7.0 g/dl<br>(N.B. transfusions will be allowed) | ≥ 8.0 g/dl<br>(N.B. transfusions will be allowed) |
| Absolute neutrophil count (ANC) | ≥ 0.2 x $10^9$/L<br>(N.B. G-CSF support will be allowed) | ≥ 0.5 x $10^9$/L<br>(N.B. G-CSF support will be allowed) |
| Platelet count | ≥ 10 x $10^9$/L<br>(N.B. transfusions will be allowed) | ≥ 50 x $10^9$/L<br>(N.B. transfusions will be allowed) |
| Serum bilirubin | ≤ 2.5 x upper limit of normal (ULN) | ≤ 2.5 x upper limit of normal (ULN) |
| Alanine amino-transferase (ALT), aspartate amino-transferase (AST), and/ or alkaline phosphatase (ALP) | ≤ 5 x ULN | ≤ 5 x ULN |
| | Calculated creatinine clearance using revised Schwartz formula<br>≥ 60 mL/min/1.73m$^2$ | Estimated Glomerular Filtration Rate (eGFR)<br>≥ 60 mL/min/1.73m$^2$ |

4. Menarchal female patients must have a negative serum or urine pregnancy test before administration of [$^{124}$I]*m*IBG Solution for Injection on Day 1 and agree to use two highly effective forms of contraception (oral, injected or implanted hormonal contraception and condom, have an intra-uterine device and condom, diaphragm with spermicidal gel and condom) to be effective from Day 1 and for 7 days afterwards.
5. Male patients with partners of child-bearing potential must agree to take measures not to father children by using one form of highly effective contraception [condom plus spermicide] from Day 1 and for 7 days afterwards. Male patients with pregnant or lactating partners must agree to use barrier method contraception (e.g. condom plus spermicidal gel) to prevent exposure to the foetus or neonate.

## 4.2 PATIENT ENROLMENT

Recruitment to the study will be competitive between centres. There is no minimum time interval required between patients after review of the imaging data from the first patient.

Informed Consent from the patient's parent or guardian is required for all patients under 16 years old. Written or verbal assent will be sought from all patients under 16 years old. Informed consent is required for all patients aged 16 or older. All patients for whom informed consent has been provided must be added to the study clinical database via the electronic data capture (EDC) system by the site staff. This includes those patients who fail screening and do not go on to be enrolled on the study. Through this process a screening number will be automatically allocated for all consented patients.

The Investigator or designated representative should determine the eligibility of the patient during Screening. The Investigator should inform the Clinical Study Manager (CSM) at the Centre for Drug Development (CDD) of the outcome of the Screening assessment. Eligible patients must be enrolled in the study clinical database by completing the Enrolment and date of Pre-study i.e. Screening visit. A subject number will be automatically allocated to eligible patients. The patient will be registered by the CSM at the CDD as sponsor. The CSM will send confirmation of the patient registration by email to the Investigator after which the patient can start the thyroid blockade.

# 5 DOSE AND ADMINISTRATION

## 5.1 [$^{123}$I]*m*IBG DOSE AND ADMINISTRATION

[$^{123}$I]*m*IBG will be administered according to the current SPC. The radioactive dose will be selected according to the EANM dosage card for paediatric patients and according to the SPC for adult patients.

## 5.2 [$^{124}$I]*m*IBG DOSE AND ADMINISTRATION

### 5.2.1 Selection of the Dose of radioactivity to be administered

The proposed activities to be administered have been calculated based on previous studies with iodine-124 and on the calculation of activities that would deliver a similar effective dose to that delivered by a standard diagnostic [$^{18}$F]FDG PET scan but greater that delivered by an [$^{123}$I]*m*IBG scan. It is proposed to administer activities of [$^{124}$I]*m*IBG of 50 MBq for adult patients and paediatric patients will be scaled appropriately according to the EANM dosage card (Lassmann, Biassoni et al. 2007) such that the absorbed dose will be less than that of a [$^{131}$I]*m*IBG scan.

To date the relatively few clinical studies using [$^{124}$I] have been restricted to adults and have largely been limited to dosimetry studies for ablation or therapy of thyroid cancer. As yet there are no guidelines regarding recommended administered doses of radioactivity. Phan *et al.* administered 74 MBq for diagnostic imaging of advanced thyroid cancer (Phan, Jager et al. 2008), Freudenberg *et al.* administered 24 to 100 MBq of [$^{124}$I]NaI to predict absorbed doses delivered to lung metastases from thyroid cancer (Freudenberg, Antoch et al. 2008), and Sgouros *et al.* administered 74 to 158 MBq for a similar purpose (Sgouros, Kolbert et al. 2004). In a two patient study of [$^{124}$I]*m*IBG imaging for radionuclide therapy treatment planning for adult neuroendocrine tumours, 22 MBq and 40 MBq were administered (Ott, Tait et al. 1992).

## 5.3 DOSE SCHEDULE

Patients will receive one intravenous injection of [$^{124}$I]*m*IBG Solution for Injection on Day 1.

All patients will receive a minimum injected dose of 10 MBq and a maximum injected dose of 50 MBq [$^{124}$I]*m*IBG equating to a maximum chemical dose of 10 µg of stable *m*IBG. The maximum activity administered to adult patients will be 50 MBq. This maximum activity, 50 MBq, will be requested for each adult patient as the specified target dose. On occasions that the maximum activity, 50 MBq, is not met, but is still within the required range of 10 to 50 MBq, patient administration will proceed and the scanning time adjusted accordingly. The maximum activity to paediatric patients will be scaled by weight based upon the EANM paediatric dose card (Lassmann, Biassoni et al. 2007). This maximum activity will be requested for each paediatric patient as the specified target dose. With reference to the EANM scheme, a baseline activity of 3.5 MBq, a minimum activity of 10 MBq and class B scaling factors are deemed appropriate. This will result in an administered activity between 10 MBq and 50 MBq depending on the patient's weight.

Administration of [$^{124}$I]*m*IBG Solution for Injection on Day 1 will be approximately 3-21 days after the routine [$^{123}$I]*m*IBG scan. A minimum interval of 72 hours is required between injection of [$^{123}$I]*m*IBG tracer and the [$^{124}$I]*m*IBG PET/CT scan. There is no minimum interval between patients.

The scanning schedule will take between approximately 30 and 75 minutes depending on whether the scanning time is to be adjusted to account for administration of lower activity than specified target dose. If the scan schedule is likely to exceed 75 minutes then this should be discussed with the patient prior to the injection of [$^{124}$I]*m*IBG to seek verbal consent. Any discussions should be documented in the patients' medical notes.

## 5.4 DOSE MODIFICATIONS

The [$^{124}$I]*m*IBG PET/CT scans of the first patient will be assessed shortly after being performed to determine whether a lesser amount of radioactivity can be administered. Any reduction will then be implemented from the second patient onwards. The maximum injected dose will then be fixed and will not be further reduced for subsequent patients.

## 5.5 REPLACEMENT OF PATIENTS

Patients who do not complete the [$^{124}$I]*m*IBG PET/CT scan or who are subsequently found to have been ineligible for the study will be replaced.

## 5.6 CONCOMITANT MEDICATION

Concomitant medication may be given as medically indicated, with the exception of the drugs listed in Appendix 4 which are contra-indicated with *m*IBG scanning. These drugs should be stopped before administration as indicated in this list (usually for four biological half-lives to allow almost complete wash-out but refer to list). **The Investigator should seek prospective approval of any planned variation from this list from the responsible Nuclear Medicine Consultant, CI and sponsor Medical Advisor.** They include of note: reserpine, labetalol, calcium-channel blockers (diltiazem, nifedepine, verapamil), tricyclic antidepressants (amitryptiline, imipramine and derivatives), sympathomimetic agents (present in nasal decongestants, such as phenylephrine, ephedrine or phenylpropanolamine), cocaine, phenothiazine.

Blood and platelet transfusions and granulocyte-colony stimulating factor (G-CSF) are allowed.

The patient should not receive any anti-cancer therapy or investigational drugs until the Investigator has assessed whether there are ongoing toxic manifestations related to [$^{124}$I]*m*IBG Solution for Injection administration unless this therapy is required in response to an urgent medical need. This assessment should take place between Day 3 to Day 7 either during a routine visit to the clinic or by telephone.

Details of all concomitant medications given should be recorded in the patient's medical records. Relevant details of concomitant medications should be entered in the electronic case report form (eCRF).

# 6 PHARMACEUTICAL INFORMATION

## 6.1 SUPPLY OF [$^{123}$I]*m*IBG

[$^{123}$I]*m*IBG is available commercially from multiple suppliers. The Investigators will be responsible for their own supply of [$^{123}$I]*m*IBG. Dispensed [$^{123}$I]*m*IBG will be labelled by the Radiopharmacy according to the requirements of Article 14 of EU directive 2001/20/EC and paragraph 32 Eudralex volume 4: Annex 13 'Investigational Medicinal Products of the EU guide to GMP'. An example of the label(s) will be approved by the CDD before use and filed in the Pharmacy Folder.

## 6.2 SUPPLY OF [$^{124}$I]*m*IBG SOLUTION FOR INJECTION

The maximum shelf-life of the IMP is 96 h from the end of manufacture when stored in a vial shield (lead or tungsten) in the absence of light and at ≤ 25°C. A certificate of analysis and Qualified Person (QP) certification must be provided for each batch of [$^{124}$I]*m*IBG Solution for Injection prior to patient administration. [$^{124}$I]*m*IBG Solution for Injection must be used before the expiry date and time stated (use within period) on the shield label.

Refer to Section 7.5 Supply of [$^{124}$I]*m*IBG Solution for Injection and to the [$^{124}$I]*m*IBG Supply Guidelines for details of the ordering process and logistics of supply to the investigational site. For information on [$^{124}$I]*m*IBG and re-ordering of supplies, contact the Clinical Research Associate (CRA) or Clinical Study Manager (CSM) responsible for the study who will arrange further supplies. The IMP will be manufactured in compliance with GMP and supplied by:

Wolfson Molecular Imaging Centre (WMIC)
[redacted]

The primary and secondary packaging for the IMP will be labeled according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the EU guide to GMP.

## 6.3 PHARMACEUTICAL DATA

### 6.3.1 Pharmaceutical Presentation of [$^{123}$I]*m*IBG

Details for [$^{123}$I]*m*IBG can be found in the current SPC provided by the manufacturer of [$^{123}$I]*m*IBG.

### 6.3.2 Pharmaceutical Presentation of [$^{124}$I]*m*IBG Solution for Injection

[$^{124}$I]*m*IBG Solution for Injection is prepared as a single patient dose unit just prior to clinical use. [redacted] the maximum concentration of *m*IBG per vial will be 10 µg. The product is aseptically filtered into a type I glass vial sealed with a Type I synthetic rubber closure and aluminium overseal. Each drug product vial will be stored within a vial shield (lead or tungsten) container in the absence of light at a temperature of ≤ 25 °C.

### 6.3.3 Storage conditions

Both IMPs must be stored in a secure, limited access storage area.

Storage conditions for [$^{123}$I]*m*IBG will be stated in the current SPC supplied by the manufacturer and on the vial shield label.

[$^{124}$I]*m*IBG Solution for Injection must be used before the expiry date and time stated on the shield label. The vials of [$^{124}$I]*m*IBG Solution for Injection must be stored and transported within a vial shield (lead or tungsten). The IMP must be maintained at a temperature of ≤ 25°C.

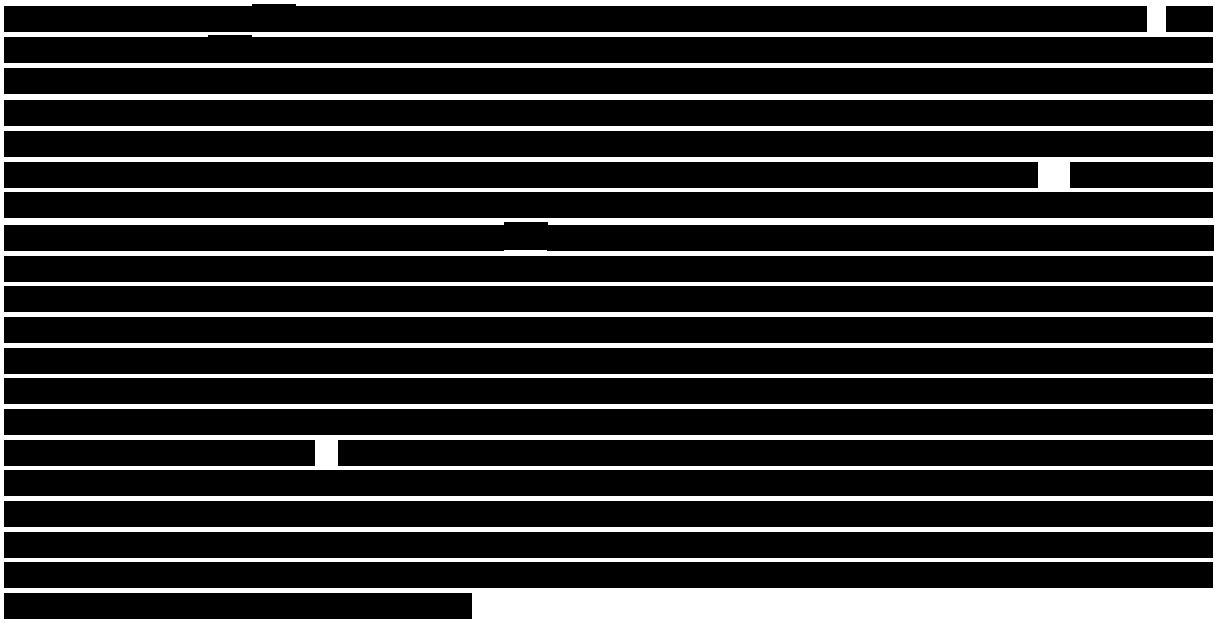
## 6.4 [$^{123}$I]*m*IBG ADMINISTRATION

[$^{123}$I]*m*IBG should be administered in accordance with the dosage scheme described in the current SPC supplied by the manufacturer.

## 6.5 [$^{124}$I]*m*IBG SOLUTION FOR INJECTION ADMINISTRATION

Aseptic technique must be employed when preparing the drug for administration.

[$^{124}$I]*m*IBG Solution for Injection is radioactive and must be handled to ensure the safety of the operators and patients. This will be achieved by adhering to the local rules and Ionising Radiation (Medical Exposure) Regulations (IRMER) requirements which define practice, and the IRR99 regulations which cover radiation doses to staff.



[$^{124}$I]*m*IBG Solution for Injection must be used before the expiry date and time stated (use within period) on the shield label.

Before administering [$^{124}$I]*m*IBG Solution for Injection, the exact radioactive dosage must always be double-checked by a second suitably qualified healthcare professional. All checks and double-checks must be documented (signed and dated) and the documentation must be available for the CRA/CSM to verify.

The [$^{124}$I]*m*IBG Solution for Injection must be administered slowly over several minutes by intravenous infusion either into a peripheral vein or through an existing central line. This must occur before the expiry date and time stated on the vial shield label. The start and end time of the infusion must be recorded.

## 6.6 VEIN EXTRAVASATION/ ACCIDENTAL SPILLAGES

Please refer to the current SPC and Patient Information Leaflet for instructions for [$^{123}$I]*m*IBG.

[$^{124}$I]*m*IBG Solution for Injection is not a vesicant agent. Vein extravasation should be managed according to hospital policy for extravasation of non-vesicant agents. As the total levels of [$^{124}$I]*m*IBG and radioactivity being administered to each patient are low there is no significant radiation risk even in the event that the full dose is extravasated. Accidental spillages should be dealt with according to hospital policy and local Nuclear Medicine Departmental procedure.

## 6.7 DRUG ACCOUNTABILITY

### 6.7.1 Accountability of [$^{123}$I]*m*IBG

Accurate records relating to the dispensing and administration (including the exact date and time the [$^{123}$I]*m*IBG was administered) to the patient must be maintained. These records must be available for inspection at any time by a CRA/CSM of the CDD. [$^{123}$I]*m*IBG employed for imaging of patients must be used in accordance with the SPC and under the supervision of the Investigator. Any discrepancies between the number of vials dispensed and the volumes administered to patients must be accounted for in the Radiopharmacy records and Investigator Trial File (ITF).

As [$^{123}$I]*m*IBG is a marketed product and used as an IMP in this trial any unused [$^{123}$I]*m*IBG should be retained as per local policy/procedures before being destroyed when radioactivity levels are safe. Destroyed vials and unused [$^{123}$I]*m*IBG must be accounted for on an IMP Destruction Form and IMP accountability records.

### 6.7.2 Accountability of [$^{124}$I]*m*IBG Solution for Injection

Accurate records relating to the receipt for the IMP, dispensing of the IMP, and administration (including the exact date and time the IMP was administered) to the patient must be maintained. These records must be available for inspection at any time by a CRA/CSM of the CDD. IMP employed for imaging of patients must be used in accordance with this protocol and under the supervision of the Investigator. Any discrepancies between the number of vials dispensed and the volumes administered to patients must be accounted for in the Radiopharmacy records and Investigator Trial File (ITF).

If there is any [$^{124}$I]*m*IBG Solution for Injection left after the administration this should be retained for six months as per GMP requirements in an appropriate controlled storage area at ≤ 25°C. Any unused [$^{124}$I]*m*IBG Solution for Injection should be retained for six months as per GMP requirements in an appropriate controlled storage area at ≤ 25°C and then must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form and IMP Accountability Record. At the conclusion of the study the overall numbers of vials of [$^{124}$I]*m*IBG Solution for Injection shipped to the centre and the number destroyed will be provided by the pharmacy, and an account given of any discrepancy.

# 7 INVESTIGATIONS SCHEDULE

All required assessments for Screening through to Follow-up are shown in the tabulated Schedule of Events in Section 7.9 as well as being described here.

Details of all evaluations/investigations for enrolled patients, including relevant dates, required by the protocol must be recorded in the medical records so that the eCRF can be checked against the source data.

In cases where a patient has investigations at a different hospital, for example blood samples, then it is the Investigator's responsibility to ensure he/she receives and reviews the results. The results should be recorded on the eCRF and the reports from the other hospitals should be made available for source data verification. Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used.

## 7.1 OBTAINING WRITTEN INFORMED CONSENT

Patients of 16 years of age or older must provide written informed consent for the study. Parents or guardians of patients under 16 years of age must provide written informed consent. Written or verbal assent will be sought from patients under 16 years of age. Information sheets and consent or assent forms will be provided as below.

- Patients 16 years of age or older (information sheet and consent form)
- Parents / legal guardians of patients under 16 years of age (information sheet and consent form)
- Patients below 16 years of age (information sheet and assent form)
    - Patients 13-15 years of age
    - Patients 8-12 years of age
    - Patients < 8 years of age

Written informed consent / assent must be obtained from the patient and / or the patient's parent or guardian before any protocol-specific procedures are carried out. The patient and/or the patient's parent or guardian must be given adequate time to think about their commitment to the study. If more than 28 days has passed since informed consent was obtained before the patient receives the [$^{124}$I]*m*IBG intravenous injection then the Investigator should consider whether repeat consent should be sought.

Only the Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI as documented on the Study Team Responsibilities Signature Log are permitted to take informed consent from patients or the patient's parent / guardian and to sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (International Conference on Harmonisation of Good Clinical Practice (ICH GCP) 4.8.8 and 8.3.1.2). The patient or parent/guardian should sign and date the consent form in the presence of the Investigator, followed by the Investigator signature. The date of the signatures of the patient, patient's parent / guardian and the PI/Sub-Investigator should be the same.

The PI or the Sub-Investigator must inform the patient about the background to the study and must also ensure that the patient and/or parent(s)/ legal guardian(s) are aware of the following points:

- The known toxicity of [$^{123}$I]*m*IBG and [$^{124}$I]*m*IBG scanning and the possibility of experiencing side-effects.

- That [$^{124}$I]*m*IBG PET/CT scanning is new and that because the accuracy of diagnosis of neuroblastoma using this modality is at present unknown the results of the scanning will not be used to inform the staging of their disease and so will have no direct benefit for them but that scanning him/her will contribute to further knowledge of this imaging modality.

- For menarchal female patients the potential dangers of becoming pregnant, or for male patients the potential dangers of their partner becoming pregnant and that he/she has been given information about appropriate medically approved contraception (refer to Section 8.8).

- That he/she may refuse to receive [$^{123}$I]*m*IBG or [$^{124}$I]*m*IBG or participate in the study scan(s) during the study and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled nor impact on their treatment.

- Who to contact for answers to questions about the research and their rights, and also who to contact in the event of a research-related injury.

A copy of the consent / assent form(s) and patient information sheet must be given to the patient/parent(s) or guardian(s) to keep. The original consent / assent form (s) and patient information sheet should be filed in the Investigator Trial File (ITF) unless otherwise agreed to be filed in the medical records with copies kept in the ITF.

If the scan schedule is likely to exceed 75 minutes as described in the study information sheets and consent or assent forms then this should be discussed with the patient prior to the injection of [$^{124}$I]*m*IBG to seek verbal consent. Any discussions should be documented in the patients' medical notes.

## 7.2 SCREENING EVALUATIONS (DAY -28 TO ENROLMENT)

The following assessments must be performed before administration of [$^{123}$I]*m*IBG in preparation for routine diagnostic [$^{123}$I]*m*IBG planar scintigraphy performed as part of standard disease assessment.

- Written informed consent / assent (as detailed in Section 7.1.2)

- Demographic details

- Relevant medical history including prior diagnosis, genetic findings to include *MYCN*, 11q, 17q and other segmental chromosomal abnormalities of prognostic impact in neuroblastoma, histological findings according to The International Neuroblastoma Pathology Classification (the Shimada system), prior treatments for neuroblastoma (stage 4 disease only), concomitant diseases.

- Routine imaging for assessment of neuroblastoma including conventional cross sectional CT and/or MRI as clinically indicated. This routine imaging must be performed during a break in treatment and within the 28 days before administration of [$^{124}$I]*m*IBG. If a diagnostic CECT has not already been performed as part of this routine imaging assessment this should be performed sequentially following the [$^{124}$I]*m*IBG PET/CT scan where possible.

- Adverse events (AEs), including serious adverse events (SAEs), must be monitored from the time that consent is given. The Investigator should determine the start and stop date of an AE together with the relationship of the event to [$^{123}$I]*m*IBG and/or [$^{124}$I]*m*IBG. All AEs must be graded according to NCI CTCAE Version 4.02. All AEs and any concomitant treatment must be recorded in the medical records and in the eCRF. (See Section 8.3 for further details regarding the definition of AEs and reporting requirements.)

- Schedule [$^{124}$I]*m*IBG PET/CT scan and any applicable sub-study scans.
  N.B. A minimum interval of 72 hours is required between the planned injection of [$^{123}$I]*m*IBG and the performance of the novel [$^{124}$I]*m*IBG PET/CT scan.

- Physical examination

- Height in cm and weight in kg
- World Health Organisation (WHO) performance status (see Appendix 2) or Lansky play scale score (see Appendix 3)
- Assessment of eligibility criteria (see sections 4.1.1 and 4.1.2)

At this point eligible patients should be enrolled on the trial. Site staff should enrol patients in the clinical database by completing the Enrolment form and entering the date of the Pre-study (i.e. Screening) visit following the guidance in Section 4.2 Patient Enrolment. Confirmation of the patient registration from the CSM at the CDD must be received by the site staff before administration of [$^{123}$I]*m*IBG for routine diagnostic imaging because this is classified as an IMP for this clinical imaging study.

## 7.3 EVALUATIONS DURING THE STUDY (DAY -21 TO -3)

- Administration of thyroid blockade given in accordance with local standard operating procedure for diagnostic use of [$^{123}$I]*m*IBG
- Administration of [$^{123}$I]*m*IBG
- [$^{123}$I]*m*IBG planar scintigraphy with 3D SPECT as available, performed for the routine assessment of neuroblastoma. N.B. This should be performed following an interval of at least 7 days from previous anti-cancer therapy between Day -21 to Day -3.

## 7.4 EVALUATIONS DURING THE STUDY (DAY -7 TO DAY 1)

- Menarchal female patients should have a serum or urine human chorionic gonadotrophin (HCG) test; a negative result is required before administration of [$^{124}$I]*m*IBG
- Temperature, blood pressure (BP) and pulse rate
- Blood sample for full blood count and biochemistry (refer to criteria in Section 4.1.3 for required values) to include:
    - Haematology – haemoglobin, white blood cells (WBC) with differential count (absolute neutrophil count (ANC) and lymphocytes) and platelets
    - Biochemistry – serum bilirubin, alanine aminotransferase (ALT) and/or aspartate amino-transferase (AST) and/or alkaline phosphatase (ALP), creatinine
- *PLEASE NOTE: All evaluations required during the study between Day -7 and Day 1 must be completed and all results received prior to administration of [$^{124}$I]mIBG.*

## 7.5 SUPPLY OF [$^{124}$I]*m*IBG SOLUTION FOR INJECTION

Please refer to the current version of the [$^{124}$I]*m*IBG Solution for Injection Supply Guidelines available through the CRA or CSM at the Centre for Drug Development (CDD). The Investigator should inform the CSM and CRA when informed consent has been obtained from a patient. The Investigator should inform the CSM and CRA of the planned dates of the [$^{123}$I]*m*IBG planar scintigraphy ± SPECT scan and the [$^{124}$I]*m*IBG PET/CT scan as soon as they are known. The CSM or CRA will complete a manufacture request form and submit this to the WMIC. The Investigator must not submit a request for manufacture directly to the WMIC as this must be approved by the CDD as sponsor. The Investigator should inform the CSM and CRA as soon as they are aware that a patient will not be participating in the [$^{124}$I]*m*IBG scanning.

Each imaging centre will agree the local scheduling options for [$^{124}$I]*m*IBG PET/CT scanning with the WMIC and the CSM at the CDD before they open to recruitment of patients. The agreed schedules will be based on the [$^{124}$I]*m*IBG Solution for Injection Supply Guidelines and the schedule of the local imaging department with scenarios for the main study and the appropriate sub-study.

## 7.6 EVALUATIONS DURING THE STUDY (NOVEL IMAGING)

Following [$^{123}$I]*m*IBG planar scintigraphy ± SPECT for routine clinical care of neuroblastoma, patients will only continue in the study and undergo [$^{124}$I]*m*IBG imaging if they fulfil the additional clinical criteria outlined in Section 4.1.3.

### 7.6.1 [$^{124}$I]*m*IBG PET/CT scan

**Day -1 Thyroid blockade**
All patients will receive thyroid blockade (i.e. potassium iodide) for five consecutive days, starting the day before administration of [$^{124}$I]*m*IBG solution injection, i.e. one dose of potassium iodide taken on the day before the administration of [$^{124}$I]*m*IBG solution and 4 once daily doses of potassium iodide following the administration of [$^{124}$I]*m*IBG solution for a total of 4 days (please see section 7.9 Schedule of Events). Apart from the duration of dosing (i.e. the total number of days), the thyroid blockade administration should be administered according to the standard local practice for [$^{131}$I]*m*IBG therapy.

**Day 1 [$^{124}$I]*m*IBG administration**
A minimum interval of 72 hours is required between injection of [$^{123}$I]*m*IBG and the [$^{124}$I]*m*IBG PET/CT scan to ensure scan quality. See Sections 5.2 and 6.3 for guidance on dose and administration.

**Day 2 [$^{124}$I]*m*IBG PET/CT scan**

To be performed **24 h (± 3 h) post-administration of [$^{124}$I]*m*IBG**. The patient's temperature, BP and pulse should be measured and an assessment of AEs and concomitant medications made during this visit to assess the safety of the [$^{124}$I]*m*IBG tracer administered on the previous day. If the scan schedule is likely to exceed 75 minutes as described in the study Information sheets and consent or assent forms then this should be discussed with the patient prior to the injection of [$^{124}$I]*m*IBG to seek verbal consent. Any discussions should be documented in the patients' medical notes.

### 7.6.2 [redacted]

[redacted]

### 7.6.3 [redacted]

[redacted]

## 7.7 'OFF-STUDY' ASSESSMENT (DAY 3 TO DAY 7)

The patient should not receive any anti-cancer therapy or investigational drugs until the Investigator has assessed whether there are any ongoing toxic manifestations related to [$^{123}$I]*m*IBG or [$^{124}$I]*m*IBG administration unless this therapy is required in response to an urgent medical need. This assessment of AEs and concomitant medications should either take place between Day 3 to Day 7, either during a routine visit to the clinic or by telephone. Anti-cancer therapy or investigational drugs may commence at the earliest on Day 3 after the Off-Study assessment has been completed.

## 7.8 FOLLOW-UP

AEs considered to have a highly probable, probable or possible causal relationship to [$^{123}$I]*m*IBG and/or [$^{124}$I]*m*IBG present at the time of the Off-Study assessment should be followed until resolution, recovery to baseline, or stabilisation of these events, unless the patient starts another anti-cancer therapy.

## 7.9 SCHEDULE OF EVENTS

| Observation/Investigation | Screening | During the study | | | | | | Off-study |
|---|---|---|---|---|---|---|---|---|
| | Day -28 to enrolment | Day -21 to -3[e] | Day -7 to 1[f] | Day 1 | Day 2 | Day 3 | Day 4 | Day 3-7[m] |
| Written informed consent[a] | X | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | |
| Demographics | X | | | | | | | |
| Medical history[b] | X | | | | | | | |
| Routine imaging: conventional cross sectional CT/MRI[c] | X | | | | | | | |
| Adverse event evaluation[d] | Continuously monitored from time of consent until Off-study | | | | | | | |
| Concomitant treatments | Continuously monitored from time of consent until Off-study | | | | | | | |
| Physical examination | X | | | | | | | |
| Height and weight | X | | | | | | | |
| WHO or Lansky performance status | X | | | | | | | |
| Enrolment on the study | X | | | | | | | |
| [$^{123}$I]*m*IBG administration[e] | | X | | | | | | |
| [$^{123}$I]*m*IBG planar scintigraphy ± 3D imaging by SPECT[e] | | X | | | | | | |
| Serum or urine pregnancy test[g] | | | X[f] | | | | | |
| Temperature, blood pressure, pulse | | | X[f] | | X | | | |
| Full blood count and biochemistry[h] | | | X[f] | | | | | |
| Thyroid blockade[i] | | | X | X | X | X | X | |
| [$^{124}$I]*m*IBG administration | | | | X | | | | |
| [$^{124}$I]*m*IBG PET/CT scan[j] | | | | | X | | | |

[redacted]

Footnotes:

a **Informed consent** from the patient's parent or guardian is required for all patients under 16 years of age. Written or verbal assent will be sought form all patients under 16 years of age. Informed consent is required from all patients aged 16 or above.

b Relevant **medical history** including prior diagnosis, genetic findings to include *MYCN*, 11q, 17q and other segmental chromosomal abnormalities of prognostic impact in neuroblastoma, histological findings according to The International Neuroblastoma Pathology Classification (the Shimada system), prior treatment for neuroblastoma (stage 4 disease only) and concomitant diseases.

c Routine **imaging** for assessment of neuroblastoma including conventional cross sectional CT and/or MRI as clinically indicated. This routine imaging must be performed during a break in treatment and within the 28 days before administration of [$^{124}$I]*m*IBG.

d **Adverse events (AEs)**, including serious adverse events (SAEs), must be monitored from the time the patient consents/assents to any protocol-specific procedure. The Investigator should determine the start and stop date of an AE together with the relationship of the event to [$^{124}$I]*m*IBG. All AEs must be graded according to NCI CTCAE Version 4.02. All AEs and any concomitant treatment must be recorded in the medical records and in the eCRF. (See Section 8.3 for further details regarding the definition of AEs and reporting requirements.)

e **[$^{123}$I]*m*IBG planar scintigraphy ± SPECT** should be performed following an interval of at least 7 days from previous anti-cancer therapy. A minimum interval of 72 hours is required between injection of [$^{123}$I]*m*IBG tracer and the [$^{124}$I]*m*IBG PET/CT scan. Thyroid blockade should be given according to local practice for administration of [$^{123}$I]*m*IBG.

f Day -7 to 1 assessments should only be performed after the results of [$^{123}$I]*m*IBG planar scintigraphy confirm the presence of at least 1 lesion.

g Menarchal females should have a serum or urine HCG test to rule out **pregnancy**. A negative result must be obtained before the administration of [$^{124}$I]*m*IBG.

h **Full blood count** to include haemoglobin, WBC with differential count (ANC and lymphocytes) and platelets, and biochemistry to include serum bilirubin, ALT or AST or ALP, creatinine). Refer to Section 4.1.3 Clinical Criteria for [$^{124}$I]*m*IBG imaging for required values.

i For administration of [$^{123}$I]*m*IBG **thyroid blockade** should be given according to local practice. For administration of [$^{124}$I]*m*IBG, potassium iodide should be given for five consecutive days, starting the day before [$^{124}$I]*m*IBG administration, according to local practice for administration of [$^{131}$I]*m*IBG.

j **[$^{124}$I]*m*IBG PET/CT scan** to be performed 24 h (± 3 h) after the administration of [$^{124}$I]*m*IBG. A minimum interval of 72 hours is required between injection of [$^{123}$I]*m*IBG tracer and the [$^{124}$I]*m*IBG PET/CT scan. The Investigator must ensure patients meet the Clinical Criteria for [$^{124}$I]*m*IBG imaging described in section 4.1.3 before administration of [$^{124}$I]*m*IBG Solution for Injection.

k [redacted]

l [redacted]

m The Investigator should make an assessment of AEs and record concomitant medications either during a routine visit to the clinic or by telephone between Day 3 to Day 7. Patients should not receive any anti-cancer therapy or investigational drugs until after this Off-Study Assessment. AEs considered to have a highly probable, probable or possible causal relationship to [$^{124}$I]*m*IBG still present at the Off-study assessment should be followed until resolution, recovery to baseline, or stabilisation of these events, unless the patient starts another anti-cancer therapy.

# 8 ASSESSMENT OF SAFETY

## 8.1 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for monitoring the safety of patients who have enrolled in the study and for accurately documenting and reporting information as described in the following sections.

## 8.2 MEDICAL COVER

The Principal Investigator (PI) is responsible for ensuring patients have access to 24 hour advice and/or care. Patients will be provided with the necessary contact numbers for both normal working and out of hours care. A copy of the protocol must be made available out of hours to ward staff and clinicians on call so that the appropriate advice may be given to the patient, the patient's relative or other care giver (for example General Practitioner (GP)). The CI/PI must ensure that should the on call clinician or ward staff require more advice than is in this protocol, that they have access to the Investigator or delegated members of the clinical team who can answer any questions.

## 8.3 ADVERSE EVENT DEFINITIONS

### 8.3.1 Adverse event (AE)

An AE is any untoward, undesired or unplanned occurrence in a patient administered an IMP, a comparator product or an approved drug. An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP or comparator.

An AE includes but is not limited to those in the following list.

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.
- AEs occurring from lack of efficacy of an IMP, for example, if the Investigator suspects that a drug batch is not efficacious.

Other reportable events that must be treated as AEs are listed below.

- Pregnancy exposure to the IMP. Any pregnancy occurring in a patient or a patient's partner during exposure to an IMP or occurring within 7 days of the last IMP administration, must be reported to the Pharmacovigilance Department in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the study.
- Overdose with or without an AE.
- Inadvertent or accidental exposure to an IMP with or without an AE, including for example, spillage of the IMP that contaminates staff.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the study.

### 8.3.2 Serious adverse event (SAE)

An SAE is any AE, regardless of dose, causality or expectedness, that:

- results in death;

- is life-threatening*;
- requires in-patient hospitalisation or prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting – see Section 8.4);
- results in persistent or significant incapacity or disability;
- is a congenital anomaly or birth defect;
- is any other medically important event.**

* A life-threatening event is defined as an event when the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

** A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

For fatal SAEs, wherever possible report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term. When available the autopsy report will be provided to the Sponsor.

If during the course of the study, other medically important events are identified and there is a requirement to report specific events outside of the standard criteria, this will be communicated to site and the protocol will be updated to reflect this.

### 8.3.3 Determining AE causality

The relationship of an AE to the IMP is determined as follows.

| |
|---|
| **Highly probable**<br>• Starts within a time related to the IMP administration and<br>• No obvious alternative medical explanation. |
| **Probable**<br>• Starts within a time related to the IMP administration and<br>• Cannot be reasonably explained by known characteristics of the patient's clinical state. |
| **Possible**<br>• Starts within a time related to the IMP administration and<br>• A causal relationship between the IMP and the AE is at least a reasonable possibility. |
| **Unlikely**<br>• The time association or the patient's clinical state is such that the study drug is not likely to have had an association with the observed effect. |
| **Not related** |

- The AE is definitely not associated with the IMP administered.

*Note: Drug-related refers to events assessed as possible, probable or highly probable.*

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP(s), other illness, progressive malignancy etc) and must provide his/her opinion of the causal relationship between each AE and each IMP(s). This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

### 8.3.4 Expectedness

Assessment of expectedness will be made by the Pharmacovigilance Department against the current version of the Investigator Brochure for [$^{124}$I]*m*IBG and the current SmPC for [$^{123}$I]*m*IBG.

### 8.3.5 Suspected, unexpected, serious, adverse reactions (SUSARs)

A SUSAR is a suspected, unexpected, serious adverse reaction. All AEs and SAEs will be assessed by CDD for seriousness, causality and expectedness. The Pharmacovigilance Department will expedite all SUSARs to the relevant Competent Authority/Authorities and the relevant Research Ethics Committee (REC) within the timelines specified in legislation (SI 2004/1031 as amended).

## 8.4 COLLECTION OF SAFETY INFORMATION

### 8.4.1 Screening failures

For patients who fail screening, SAEs must be reported to the Pharmacovigilance Department, CDD from the date of consent until the date the patient is confirmed as ineligible.

### 8.4.2 Eligible patients

For eligible patients, SAE and AE collection and monitoring will commence at the time the patient gives their written consent to participate in the trial by signing the main study consent form and will continue until 7 days after the last administration of IMP or until the patient starts another anti-cancer therapy.

Should an Investigator become aware of any drug-related SAEs after this 7 day period, these must also be reported to the CDD within the expedited timelines in Section 9.4.

### 8.4.3 Follow-up of AEs and SAEs

Follow-up of AEs with a causality of possible, probable or highly probable will continue until the events resolve, stabilise or the patient starts another anti-cancer therapy.

The Pharmacovigilance Department will make requests for further information on SAEs to the trial site at regular intervals. Requested follow-up information should be reported to the Pharmacovigilance Department in a timely manner and as soon as possible after receipt of the follow-up request. For fatal or life-threatening cases, follow-up information must be reported to the Pharmacovigilance Department as soon as possible.

### 8.4.4 Other safety information of interest

We will also collect information on the following situations, whether they are associated with an AE or not:

- Overdose *(any dose above that specified in the protocol, not necessarily intentional)*

- Abuse or misuse
- Medication error *(any unintentional error in the dispensing or administration of an IMP)*
- Occupational exposure *(to a person other than the patient, for example spilling of IMP on hands of nurse or splashing in the eye)*

Any occurrences of these should be reported in the same manner as SAEs (Section 9.4).

## 8.5 EXPEDITED REPORTING OF SAEs TO PHARMACOVIGILANCE

All SAEs, regardless of causality, must be reported to the Pharmacovigilance Department in an expedited manner.

SAEs should be documented on an SAE report form, using the completion guidelines provided.

**The SAE report form should be emailed to Pharmacovigilance Department within 24 hours of site staff becoming aware of the SAE.**

**Email: SAE@cancer.org.uk**

Each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 4.02 must be used to grade each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the Pharmacovigilance Department on a new SAE report form.

If the SAE has not been reported within the specified timeframes, a reason for lateness must be added on the email cover sheet when sending the SAE report form to the Pharmacovigilance Department.

Should the Investigator become aware of any drug-related SAEs after the patient goes 'off study', these must also be reported to the Pharmacovigilance Department within the specified timelines above.

### 8.5.1 Events exempt from reporting as SAEs to Pharmacovigilance

Events specified in this section do not require reporting as SAEs in this study, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the eCRF.

**Elective admissions** – Elective admissions to hospital for procedures which were planned prior to entering the trial are not SAEs. Hospitalisation for administration of an IMP and conduct of scans according to the study protocol is also exempt from being reported as an SAE.

## 8.6 RECORDING OF AEs AND SAEs IN eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the study. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The CDD Medical Advisor and the Investigator(s) will regularly review the safety data from both the safety and the clinical database.

## 8.7 FOLLOW-UP OF AEs AND SAEs

Follow-up will continue until all the necessary safety data for the event has been gathered and until resolution, recovery to baseline, or stabilisation of these events, unless the patients starts another

anti-cancer therapy. The Pharmacovigilance Department will make requests for further information to the study site at regular intervals. Requested follow-up information should be reported to the Pharmacovigilance Department in a timely manner and as soon as possible after receipt of the follow-up request. For fatal or life-threatening cases, follow-up information should be reported to the Pharmacovigilance Department as soon as possible.

## 8.8 URGENT SAFETY MEASURES

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical study against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority.

The Medicines and Healthcare products Regulations Agency (MHRA) and the REC must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

- email: sae@cancer.org.uk; or
- telephone: 0203 469 6905;

The notification must include:

- the date of the USM;
- who took the decision; and
- why action was taken.

The Sponsor will then notify the MHRA and the REC within three days of USM initiation.

## 8.9 PREGNANCY

Female patients who become pregnant from the time of informed consent being signed to off-study, must be withdrawn from study treatment immediately.

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for seven days afterwards. This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

- oral contraceptives and condom;
- intra-uterine device (IUD) and condom;
- diaphragms with spermicidal gel and condom.
- Contraception should be effective before the patient is enrolled on the trial, throughout the trial and for six months after the administration of [$^{124}$I]*m*IBG.

- It should be explained to the patient that if his partner is pregnant or breast-feeding when he is enrolled on the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn baby or the baby being exposed to the [$^{124}$I]*m*IBG.

- However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed.

Any pregnancy occurring in a patient or a patient's partner occurring within seven days of administration of either [$^{123}$I]*m*IBG or [$^{124}$I]*m*IBG must be reported to the Pharmacovigilance Department within 24 hours of the site staff becoming aware of it using a Pregnancy Report Form (provided in the ITF). It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. In addition, the Investigator must be made aware of the need to obtain contact details for the patient's partner's General Practitioner. The Pharmacovigilance Department will follow-up all pregnancies for the pregnancy outcome via the Investigator, using a Pregnancy Report Form.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to seven days after the last [$^{124}$I]*m*IBG administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until the conclusion of the pregnancy, if the patient or patient's partner has consented to this. Monitoring of the baby should continue until 12 months after birth, if the patient or patient's partner has consented to this.

# 9 ASSESSMENT OF IMAGING TECHNIQUES

## 9.1 PRIMARY ANALYSIS

Analysis of [$^{124}$I]*m*IBG PET/CT and [$^{123}$I]*m*IBG planar scintigraphy will be performed retrospectively by an agreed number of observers who are experienced in the assessment of neuroblastoma. The observers will perform the analysis separately from each other and will be blinded from the scores of the other observers. An observer will perform their review of each modality for a patient several weeks apart. [$^{123}$I]*m*IBG imaging and [$^{124}$I]*m*IBG PET/CT imaging will be reviewed on a Hermes workstation (Hermes Medical Solutions, Sweden). Observers may perform their assessment of study imaging data in batches throughout the study but will not share their scores until the conditions are met to trigger the interim and final analyses as described in section 12.2.

For each modality, suspected lesions will be judged positive, negative, or equivocal with regard to neuroblastoma involvement by each observer. A final determination of each lesion as positive, negative or equivocal will be established through consensus between all observers:

- Positive – all reviewers consider it positive
- Negative – all reviewers consider it negative
- Equivocal – fewer than all reviewers can agree on whether the lesion is positive or negative

The scores for each modality will be submitted to the statistician at the interim and final analyses to meet the primary endpoint. The percentage of positive findings identified on routine [$^{123}$I]*m*IBG planar scintigraphy also identified by the novel [$^{124}$I]*m*IBG PET/CT will be determined. Recruitment will cease during the interim analysis.

## 9.2 SECONDARY ANALYSIS

The agreed number of experienced observers will perform the same analysis of [$^{123}$I]*m*IBG scintigraphy by 3D SPECT where this was performed as part of the routine imaging for a patient. Using the method described in Section 9.1 the observers will score suspected lesions for this modality. The percentage of positive findings identified on routine [$^{123}$I]*m*IBG scintigraphy by 3D SPECT also identified by the novel [$^{124}$I]*m*IBG PET/CT will be determined.

## 9.3 TERTIARY ANALYSES

[redacted]

[redacted]

[redacted]

[redacted]

# 10 PATIENT WITHDRAWAL BEFORE COMPLETION OF IMAGING SCHEDULE

The Investigator must make every reasonable effort to keep each patient on study for the whole duration of the study (i.e. until the Off-Study assessment has been completed). However, if the Investigator removes a patient from the study or if the patient declines further participation, the 'off-study' assessments should ideally be performed before any subsequent therapeutic intervention. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the study, must be recorded in the medical records and in the eCRF.

Patients who are removed from the study due to AEs (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the SAE report form where necessary.

The following are justifiable reasons for the Investigator to withdraw a patient from the study.

- AE/SAE
- Withdrawal of consent or assent by a parent/guardian or by the patient as applicable
- Serious violation of the study protocol
- Sponsor's decision to terminate the study
- Failure to meet the Clinical Criteria for [$^{124}$I]*m*IBG imaging (section 4.1.3)
- Withdrawal by the Investigator for clinical reasons not related to the study imaging (including pregnancy)

# 11 DEFINING THE END OF TRIAL

The 'end of trial' will be declared when one of the following is fulfilled:

- [$^{124}$I]*m*IBG Solution for Injection is considered too toxic to scan any further patients before the required number of patients have been recruited.
- Following the interim analysis, it is confirmed the trial is to stop due to futility as per Section 12.1 (end of trial will be the date of this decision).
- Following the interim analysis, it is confirmed the trial is to stop due to efficacy as per Section 12.1 (end of trial will be the date of this decision).
- If recruitment continues as allowed under the protocol beyond the interim analysis. Last Patient Last Visit is defined as the date when the last patient completes their participation in the trial, which will be either completion of the Off-study assessment or early withdrawal from the trial.

It is the responsibility of the CDD to notify the MHRA and the REC of the 'end of the trial'.

In cases of early termination of the study (for example, due to toxicity) or a temporary halt by the CDD, the CDD will notify the MHRA and the REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given. The entire study will be terminated when:

- [$^{124}$I]*m*IBG Solution for Injection is considered too toxic to scan any further patients before the required number of patients have been recruited.
- The stated minimum number of evaluable patients has been reached.
- The stated objectives of the study are achieved.

Regardless of the reason for termination, all data available for patients at the time of termination of the study must be recorded in the eCRF.

# 12 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

## 12.1 SAMPLE SIZE

The primary endpoint of the study is the percentage of lesions identified as positive using [$^{123}$I]*m*IBG planar scintigraphy which are also identified as positive on [$^{124}$I]*m*IBG PET/CT. The definition of a positive lesion is described in section 9.1. The aim is to prove that there is more than 90% agreement between the methods, with an expected level of agreement of 97%. Patients are expected to have a median of 3 lesions. Lesions are assumed to be independent within patients for the primary analysis. The following two stage design will be used, where the true proportion of agreement is denoted by P:

In the first stage, a total of at least 9 patients will be recruited, with a combined total of at least 50 lesions positive on [$^{123}$I]*m*IBG. Initially an exact one-sided binomial test of the null hypothesis: P>=97% will be done using alpha=0.05. If this is rejected in favour of the alternative hypothesis P<97%, the trial will be stopped early for futility. With a total of exactly 50 lesions this will occur if 45 or fewer lesions are also positive on [$^{124}$I]*m*IBG PET/CT.

If the null hypothesis is accepted, a further one-sided binomial test of the null hypothesis: P<=90% will be done using alpha=0.025. If this is rejected in favour of the alternative hypothesis P>90% then the trial may be stopped early for efficacy. With a total of 50 lesions this will occur only if all 50 lesions are also positive in [$^{124}$I]*m*IBG PET/CT. If this null hypothesis is not rejected, the trial will continue to the second and final stage.

The second stage will end when an overall total of at least 33 patients with at least 100 lesions have been recruited. An exact one-sided binomial test of the null hypothesis: P<=90% will be done using alpha=0.025. If this is rejected in favour of the alternative hypothesis P>90% then the trial will be declared a success. With a total of 100 lesions this will occur if at least 96 lesions are also positive on [$^{124}$I]*m*IBG PET/CT.

Overall this design has 82% power and an alpha of 0.03. If the true percentage of agreement is 97% then there is a 22% chance of stopping early for efficacy, and if the true percentage of agreement of 90% then there is a 57% chance of stopping early for futility. The total sample size of 100 lesions was calculated based on a single stage A'hern design with p0=0.9 and p1=0.97, and the overall power and alpha has been calculated based on exact binomial probabilities.

## 12.2 INTERIM AND FINAL ANALYSIS

The interim analysis will be conducted once both of the following conditions are met:

- At least 50 lesions have been identified on [$^{123}$I]*m*IBG planar scintigraphy. These lesions will have been identified as positive by a Nuclear Medicine physician at the investigational site.

- A minimum of 9 evaluable patients have completed the study.

The analysis will be done using all identified lesions from at least 9 patients. Therefore, the total number of lesions is expected to be more than 50. The number of lesions identified on [$^{123}$I]*m*IBG planar scintigraphy will be reported to the CSM at the CDD at the time of sponsor authorisation of the supply of the [$^{124}$I]*m*IBG tracer from the manufacturing organisation to the investigational site. The CSM will communicate to the observers and the statistician when the conditions have been met to trigger the interim analysis.

The interim analysis will assess the primary endpoint by comparison of the number of positive lesions detected on [$^{123}$I]*m*IBG planar scintigraphy and [$^{124}$I]*m*IBG PET/CT in order to compare the two modalities. The imaging data will be analysed and scored separately by an agreed number of observers using the same scoring method as described in Section 9.1 in order to prevent subjective bias. Observers may perform their assessment of study imaging data prior to the interim and final

analyses in batches but will remain blinded to the scores of the other observers until the interim and final analyses are triggered and they meet to perform the consensus reviews. Assessment of the reported safety data will be performed at the interim review and will be considered as part of the decision whether to continue recruitment. The feasibility of recruitment of the required minimum number of patients will also be considered in this decision.

The final analysis will be conducted after one of the following conditions is met:

- The study is terminated early
- The end of trial as defined in Section 11 has been reached.

Following lesion detection the agreed number of experienced observers will also perform a semi-quantitative assessment of [$^{124}$I]*m*IBG PET/CT scans and [$^{123}$I]*m*IBG imaging employing SUVmean and SUVmax. The level of disease involvement will be assessed using the International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN) scoring method and the Curie scoring method (see Appendix 5).

### 12.2.1 Statistical Analysis of Primary Endpoint

The proportion of positive lesions detected by routine [$^{123}$I]*m*IBG planar scintigraphy which are also identified as positive using [$^{124}$I]*m*IBG PET/CT will be calculated. An exact one-sided binomial test of the null hypothesis that this proportion is not more than 90% will be performed, using an alpha of 0.025 to define significance.

### 12.2.2 Statistical Analysis of Secondary Endpoint

The proportion of positive lesions detected by routine [$^{123}$I]*m*IBG imaging using 3D SPECT which are also identified as positive using [$^{124}$I]*m*IBG PET/CT will be calculated. An exact one-sided binomial test of the null hypothesis that this proportion is not more than 90% will be performed, using an alpha of 0.05 to define significance.

### 12.2.3 Statistical Analyses of Tertiary Endpoints

[redacted]

[redacted]

### 12.2.4 Safety

Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics. Laboratory variables will be described using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02.

AEs will be reported and presented as tables of frequency of AEs by body system and by worse severity grade observed. Tables should indicate related and unrelated events.

## 12.3 PRESENTATION OF DATA

Data will be presented in a descriptive fashion. Variables will be analysed to determine whether the criteria for the study conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol violations, IMP accountability and other data that impact on the general conduct of the study.

Baseline characteristics will be summarised for all enrolled patients.

# 13 ADMINISTRATION

This study is conducted under a clinical trial authorisation (CTA) from the MHRA. The favourable opinion of the responsible REC will be obtained before the start of this study. This study is sponsored and monitored by the Cancer Research UK CDD. Applicable regulatory requirements are described in this section.

## 13.1 PROTOCOL DEVIATIONS AND AMENDMENTS

Do not deviate from the protocol unless approval has been obtained prospectively from the CDD.

Amendments to the protocol may only be made with the approval of the CDD. A protocol amendment may be subject to review by Cancer Research UK's Protocol Safety and Review Board (PSRB). Depending on the type of protocol amendment, the favourable opinion of the responsible Regulatory Ethics Committee (REC), Health Research Authority (HRA), and the approval of the Medicines and Healthcare products Regulatory Agency (MHRA) may be required. Where these approvals are required, written documentation must be received before the amendment can be implemented.

## 13.2 COMPLETION OF THE ELECTRONIC CASE REPORT FORM (ECRF)

Electronic CRFs approved by the CDD will be used to collect the data. The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs with reference to the timelines described in the agreement between the CDD and the NHS Trust.

Only the Investigator and those personnel who have signed the Delegation Log provided by the CDD and have been authorised by the Investigator should enter or change data in the eCRFs. Authorised users will be included on a User Management Tool form in order to be provided access to the eCRF. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference.

Data will be entered directly into electronic screens by authorised site personnel. Amendments to eCRF data will be made directly to the system and the system audit trail will retain details of the original value(s), who made the change, a date and time, and a reason for the change.

Once an eCRF form has been entered by the site personnel, the data are cleaned using manual and automated checks. Queries will be issued electronically to the site. Authorised personnel must answer the queries by making relevant amendments to data or providing a response. Answered queries will be closed or reissued as appropriate.

Once the patient is 'off study' and the eCRF has been fully completed, the Investigator must provide an electronic signature to authorise the complete subject casebook.

At the end of the study all eCRFs are retained and archived by the CDD and a PDF copy provided to the Investigator who is responsible for archiving at site.

## 13.3 STUDY PERFORMANCE AND MONITORING

Before the study can be initiated, the prerequisites for conducting the study must be clarified and the organisational preparations made with the study centre. The CDD must be informed immediately of any change in the personnel involved in the conduct of the study.

During the study the CDD Clinical Research Associate (CRA) is responsible for monitoring data quality in accordance with CDD's standard operating procedures (SOPs). Before the study start, the Investigator will be advised of the anticipated frequency of the monitoring visits and plans for remote monitoring by the CRA. The Investigator will receive reasonable notification before a monitoring visit.

A strategic monitoring approach, including targeted source data verification, will be implemented where appropriate

It is the responsibility of the CRA to:

- review study records and compare them with source documents
- discuss the conduct of the study and the emerging problems with the Investigator
- check that the drug storage, dispensing and retrieval are reliable and appropriate
- verify that the available facilities remain acceptable

Unused IMP will be safely secured and allowed to decay to acceptable limits (according to the local centre) for disposal via normal hospital route. Following disposal the authorised person will provide written confirmation.

It is the responsibility of the Sponsor to notify the REC of the 'end of the trial' (see definition in Section 11).

## 13.4 SOURCE DOCUMENT VERIFICATION

Unless agreed in writing, all data collected in the eCRF must be verifiable by the source data. Therefore it is the Investigator's responsibility to ensure that both he/she and his/her study team records all relevant data in the medical records. The Investigator must allow the CRA direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the verification will be recorded in the eCRF.

Some source data may exist only electronically and be entered, or loaded directly into the eCRF.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the CDD appointed to audit the study, NHS trust staff and by regulatory authorities and/or by National Health Service (NHS) Trust staff. Details will remain confidential and patients' names will not be recorded outside the hospital.

## 13.5 CLINICAL STUDY REPORT

At the interim analysis, the interim analysis report, and at regular intervals during the study data listings, will be prepared to give the Investigators and the CDD the possibility to review the data and check the completeness of information collected. All clinical data will be presented at the end of the study on final data listings. CDD will prepare a clinical study report based on the final data listings, formal analysis reports and imaging reports. The report will be submitted to the Investigators for review and confirmation it accurately represents the data collected during the course of the study. Summary results of the trial will be provided by the CDD to the MHRA and to the REC.

## 13.6 RECORD RETENTION

During the clinical study and after study closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical study and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the EU based upon Section 8 of the ICH GCP Guidelines), including source documents such as scans, study related documents and copies of the eCRFs, associated audit trail and SAE report forms, shall show whether the Investigator has complied with the principles and guidelines of GCP.

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the

minimum period required by national legislation or for longer if needed by CDD. Records must not be destroyed without prior written approval from CDD.

The medical files of study subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

## 13.7 ETHICAL CONSIDERATIONS

Before starting the study, the protocol, patient information sheet and consent/assent forms must go through the CDD's external review process, and be approved by the PSRB and the responsible REC.

It is the Chief/Principal Investigator's responsibility to update patients and/or the patient's parent or guardian as applicable whenever new information (in nature or severity) becomes available that might affect the patient's, or parent or guardian's willingness for the patient, to continue in the study. The Chief/Principal Investigator must ensure this is documented in the patient's medical notes and the patient and/or the patient's parent or guardian as applicable provides informed consent.

The Sponsor and Chief/Principal Investigator must ensure that the study is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended), the ICH GCP guidelines and the WMA Declaration of Helsinki (Appendix 1).

## 13.8 INDEMNITY

This study is sponsored by Cancer Research UK and therefore injury to a patient caused by the compounds under study will not carry with it the right to seek compensation from the pharmaceutical industry. Cancer Research UK will provide patients with compensation for adverse side effects, in accordance with the principles set out in the Association of the British Pharmaceutical Industry (ABPI) guidelines on compensation for medicine-induced injury.

## 13.9 PUBLICATION POLICY AND PRESS RELEASES

Results of this study must be submitted for publication. The CDD must be involved in reviewing all drafts of the manuscripts, abstracts, press releases and any other publications. Manuscripts must be submitted to CDD at least 60 days in advance of being submitted for publication to allow time for CDD to schedule a review and resolve any outstanding issues. Abstracts and press releases must be submitted to CDD at least 30 days in advance of being released. Authors must acknowledge that the study was sponsored by and performed with the support of CDD. The contribution of the CDD should be recognised by at least one member of staff being included as an author on publications.

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# 15 APPENDICES

## 15.1 APPENDIX 1: DECLARATION OF HELSINKI

**Recommendations guiding physicians in biomedical research involving human subjects**

**Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964,
amended by the 29th World Medical Assembly Tokyo, Japan, October 1975,
and the 35th World Medical Assembly, Venice, Italy, October 1983
and the 41st World Medical Assembly, Hong-Kong, September 1989
and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996**

**INTRODUCTION**

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

**I - BASIC PRINCIPLES**

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and

regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

**II - <u>MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE</u>**
**(Clinical research)**

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent Committee (1,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

**III - <u>NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS</u>**
**(Non-clinical biomedical research)**

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

## 15.2 APPENDIX 2: WHO PERFORMANCE SCALE

For patients aged 13 years or older.

| Activity Performance Description | Score |
|---|---|
| Fully active, able to carry out all normal activity without restriction. | 0 |
| Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work. | 1 |
| Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 2 |
| Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours. | 3 |
| Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair. | 4 |

## 15.3 APPENDIX 3: LANSKY PLAY SCALE

Recommended for children aged 1 to 12 years as follows:

| | |
|---|---|
| Fully active and normal. | 100 |
| Minor restrictions in physically strenuous activity | 90 |
| Active, but tires more easily | 80 |
| Both greater restriction of, and less time spent in, active play | 70 |
| Up and around, but minimal active play; keeps busy with quieter activities | 60 |
| Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities | 50 |
| Mostly in bed; participates in quiet activities | 40 |
| In bed; needs assistance even for quiet play | 30 |
| Often sleeping; play entirely limited to very passive activities | 20 |
| No play; does not get out of bed | 10 |
| Unresponsive | 0 |

## 15.4 APPENDIX 4: DRUG INTERACTIONS WITH mIBG

(adapted from the Radiopharmacy Protocol of the Nuclear Medicine Department, Queen Elizabeth Hospital, Birmingham, UK and taken from the EANM 131I/123I-Metaiodobenzylguanidine (*m*IBG) Scintigraphy – Procedures Guidelines For Tumour Imaging)

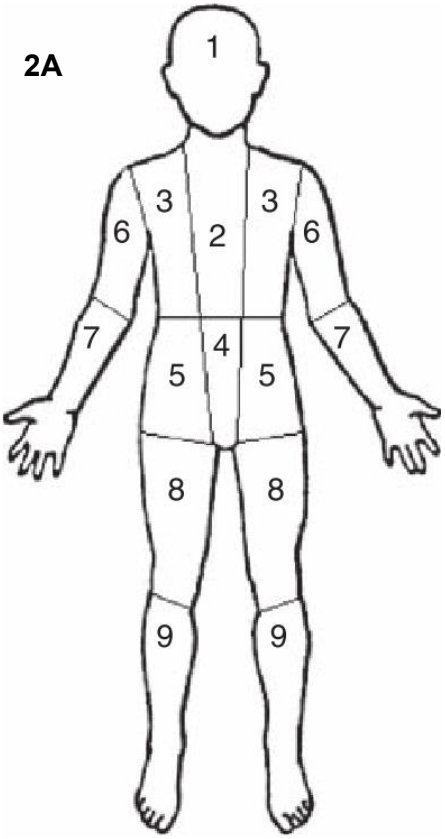
*Mechanisms of interaction
1 Inhibition of sodium-dependent uptake system (i.e. uptake-one inhibition)
2 Transport interference - inhibition of uptake by active transport into vesicles i.e. inhibition of granular uptake, and competition for transport into vesicles i.e. competition for granular uptake
3 Depletion of content from storage vesicles/granules
4 Calcium mediated
5 Other, possible, unknown mechanisms

| Drug Group | Approved name | Recommended withdrawal time | Mechanism of interaction * |
|---|---|---|---|
| **CARDIOVASCULAR AND SYMPATHOMIMETIC DRUGS** | | | |
| Anti-arrhythmics for ventricular arrhythmias | Amiodarone | Not practical to withdraw | **1,3** |
| Combined □□blocker | Labetalol | 72 hours | **1,3** |
| Adrenergic neurone blockers | Brethylium | 48 hours | *2,3* |
| | Guanethidine | 48 hours | *2,3* |
| | Reserpine | 48 hours | 2,3 |
| □- blockers | Phenoxybenzamine (IV doses only) | 15 days | **5** |
| Calcium channel blockers | Amlodipine | 48 hours | *4,5* |
| | Diltiazem | 24 hours | 4,5 |
| | Felodipine | 48 hours | *4,5* |
| | Isradipine | 48 hours | *4,5* |
| | Lacidipine | 48 hours | *4,5* |
| | Lercanidipine | 48 hours | *4,5* |
| | Nicardipine | 48 hours | 4,5 |
| | Nifedipine | 24 hours | 4,5 |
| | Nimodipine | 24 hours | 4,5 |
| | Nisoldipine | 48 hours | *4,5* |
| | Verapamil | 48 hours | **4,5** |
| Inotropic sympatho-mimetics | Dobutamine | 24 hours | *3* |
| | Dopamine | 24 hours | *3* |
| | Dopexamine | 24 hours | *3* |
| Vasoconstrictor sympathomimetics | Ephedrine | 24 hours | 1 |
| | Metaraminol | 24 hours | 3 |
| | Norepinephrine | 24 hours | 3 |
| | Phenylephrine | 24 hours | 3 |
| □2 stimulants (sympathomimetics) | Salbutamol | 24 hours | *3* |
| | Terbutaline | 24 hours | *3* |
| | Eformoterol | 24 hours | *3* |
| | Bambuterol | 24 hours | *3* |
| | Fenoterol | 24 hours | *3* |
| | Salmeterol | 24 hours | *3* |

| | | | |
|---|---|---|---|
| Other adrenoreceptor stimulants | Orciprenaline | 24 hours | *3* |
| Systemic and local nasal decongestants, compound cough and cold preparations | Pseudoephedrine | 48 hours | **3** |
| | Phenylephrine | 48 hours | **3** |
| | Ephedrine | 24 hours | **1** |
| | Xylometazoline | 24 hours | **3** |
| | Oxymetazoline | 24 hours | **3** |
| Sympathomimetics for Glaucoma | Brimonidine | 48 hours | *3* |
| | Dipivefrine | 48 hours | *3* |
| **NEUROLOGICAL DRUGS** | | | |
| Antipsychotics (neuroleptics) | Chlorpromazine | 24 hours | *1* |
| | Benperidol | 48 hours | *1* |
| | Flupentixol | 48 hours, or 1 month for depot | *1* |
| | Fluphenazine | 24 hours, or 1 month for depot | *1* |
| | Haloperidol | 48 or 1 month for depot | *1* |
| | Levomepromazine | 72 hours | *1* |
| | Pericyazine | 48 hours | *1* |
| | Perphenazine | 24 hours | *1* |
| | Pimozide | 72 hours | *1* |
| | Pipotiazine | 1 month for depot | *1* |
| | Prochlorperazine | 24 hours | *1* |
| | Promazine | 24 hours | *1* |
| | Sulpiride | 48 hours | *1* |
| | Thioridazine | 24 hours | *1* |
| | Trifluoperazine | 48 hours | *1* |
| | Zuclopenthixol | 48 hours, or 1 month for depot | *1* |
| | Amisulpride | 72 hours | *1* |
| | Clozapine | 7 days | *1* |
| | Olanzapine | 7 – 10 days | *1* |
| | Quetiapine | 48 hours | *1* |
| | Risperidone | 5 days or 1 month for depot | *1* |
| | Sertindole | 15 days | *1* |
| | Zotepine | 5 days | *1* |
| Sedating antihistamines | Promethazine | 24 hours | *1* |
| Opioid analgesics | Tramadol | 24 hours | **1** |
| Tricyclic anti-depressants | Amitriptyline | 48 hours | **1** |
| | Amoxapine | 48 hours | 1 |
| | Clomipramine | 24 hours | **1** |
| | Dosulepin (Dothiepin) | 24 hours | **1** |
| | Doxepin | 24 hours | 1 |
| | Imipramine | 24 hours | **1** |
| | Lofepramine | 48 hours | **1** |
| | Nortriptyline | 24 hours | 1 |
| | Trimipramine | 48 hours | **1** |
| Tricyclic-related anti-depressants | Maprotiline | 48 hours | *1* |
| | Mianserin | 48 hours | *1* |
| | Trazolone | 48 hours | *1* |
| | Venlaflaxine | 48 hours | *1* |
| | Mirtazepine | 8 days | *1* |
| | Reboxetine | 3 days | *1* |
| CNS Stimulants | Amphetamines eg Dexamfetamine | 48 hours | *3* |
| | Atomoxetine | 5 days | *1* |
| | Methylphenidate | 48 hours | *5* |
| | Modafinil | 72 hours | *5* |
| | Cocaine | 24 hours | **1** |
| | Caffeine | 24 hours | *5* |

## 15.5 APPENDIX 5: CURIE & SIOPEN SCORING METHODS FOR NEUROBLASTOMA

Figures 2A & 2B:



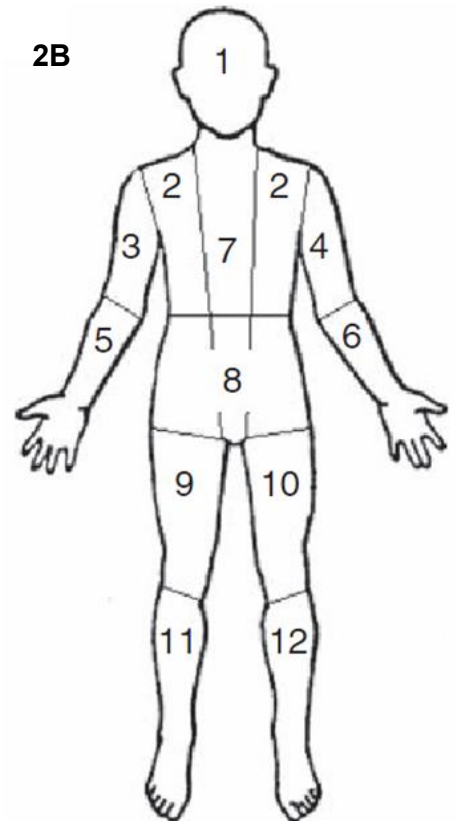




**Figure 2A; The Curie method.** This method divides the skeleton into nine segments to view osteomedullary involvement and adds a tenth sector that counts any soft tissue involvement to the score. The extension score for this method is graded as: 0. no sites per segment; 1. one site per segment; 2. more than one site per segment; and 3. diffuse involvement (>50% of the segment). The intensity score is graded as: 0. for no uptake; 1. for doubtful uptake; 2. for definite uptake less than liver; and 3. for intense uptake greater than that of liver. Thus, the maximum score for either extension or intensity would be 30. The Curie score has been shown to have a good inter-observer concordance of 92 and 95% in two independent studies. It has been validated in France and is now widely used in North America for the New Approaches to Neuroblastoma Therapy consortium and the Children's Oncology Group (COG).

**Figure 2B: The SIOPEN method**: the skeletal distribution of *m*IBG is recorded in 12 anatomical body segments as follows: skull, thoracic cage, proximal right upper limb, distal right upper limb, proximal left upper limb, distal left upper limb, spine, pelvis, proximal right lower limb, distal right lower limb, proximal left lower limb and distal left lower limb. The extent and pattern of skeletal *m*IBG involvement is scored using a 0–6 scale to discriminate between focal discrete lesions and patterns of more diffuse infiltration. Each segment is scored as 0. no involvement; 1. one discrete lesion; 2. two discrete lesions; 3. three discrete lesions; 4. > 3 discrete foci or a single diffuse lesion involving < 50% of a bone; 5. diffuse involvement of > 50 to 95% of an entire bone; 6, diffuse involvement of the entire bone, with a maximum score of 72. The SIOPEN score is the current method being used in Europe for a prospective phase 3 neuroblastoma trial.

# CANCER RESEARCH UK
# Statistical Analysis Plan

# A Cancer Research UK Phase I/II study to compare [$^{124}$I]*m*IBG PET/CT to [$^{123}$I]*m*IBG imaging in patients with metastatic neuroblastoma.

Sponsor protocol number: CRUKD/12/002

EudraCT number: 2012-002029-31


**Chief Investigator:**

Dr Sue Chua
Nuclear Medicine and PET
Department
Royal Marsden Hospital
[redacted]

**Sponsor:**

Cancer Research UK
Centre for Drug Development
[redacted]

## TABLE OF CONTENTS PAGE

## LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event |
| CRUK | Cancer Research UK |
| CT | computerised tomography |
| *m*IBG | *meta*-Iodobenzylguanidine |
| MRI | Magnetic resonance imaging |
| PET | Positron emission tomography |
| SPECT | Single-photon emission computed tomography |
| SUV | Standardised uptake value |
| UCLH | University College London Hospital |

## AMENDMENT HISTORY

| Date | Brief description of change | Justification for change |
|---|---|---|
| 07Sep2020 | Clarification to tertiary endpoint | [redacted]<br>Typography corrections. |
| 13Mar2020 | Update to study endpoints | Inclusion of confidence score method as a secondary objective.<br>To bring the Statistical Analysis Plan in line with protocol amendment 10 and 11.<br>Inclusion of details of the trial populations for clarity. |
| 01Aug2017 | Update to objectives | To bring the Statistical Analysis Plan in line with protocol amendment 9. |
| | N/A | |

# 1 Study Details

## *1.1 Protocol Synopsis and Background*

**Full Title:** A Cancer Research UK Phase I/II study to compare [$^{124}$I]*meta*-Iodobenzylguanidine (*m*IBG) positron emission tomography/computerised tomography (PET/CT) to [$^{123}$I]*m*IBG imaging in patients with metastatic neuroblastoma.

**Short Title:** A Phase I/II study of [$^{124}$I]*m*IBG PET/CT in neuroblastoma.

This is a multi-centre, non-therapeutic Phase I/II study directly comparing [$^{124}$I]*m*IBG positron emission tomography/computerised tomography (PET/CT) and conventional [$^{123}$I]*m*IBG imaging in patients with newly diagnosed, relapsed or refractory metastatic neuroblastoma. A minimum of nine evaluable patients will be scanned at two centres in the UK.

## *1.2 Clinical Study Objectives and Endpoints*

| **Primary objective** | **Endpoint** |
|---|---|
| 1. To show that [$^{124}$I]*m*IBG PET/CT can detect an equal or greater number of neuroblastoma lesions compared to conventional [$^{123}$I]*m*IBG planar scintigraphy. | 1. Comparison of the percentage of lesions detected as positive by [123I]mIBG planar scintigraphy which are also considered positive with [124I]mIBG PET/CT. |

| **Secondary objectives** | **Endpoints** |
|---|---|
| 1. To show that [$^{124}$I]*m*IBG PET/CT can detect an equal or greater number of neuroblastoma lesions compared to conventional [$^{123}$I]*m*IBG scintigraphy with 3D imaging by SPECT (single photon emission computerised tomography). | 1. Comparison of the percentage of lesions detected as positive by [123I]mIBG SPECT which are also considered positive with [124I]mIBG PET/CT. |
| 2. Assessing the safety and toxicity profile of a single intravenous administration of [$^{124}$I]*m*IBG. | 2. Determining the causality of each adverse event to [124I]mIBG and grading |

| Secondary objectives | Endpoints |
|---|---|
| | severity according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.02. |

| Tertiary objectives | Endpoints |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

| Tertiary objectives | Endpoints |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |

### *1.3 Study Design*

This is a multi-centre, non-therapeutic Phase I/II study directly comparing [$^{124}$I]*m*IBG PET/CT and conventional [$^{123}$I]*m*IBG imaging in patients with newly diagnosed, relapsed or refractory metastatic neuroblastoma. The study uses a modified Simon two-stage phase II design.

Patients who require routine conventional [$^{123}$I]*m*IBG planar scintigraphy as a means of assessing response to their ongoing treatment or for staging of their disease will be recruited. The majority of patients will also be planned to undergo 3D imaging by single-photon emission computed tomography (SPECT) as part of routine care where this is available. Additional [$^{124}$I]*m*IBG PET/CT imaging will take place approximately 3 to 21 days after routine [$^{123}$I]*m*IBG imaging and before the commencement of any new anti-cancer therapy.

There is one planned interim analysis which will be performed after a minimum of 50 lesions have been identified by [$^{123}$I]*m*IBG planar scintigraphy from a minimum of 9 evaluable patients

### *1.4 Number of Subjects*

The primary endpoint of the study is the percentage of lesions identified as positive using [$^{123}$I]*m*IBG planar scintigraphy which are also identified as positive on [$^{124}$I]*m*IBG PET/CT. The definition of a positive lesion is described in Section 9.1 of the clinical study protocol. The aim is to prove that there is more than 90 % agreement between the methods, with an expected level of agreement of 97 %. Patients are anticipated to have a median of 3 lesions. Lesions are assumed to be independent within patients for the primary analysis. The following two stage design will be used, where the true proportion of agreement is denoted by p.

In the first stage, a total of at least 9 evaluable patients will be recruited, with a combined total of at least 50 lesions positive on [$^{123}$I]*m*IBG PET/CT. Initially an exact one-sided binomial test of the null hypothesis: p>=97 % will be done using alpha (α)=0.05. If this is rejected in favour of the alternative hypothesis p<97 %, the study will be stopped early for futility. With a total of exactly 50 lesions this will occur if 45 or fewer lesions are also positive on [$^{124}$I]*m*IBG PET/CT.

If the null hypothesis is accepted, a further one-sided binomial test of the null hypothesis, p<=90%) will be done using α=0.025. If this is rejected in favour of the alternative hypothesis p>90% then the study may be stopped early for efficacy. With a total of 50 lesions this will occur only if all 50 lesions are also positive on [$^{124}$I]*m*IBG PET/CT. If this null hypothesis is not rejected, the study will continue to the second and final stage.

Only if following the interim analysis recruitment is to continue, a second stage will be required and will end when an overall total of at least 33 evaluable patients with at least 100 lesions have been recruited. An exact one-sided binomial test of the null hypothesis, p<=90%, will be done using alpha=0.025. If this is rejected in favour of the alternative hypothesis p>90% then the study will be declared a success. With a total of 100 lesions this will occur if at least 96 lesions are also positive on [$^{124}$I]*m*IBG PET/CT.

The overall study design including the second stage has 82 % power and an α of 0.03. If the true percentage of agreement is 97 % then there is a 22 % chance of stopping early for efficacy; if the true percentage of agreement of 90% then there is a 57 % chance of stopping early for futility. The total sample size of 100 lesions was calculated based on a single stage A'hern design with p0=0.90 and p1=0.97, and the overall power and α has been calculated based on exact binomial probabilities.

# 2 Analysis Sets

## *2.1 Definition of Analysis Sets*

The following trial populations have been defined for reporting purposes:

- Full Analysis Population: All patients enrolled to the study.
- Safety [$^{123}$I]*m*IBG Population: All patients who receive [$^{123}$I]*m*IBG (these patients may or may not have received [$^{124}$I]*m*IBG).
- Safety [$^{123}$I]*m*IBG and [$^{124}$I]*m*IBG Population: All patients who receive both [$^{123}$I]*m*IBG and [$^{124}$I]*m*IBG.
- Evaluable Population: Patients who received both [$^{123}$I]*m*IBG and [$^{124}$I]*m*IBG and underwent trial scanning with both agents. All lesions from these patients are considered independent of one another.
- [redacted]
- A sensitivity analysis will be informed in those in the evaluable population and have less than 10 lesions.

The primary analysis set will consist of all patients consented to the study, with at least one positive lesion recorded on routine [$^{123}$I]*m*IBG planar scintigraphy, who have also completed [$^{124}$I]*m*IBG PET/CT within 3 to 21 days as planned i.e. the Evaluable Population. Patients who did not undergo both [$^{123}$I]*m*IBG planar scintigraphy and [$^{124}$I]*m*IBG PET/CT will be excluded from this set, as will any patient where zero positive lesions were found on [$^{123}$I]*m*IBG planar scintigraphy, and patients with more than 21 days between [$^{123}$I]*m*IBG and [$^{124}$I]*m*IBG scans.

The safety analysis set for the secondary objective will consist of all patients consented to the study who received any dose of [$^{124}$I]*m*IBG at any time whether or not they subsequently completed any of the planned imaging procedures i.e. the Safety [$^{123}$I]*m*IBG and [$^{124}$I]*m*IBG Population. Additionally, all AEs occurring post consent and prior to [$^{124}$I]*m*IBG will be summarised (including those occurring post [$^{123}$I]*m*IBG administration).

## *2.2 Violations and deviations*

Taking the date of [$^{123}$I]*m*IBG scan as Day 0, patients whose [$^{124}$I]*m*IBG scans takes place on Day 22 or more will be excluded from the primary analysis set, but included in the safety set.

Patients who do not receive the planned injection of [$^{124}$I]*m*IBG will not be included in any statistical analysis, however their safety data will be summarised as described in Sections 2.1 and

# 3 3.1.5.Primary and Secondary endpoints

Each evaluable study patient will be assessed for disease using up to five different modalities:

[$^{124}$I]*m*IBG PET/CT (the experimental modality)

[$^{123}$I]*m*IBG planar scintigraphy (the primary comparator)

[$^{123}$I]*m*IBG planar scintigraphy + SPECT (a secondary comparator)

[redacted]

[redacted]

On each modality (unless otherwise stated), each of the following endpoints is recorded. [$^{124}$I]*m*IBG PET/CT and [$^{123}$I]*m*IBG planar scintigraphy results will be assessed by an agreed number of observers independently who will record all relevant endpoints as listed below. Prior to the interim analysis, the observers will meet to establish a consensus opinion and record their agreed consensus endpoints for each patient. The same procedure will take place prior to the final analysis, for all scans which had not previously been included in the interim analysis.

### *3.1.1 Total number of positive lesions recorded*

The total number of lesions will be provided to the Statistician via validated listings from the Sponsor. Data will be recorded in the eCRF by the Trial Manager at the Central Imaging Unit and Source Data Verified (SDV'd) by a Sponsor Clinical Research Associate. The Sponsor Clinical Study Manager will perform a data review before the eCRF is locked and listings are provided to the Statistician.

In summary, the following data will be provided to the Statistician for each evaluable patient for each imaging modality as calculated by each individual Reviewer and as a consensus:

- Number of lesions in each skeletal segment and total number of lesions using the CURIE method (i.e. all lesions with a score of 4 or 5) and also:
    - Total number of lesions with a confidence score of 1
    - Total number of lesions with a confidence score of 2
    - Total number of lesions with a confidence score of 3
    - Total number of lesions with a confidence score of 4
    - Total number of lesions with a confidence score of 5
- Number of lesions in each skeletal segment and total number of lesions using the SIOPEN method (i.e. all lesions with a score of 4 or 5) and also:
    - Total number of lesions with a confidence score of 1
    - Total number of lesions with a confidence score of 2
    - Total number of lesions with a confidence score of 3
    - Total number of lesions with a confidence score of 4
    - Total number of lesions with a confidence score of 5

For example, one Patient's PET/CT scan will have the data above provided but as three or more sets (for detail of the number of reviewers, see the Imaging Review Manual):

- Reviewer 1's data set
- Reviewer 2's data set
- Consensus data set

### *3.1.2 Confidence scores*

For each lesion (or for each SIOPEN area in which diffuse disease is noted), the observer (or group of observers for the consensus opinion) will also note a confidence score to measure their certainty of the lesion being malignant, on a 5 point scale from 1 (negative) to 5 (definitively positive). See section 3.1.1 detailing how this data will be provided to the Statistician.

### *3.1.3 SIOPEN scores*

SIOPEN scores will be recorded using standard scoring methods for each of the 12 defined skeletal areas. The SIOPEN scores will be provided to the Statistician via validated listings from the Sponsor. Data will be recorded in the eCRF by the Trial Manager at the Central Imaging Unit and Source Data Verified (SDV'd) by a Sponsor Clinical Research Associate. The Sponsor Clinical Study Manager will perform a data review before the eCRF is locked and listings are provided to the Statistician.

In summary, the following data will be provided to the Statistician for each patient for each imaging modality as calculated by each individual Reviewer and as a consensus:

- SIOPEN score

### *3.1.4 CURIE scores*

CURIE scores will be recorded using standard scoring methods for each of the 9 defined skeletal areas, and for soft tissue. The CURIE scores will be provided to the Statistician via validated listings from the Sponsor. Data will be recorded in the eCRF by the Trial Manager at the Central Imaging Unit and Source Data Verified (SDV'd) by a Sponsor Clinical Research Associate. The Sponsor Clinical Study Manager will perform a data review before the eCRF is locked and listings are provided to the Statistician.

In summary, the following data will be provided to the Statistician for each patient for each imaging modality as calculated by each individual Reviewer and as a consensus:

- CURIE score

### *3.1.5 Safety and toxicity*

Safety variables will be measured in the safety populations as noted in section 2.1.

AE's will be reported and presented as tables of frequency of AE's by body system, by worse severity grade observed and by causality. These will be completed by the Sponsor and will not be provided to the Statistician.

### *3.1.6* [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

### *3.1.7* [redacted]

[redacted]

[redacted]

[redacted]

### *3.1.8* [redacted]

[redacted]

[redacted]

[redacted]

# 4 Analysis Methods

## *4.1 General Principles*

All endpoints will be summarised using descriptive statistics. Rates will be summarised using counts and percentages, continuous variables will be summarised using n, mean, standard deviation, median and quartiles. Demographics will be presented for all patients in the safety analysis sets. Total numbers of patients in each analysis set will be given with explanations for any exclusions.

Agreement between the same endpoints measured using different modalities will be reported using descriptive statistics only (summary measures of agreement with 95% confidence intervals, and cross-tabulations or line listings directly comparing two sets of measurements) unless specified below.

Additional data may be summarised by CRUK as required for reporting and will be documented separately in the Clinical Study Report.

## *4.2 Analysis Methods*

### *4.2.1 Primary endpoint*

SIOPEN total numbers of lesions detected on [$^{124}$I]*m*IBG vs [$^{123}$I]*m*IBG will be compared as follows:

In the first stage, a total of at least 9 evaluable patients will be recruited, with a combined total of at least 50 lesions positive on [$^{124}$I]*m*IBG PET/CT. Initially an exact one-sided binomial test of the null hypothesis: p>=97 % will be done using alpha (α)=0.05. If this is rejected in favour of the alternative hypothesis p<97 %, the study will be stopped early for futility.

If the null hypothesis is accepted, a further one-sided binomial test of the null hypothesis, p<=90%) will be done using α=0.025. If this is rejected in favour of the alternative hypothesis p>90% then the study may be stopped early for efficacy. If this null hypothesis is not rejected, the study will continue to the second and final stage.

Only if following the interim analysis recruitment is to continue, a second stage will be required and will end when an overall total of at least 33 evaluable patients with at least 100 lesions have been recruited. An exact one-sided binomial test of the null hypothesis, p<=90%, will be done using alpha=0.025. If this is rejected in favour of the alternative hypothesis p>90% then the study will be declared a success.

All above tests will be done using the following method: For each patient, the total number of lesions assessed as positive by consensus opinion (with confidence score 4 or 5) on [$^{123}$I]*m*IBG planar scintigraphy is referred to as $n_{123}$, and the total number of lesions assessed as positive by consensus opinion (with confidence score 4 or 5) on [$^{124}$I]*m*IBG PET/CT is referred to as $n_{124}$, with the minimum of these two numbers known as $n_{min}$. The primary endpoint will be reported by the sum of $n_{min}$ over all patients, divided by the sum of $n_{123}$ over all patients.

In addition, for each patient the difference and ratios between $n_{123}$ and $n_{124}$ will be calculated and the distribution of these variables will be summarised using the median, upper and lower quartiles. The number and percentage of patients with $n_{124}/n_{123}$ less than 1, equal to 1 and greater than 1 will be reported.

Population to be used: Evaluable population & sensitivity population

### *4.2.2 Secondary endpoints*

SIOPEN numbers of positive lesions will be compared between [$^{124}$I]mIBG PET/CT vs. [$^{123}$I]mIBG planar scintigraphy+SPECT, using the same methodology and populations as for the primary endpoint.

The primary analysis and the above secondary analysis will be re-analysed using the CURIE score.

Safety and toxicity, are reported using descriptive statistics and line listings only, using the safety population

### *4.2.3 Tertiary endpoints*

*4.2.3.1* [redacted]

[redacted]

*4.2.3.2* [redacted]

[redacted]

[redacted]

[redacted]

*4.2.3.3* [redacted]

[redacted]

*4.2.3.4* [redacted]

[redacted]

*4.2.3.5* [redacted]

[redacted]

[redacted]

[redacted]

*4.2.3.6* [redacted]

[redacted]

# 5 Interim Analyses

The interim analysis should be performed at the first available timepoint after no less than 9 evaluable patients have completed both their [$^{123}$I]*m*IBG and [$^{124}$I]*m*IBG scans, and a combined total of at least 50 lesions have been found on [$^{123}$I]*m*IBG. At this point the consensus panel should meet to evaluate and record their opinions as soon as practically possible. Once this has been done, the interim analysis can be performed.

Initially an exact one-sided binomial test of the null hypothesis: p>=97% will be done using alpha=0.05. If this is rejected in favour of the alternative hypothesis p<97%, the study will be stopped early for futility.

If the null hypothesis is accepted, a further one-sided binomial test of the null hypothesis, p<=90%, will be done using α=0.025. If this is rejected in favour of the alternative hypothesis p>90% then the trial may be stopped early for efficacy. If this null hypothesis is not rejected, the trial will continue recruitment to the second and final stage.

The results of the interim analysis should be reported to the trial sponsor.

# 6 Timing of Statistical Analysis

The interim analysis will be performed as detailed in section 5. The final analysis should be performed after all patients recruited to the trial have undergone all scheduled on-trial scans,

# 7 Data checking plan

All data checking activities will be carried out by the study sponsor before transferring data for analysis. On receipt of data by the study statistician no further formal data checks will be made.

# 8 Signatures

**Study Statistician**

[redacted] Date

**Chief Investigator**

Sue Chua Date

# ADDENDUM

## CCR4051 124ImIBG: Statistical Analysis Plan

Following the statistical report review on 9th November 2020 by the internal and external mIBG Project Team, this addendum has been written to clarify the analysis of the mIBG trial endpoints.

| Primary objective | Endpoint | Change in analysis with rationale |
|---|---|---|
| 1. To show that [$^{124}$I]*m*IBG PET/CT can detect an equal or greater number of neuroblastoma lesions compared to conventional [$^{123}$I]*m*IBG planar scintigraphy. | 1. Comparison of the percentage of lesions detected as positive by [$^{123}$I]*m*IBG planar scintigraphy which are also considered positive with [$^{124}$I]*m*IBG PET/CT. | Analysis will be done per skeletal segment as defined in table 1 below. This is because each imaging modality covers specific skeletal areas. Again, this analysis will be repeated separately for soft tissue segment. |

| Secondary objectives | Endpoints | Change in analysis with rationale |
|---|---|---|
| 1. To show that [$^{124}$I]*m*IBG PET/CT can detect an equal or greater number of neuroblastoma lesions compared to conventional [$^{123}$I]*m*IBG scintigraphy with 3D imaging by SPECT (single photon emission computerised tomography). | 1. Comparison of the percentage of lesions detected as positive by [$^{123}$I]*m*IBG SPECT which are also considered positive with [$^{124}$I]*m*IBG PET/CT. | Analysis will be done per skeletal segment as defined in table 1 below. This is because each imaging modality covers specific skeletal areas. Again, this analysis will be repeated separately for soft tissue segment. |
| 2. Assessing the safety and toxicity profile of a single intravenous administration of [$^{124}$I]*m*IBG. | 2. Determining the causality of each adverse event to [$^{124}$I]*m*IBG and grading severity according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.02. | N/A |

| Tertiary objectives | Endpoints | Change in analysis with rationale |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

| Tertiary objectives | Endpoints | Change in analysis with rationale |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

**Others:**

- Summary of SIOPEN & CURIE scores will be reported descriptively as mean, SD, median, IQR and ranges.
- Sensitivity/Specificity to be calculated on positive lesions for each imaging modality, [123I]mIBG planar scintigraphy, [123I]mIBG SPECT and [124I]mIBG PET/CT versus the gold standard of the consensus results (from the combined read of [123I]mIBG planar scintigraphy, [123I]mIBG SPECT and [124I]mIBG PET/CT) for all patients and patients with < 20 lesions.

**Table 1: Summary of skeletal segments per each imaging modality.**

| Skeletal Segments | | Subject: | | | [redacted] |
|---|---|---|---|---|---|
| Curie | SIOPEN | [$^{123}$I] *m*IBG Planar | [$^{123}$I] *m*IBG SPECT/CT | [$^{124}$I] *m*IBG PET/CT | [redacted] |
| | | Vertex to feet | Abdomen & pelvis | Vertex to feet | [redacted] |
| Skull & facial bones | Skull & facial bones | ✓ | × | ✓ | [redacted] |
| Thorax | Thorax | ✓ | ✓ | ✓ | [redacted] |
| Humeri | Humeri L | ✓ | × | ✓ | [redacted] |
| | Humeri R | ✓ | × | ✓ | [redacted] |
| Forearms | Forearms L | ✓ | × | ✓ | [redacted] |
| | Forearms R | ✓ | × | ✓ | [redacted] |
| Spine C/T (includes Sacrum) | Spine (includes Sacrum) | ✓ | ✓ | ✓ | [redacted] |
| Spine L/S (includes Sacrum) | | ✓ | ✓ | ✓ | [redacted] |
| Pelvis | Pelvis | ✓ | ✓ | ✓ | [redacted] |
| Femora | Femora L | ✓ | × | ✓ | [redacted] |
| | Femora R | ✓ | × | ✓ | [redacted] |
| Tibiae/fibulae | Tibiae/fibulae L | ✓ | × | ✓ | [redacted] |
| | Tibiae/fibulae R | ✓ | × | ✓ | [redacted] |
| Soft Tissue | Soft Tissue | ✓ | ✓ | ✓ | [redacted] |

**Authorisation**

Author

Signature: ……Date: ……

Name & Position: [redacted]

Peer Reviewer

Signature: ……Date: ……

Name & Position: [redacted]

Approval

Signature: …… Date: ……

Name & Position: Dr Sue Chua (CI)