Clinical trial results:
Diagnostic accuracy of neuroblastoma patient imaging with 18F-mFBG PET-CT compared to 123I-mIBG scanning

Summary

EudraCT number	2019-003713-33
Trial protocol	NL
Global end of trial date	01 September 2021

Results information

Result version number	v1 (current)
This version publication date	07 June 2022
First version publication date	07 June 2022

Trial information

Trial identification

Sponsor protocol code	70903

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Dutch Trial Register: NL8152

Notes:

Sponsors

Sponsor organisation name	Princess Máxima Center for pediatric oncology
Sponsor organisation address	Heidelberglaan 25, Utrecht, Netherlands, 3584CS
Public contact	Dr. G.A.M. Tytgat, Princess Máxima Center for Pediatric Oncology, G.A.M.Tytgat@prinsesmaximacentrum.nl
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2021
Global end of trial reached?	Yes
Global end of trial date	01 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To perform 18F-MFBG PET-CT imaging in neuroblastoma patients and compare results with the current standard of imaging, 123I-MIBG imaging, using the SIOPEN score for skeletal lesions and the number of detected soft tissue lesions as endpoints.

Protection of trial subjects:

- The final 18F-MFBG drug product batches underwent quality control testing, before batch release for patient administration.
- Adverse events were not expected. However, patients were monitored after injection for 180 minutes. Furthermore, 3–7 days after the procedure a medical doctor conducted a telephone consultation to check for adverse events up to 72 hours after injection.
- Monitors of the trial ensured that the clinical trial is conducted, recorded, and reported in accordance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

Background therapy:

Recently, meta-18F-fluorobenzylguanidine (18F-mFBG), was developed to overcome the 123I-mIBG-associated disadvantages. As an analogue of mIBG, 18F-mFBG also targets the norepinephrine transporter, only 18F-MFBG is labelled with a positron-emitting radioisotope, fluorine-18, enabling imaging by positron emission tomography (PET) scanning. Compared to scintigraphy/SPECT, PET is a superior imaging technique that offers high resolution imaging, more accurate quantification of tracer uptake (using SUV measurements), whole-body 3D PET-CT range, a shorter acquisition time (10min) with less procedural sedation needed. In addition, the use of 18F-mFBG allows for a single-day protocol (possible to scan ≤2h after injection), and no need for thyroid-blocking medication.

To date, there is only in-human study studying 18F-mFBG including five patients with neuroblastoma, with no adverse reaction in any of the patients. 18F-mFBG has a similar distribution as 123I-mIBG, with similar lesion uptake, but much faster uptake of the more hydrophilic 18F-MFBG enabling high-contrast visualisation of lesions as early as one hour after injection. In this small study, 18F-mFBG PET-CT detected more lesions 123I-mIBG scanning (122 vs. 63 lesions, respectively). Although 18F-mFBG is a promising tracer, there is limited experience of the use of 18F-mFBG imaging in neuroblastoma. Safety, optimal imaging time and diagnostic accuracy of 18F-mFBG scanning are yet to be established.

Evidence for comparator:

meta-123I-iodobenzylguanidine (123I-mIBG) scanning is currently the first-line nuclear imaging technique that is routinely used for diagnosis, staging, and follow-up of neuroblastoma. MIBG is a norepinephrine analogue that can specifically detect tumours expressing the norepinephrine transporter, including neuroblastoma. 123I-mIBG uptake in the primary tumour and metastatic lesions is then visualized with gamma camera imaging. The addition of single-photon emission computed tomography with computed tomography (SPECT-CT) to planar whole-body scintigraphy has become standard in gamma camera imaging to increase certainty of interpretation and anatomical localization.

Although worldwide 123I-mIBG scanning is the standard of care, it has several disadvantages. Scintigraphy and SPECT have limited image resolution (associated with gamma-camera imaging), resulting in no clear anatomical imaging. As the 3D SPECT-CT has a limited field-of-view and can only image about 40 cm, this requires a predefined area of interest, often only primary tumour. Another disadvantage is the long scan time (acquisition time of ~90 min) requiring sedation in young patients. Lastly, the use of iodine-123 also requires a two-day scanning protocol (scanning 24h after radiopharmaceutical injection) and thyroid blocking medication to prevent accumulation of free radioactive iodide.

Actual start date of recruitment	12 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	7
Children (2-11 years)	15
Adolescents (12-17 years)	3
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A prospective pilot study was conducted at the Princess Máxima Centre for Paediatric Oncology, Utrecht, the Netherlands, between July 2020 and July 2021. Paediatric patients with confirmed (or clinical suspicion of) neuroblastoma referred for standard 123I-mIBG scanning were prospectively recruited.

Pre-assignment

Screening details:

Paediatric patients with confirmed (or clinical suspicion of) neuroblastoma referred for standard MIBG scanning.
Exclusion criteria were age ≥18 years, pregnancy, critical clinical condition (Lansky scale ≤20, organ failure, sepsis, hypoxia), and/or logistic planning reasons (if the MFBG scan could not be planned <2 weeks of MIBG scan).

Pre-assignment period milestones

Number of subjects started	25
Number of subjects completed	25

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Patient intended to undergo paired MIBG and MFBG scanning

Arm description:

Single arm study

Arm type	Active comparator
Investigational medicinal product name	18F-meta-fluorobenzylguanidine
Investigational medicinal product code	not available
Other name	18F-mFBG
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Bolus of 2 MBq/kg body weight

Number of subjects in period 1	Patient intended to undergo paired MIBG and MFBG scanning
Started	25
Completed	20
Not completed	5
Consent withdrawn by subject	1
MFBG production failed	2
MIBG not performed	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Included patients to be scanned.	

Reporting group values	Overall trial	Total	
Number of subjects	25	25	
Age categorical			
Age per inclusion			
Units: Subjects			
Infants and toddlers (28 days-23 months)	3	3	
Children (2-11 years)	14	14	
Adolescents (12-17 years)	3	3	
Not recorded	5	5	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	12	12	
Not recorded	5	5	

Subject analysis sets	
Subject analysis set title	Patients who underwent MIBG scanning
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who underwent MIBG scanning (as part of regular clinical care)	
Subject analysis set title	Patients who underwent MFBG 1h scanning
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who underwent the 1h post-injection MFBG scan	
Subject analysis set title	Patients who underwent MFBG 2h scanning
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who underwent the 2h post-injection MFBG scan	

Reporting group values	Patients who underwent MIBG scanning	Patients who underwent MFBG 1h scanning	Patients who underwent MFBG 2h scanning
Number of subjects	20	20	19
Age categorical			
Age per inclusion			
Units: Subjects			
Infants and toddlers (28 days-23 months)	3	3	3
Children (2-11 years)	14	14	13
Adolescents (12-17 years)	3	3	3
Not recorded			

Gender categorical Units: Subjects			
Female	8	8	8
Male	12	12	11
Not recorded			

End points

End points reporting groups

Reporting group title	Patient intended to undergo paired MIBG and MFBG scanning
Reporting group description: Single arm study	
Subject analysis set title	Patients who underwent MIBG scanning
Subject analysis set type	Per protocol
Subject analysis set description: Patients who underwent MIBG scanning (as part of regular clinical care)	
Subject analysis set title	Patients who underwent MFBG 1h scanning
Subject analysis set type	Per protocol
Subject analysis set description: Patients who underwent the 1h post-injection MFBG scan	
Subject analysis set title	Patients who underwent MFBG 2h scanning
Subject analysis set type	Per protocol
Subject analysis set description: Patients who underwent the 2h post-injection MFBG scan	

Primary: Detection of skeletal lesions

End point title	Detection of skeletal lesions
End point description: SIOPEN score for skeletal lesions	
End point type	Primary
End point timeframe: Maximum of 2 weeks between the paired MIBG and MFBG scan	

End point values	Patients who underwent MIBG scanning	Patients who underwent MFBG 1h scanning	Patients who underwent MFBG 2h scanning	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	19	
Units: SIOPEN points				
median (inter-quartile range (Q1-Q3))	1 (0 to 5)	11 (0 to 21)	6 (0 to 17)	

Statistical analyses

Statistical analysis title	SIOPEN score MIBG vs. MFBG 1h scan
Comparison groups	Patients who underwent MIBG scanning v Patients who underwent MFBG 1h scanning

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.003
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	9.4
Variability estimate	Standard error of the mean
Dispersion value	1.6

Notes:

[1] - pilot

Primary: Detection of soft tissue lesions

End point title	Detection of soft tissue lesions
End point description:	
Absolute number of soft tissue lesions	
End point type	Primary
End point timeframe:	
Maximum of 2 weeks between the MFBG and MIBG scan	

End point values	Patients who underwent MIBG scanning	Patients who underwent MFBG 1h scanning	Patients who underwent MFBG 2h scanning	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	19	
Units: N/A				
number (not applicable)	18	52	50	

Statistical analyses

Statistical analysis title	Number of soft tissue lesions MIBG vs. MFBG 1h
Comparison groups	Patients who underwent MIBG scanning v Patients who underwent MFBG 1h scanning
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.017
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	1.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.5
Variability estimate	Standard error of the mean
Dispersion value	0.8

Notes:

[2] - pilot

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Follow-up was up to 72 hours after the MFBG scan.

Adverse event reporting additional description:

Serious adverse events that occured within 72 hours were reported within one week to the sponsor. The patient was followed up untill SAE resolved.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Patient intended to undergo MFBG scanning

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: For this pilot study there were no non serious adverse events observed / reported

Serious adverse events	Patient intended to undergo MFBG scanning		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 22 (13.64%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Hypoxia	Additional description: Patient was intubated (hypoxia due to PJP). Hypoxia CTCAE grade 4		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis	Additional description: Line infection, Sepsis CTCAE grade 3		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fever	Additional description: Viral infection, with normal ANC or grade 1 or 2 neutrophils. CTCAE grade 3.		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Patient intended to undergo MFBG scanning		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 22 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2021	Version 2.1, with the following content: 1) Clarification of section "Safety Reporting" in the protocol 2) Adding possibility of procedural sedation when scanning younger children. 3) Administrative corrections, updates and clarifications. 4) Update of the Investigator's Brochure on [18F]MFBG 5) Adjustment of the informed consent form due to above-mentioned changes. 6) Annual progress report

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Six out of 14 patients were included twice in the study.

Notes: