EMA/CHMP/140420/2020
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Axumin

International non-proprietary name: fluciclovine (18F)

Procedure No. EMEA/H/C/004197/II/0011

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	29 Dec 2018	29 Dec 2018	☐
☐	CHMP Rapporteur Assessment Report	22 Feb 2019	22 Mar 2019	☐
☐	PRAC Rapporteur Assessment Report	01 Mar 2019	01 Mar 2019	☐
☐	PRAC members comments	06 Mar 2019	06 Mar 2019	☐
☐	Updated PRAC Rapporteur Assessment Report	07 Mar 2019	07 Mar 2019	☐
☐	PRAC endorsed relevant sections of the assessment report [3]	14 Mar 2019	14 Mar 2019	☐
☐	CHMP members comments	18 Mar 2019	25 Mar 2019	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 Mar 2019	27 Mar 2019	☐
☐	Request for supplementary information	28 Mar 2019	28 Mar 2019	☐
	Submission of MAH's responses			
☐	Re-start of procedure:	27 May 2019	27 May 2019	☐
☐	CHMP Rapporteur Assessment Report	25 Jun 2019	18 July 2019	☐
☐	PRAC Rapporteur Assessment Report	28 Jun 2019	28 Jun 2019	☐
☐	PRAC members comments	3 Jul 2019	3 Jul 2019	☐
☐	Updated PRAC Rapporteur Assessment Report	4 Jul 2019	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report [3]	11 Jul 2019	11 Jul 2019	☐
☐	CHMP members comments	15 Jul 2019	15 Jul 2019	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Jul 2019	n/a	☐
☐	2nd Request for supplementary information	25 Jul 2019	25 Jul 2019	☒
	Notification of withdrawal	n/a	11 Feb 2020	

Procedure resources	
CHMP Rapporteur:	Janet Koenig
PRAC Rapporteur:	Jolanta Gulbinovic

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List of abbreviations

AA	Amino acid
AE	Adverse event
ASCT2	Alanine-serine-cysteine transporter 2
BBB	Blood-brain-barrier
BED	Blue Earth Diagnostics
BIE	Blinded Image Evaluation
^{11}C-MET	[^{11}C-methyl]-methionine
CE-MRI	Contrast-enhanced MRI
CIRC	Central Imaging Review Committee
CNS	Central nervous system
CRO	Contract research organisation
CSR	Clinical study report
CT	Computed tomography
EANO	European Association for Neuro-Oncology
EAS	Effectiveness Analysis Set
EMA	European Medicines Agency
EU	European Union
^{18}F-FDG	^{18}F-fluorodeoxyglucose
^{18}F-FDOPA	3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine
^{18}F-FET	O-(2-^{18}F-fluoroethyl)-L-tyrosine
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
ICH	International Council for Harmonisation
IIT	Investigator-initiated trial
i.v.	Intravenous
LAT1	L-type amino acid transporter 1
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
NMP	Nihon Medi-Physics
NPV	Negative predictive value
OHACBC	*anti*-1-amino-3-hydroxycyclobutane-carboxylic-acid
OUH	Oslo University Hospital
PET	Positron emission tomography

PFS	Progression-free survival
PPV	Positive predictive value
PSA	Prostate specific antigen
PSUR	Periodic Safety Update Report
PT	Preferred term
RANO	Response Assessment in Neuro-Oncology
SAE	Serious adverse event
SD	Standard deviation
sNDA	Supplemental New Drug Application
SOC	System organ class
SoT	Standard of Truth
SPECT	Single-photon emission computerised tomography
SUV	Standardised uptake value
SUV_{max}	Maximum SUV
SUV_{mean}	Mean SUV
T/N	Tumour-to-normal
T_1W	T_1-weighted
T_2W	T_2-weighted
US	United States
VOI	Volume of interest
WHO	World Health Organization

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Blue Earth Diagnostics Ltd submitted to the European Medicines Agency on 26 November 2018 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include Diagnosis and continuing assessment of Glioma in adult patients as a new indication for Axumin; as a consequence, sections 4.1, 4.2, 4.4, 4.6, 5.1, 5.2 and 11 of the SmPC and the Annex II are updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on Paediatric requirements

The European Medicines Agency has deferred the obligation to submit the results of studies with Axumin in one or more subsets of the paediatric population in diagnosis of amino acid metabolism in solid tumours.

The paediatric committee of the EMA has accepted a paediatric investigation plan for Axumin for the indication "Diagnosis of primary and recurrent brain tumours" in September 2015 (EMA/PDCO/441587/2015). The paediatric indication is different than the indication applied for in the current application for marketing authorisation.

Information relating to orphan market exclusivity

On 24 April 2015, EMA Committee for Orphan Medicinal products granted orphan designation (EMA/COMP/212725/2015 to BED for fluciclovine (18F) for the diagnosis of glioma.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

In accordance with Article 14(11) of Regulation (EC) 726/2004, an additional one year of market protection is requested for the new indication of Axumin® (fluciclovine (18F)) in adults for the detection and continuing assessment of glioma on the basis that the indication brings significant clinical benefit in comparison with existing therapies.

Scientific advice

The MAH did not seek Scientific advice at the CHMP or the Rapporteur regarding the applied indication.

2. Scientific discussion

2.1. Introduction

Fluciclovine (18F) is a diagnostic radiopharmaceutical for positron emission tomography (PET) imaging to visualize increased amino acid transport that occurs in malignant tumors. It is a synthetic amino acid which is actively transported into mammalian cells by amino acid transporters, most notably by the LAT1 and ASCT2 transporters, which are known to be upregulated in cancer cells.

Fluciclovine (18F) is not metabolized, nor is it incorporated into newly synthesized proteins. PET imaging studies have demonstrated that fluciclovine (18F) is preferentially taken up into prostate cancer and glioma compared with surrounding normal tissue and that visualization of the image is not obscured by bladder uptake. fluciclovine (18F) was approved in Europe via the centralised procedure in May 2017, under the tradename Axumin®, and is indicated for PET in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment. Fluciclovine (18F) may also be referred to as 18F fluciclovine within this application. ThisType II variation provides evidence of the diagnostic efficacy, and safety of fluciclovine (18F) PET in adults for the detection and continuing assessment of glioma. The clinical program to support this application comprises two studies conducted by Nihon Medi-Physics Co., Ltd (NMP; Studies NMP-P201, NMP-P202; hereafter referred to as Studies NMP-P201 or P201 and NMP-P202 or P202) and two studies conducted by BED (Studies BED006 and BED008). Two further studies conducted by NMP, Studies NMP-P301 and NMP-P302 (hereafter referred to as Studies NMP-P301 or P301 and NMP-P302 or P302) are also included to provide additional information about fluciclovine (18F) in primary glioma patients. In total, 172 patients with glioma were exposed to the product, including 112 patients with suspected or confirmed high grade glioma and 59 patients with suspected or confirmed low grade glioma.

In this Type II variation the MAH applies for extension of the Marketing Authorisation for 18F-fluciclovine for its use in positron emission tomography (PET) imaging in adults for the detection and continuing assessment of glioma.

18F-fluciclovine intravenous (i.v.) injection, at a proposed administered activity of 185 MBq (5 mCi), has been developed as a diagnostic radiopharmaceutical for PET imaging to visualise the increased amino acid (AA) transport that occurs in malignant tumours.

18F-fluciclovine PET images should be interpreted in combination with magnetic resonance imaging (MRI) of the brain.

On 24 April 2015, EMA Committee for Orphan Medicinal products granted orphan designation (EMA/COMP/212725/2015 to BED for fluciclovine (18F) for the diagnosis of glioma.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

Reproduction toxicity

For radiopharmaceuticals carrying a radionuclide with a high emission of radiation and a long half-life such as anticancer drugs, reproductive toxicity studies can be waived since the radiation emission of these medicinal products is causing well known DNA damage with consequences for carcinogenicity and reproductive toxicity. However, the respective risk is outlined in the product labelling.

Assessors comment:

No reproductive toxicity studies have to be submitted for the new indication. The product labelling is orientated on the core SmPC and package leaflet for fudoxyglucose (^{18}F) and acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00), an updated environmental risk assessment (ERA) for 1600 MBq/mL solution for injection and Axumin 3200 MBq/mL solution for injection has been provided for the new indication.

The new indication does not lead to a significant increase in environmental exposure of Axumin as the PECsurfacewater in phase I does not change.

Substance (INN/Invented Name): Fluciclovine (^{18}F)			
CAS-number (if available): 222727-39-1			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-2.53	Potential PBT (N)
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.00005	µg/L	> 0.01 threshold (N)

2.2.2. Discussion on non-clinical aspects

N/A

Assessment of paediatric data on non-clinical aspects

N/A

2.2.3. Conclusion on the non-clinical aspects

The new indication does not lead to a significant increase in environmental exposure further to the use of Fluciclovine (18F).

Fluciclovine (^{18}F) is not expected to pose a risk to the environment when used in accordance with the SPC. Any changes in the dosage and duration of treatment will require an updated ERA.

2.3. Clinical aspects

2.3.1. Introduction

BED is proposing to add a new indication for 18F-fluciclovine for *PET imaging in adults for the detection and continuing assessment of glioma*.

The MAH is proposing that 18F-fluciclovine be indicated for PET imaging in adults for the detection and continuing assessment of glioma.

As summarised in Figure 3, the 2016 RANO working group/EANO (Albert et al, 2016) have identified a number of clinical settings where AA PET tracers may be indicated for use; namely:

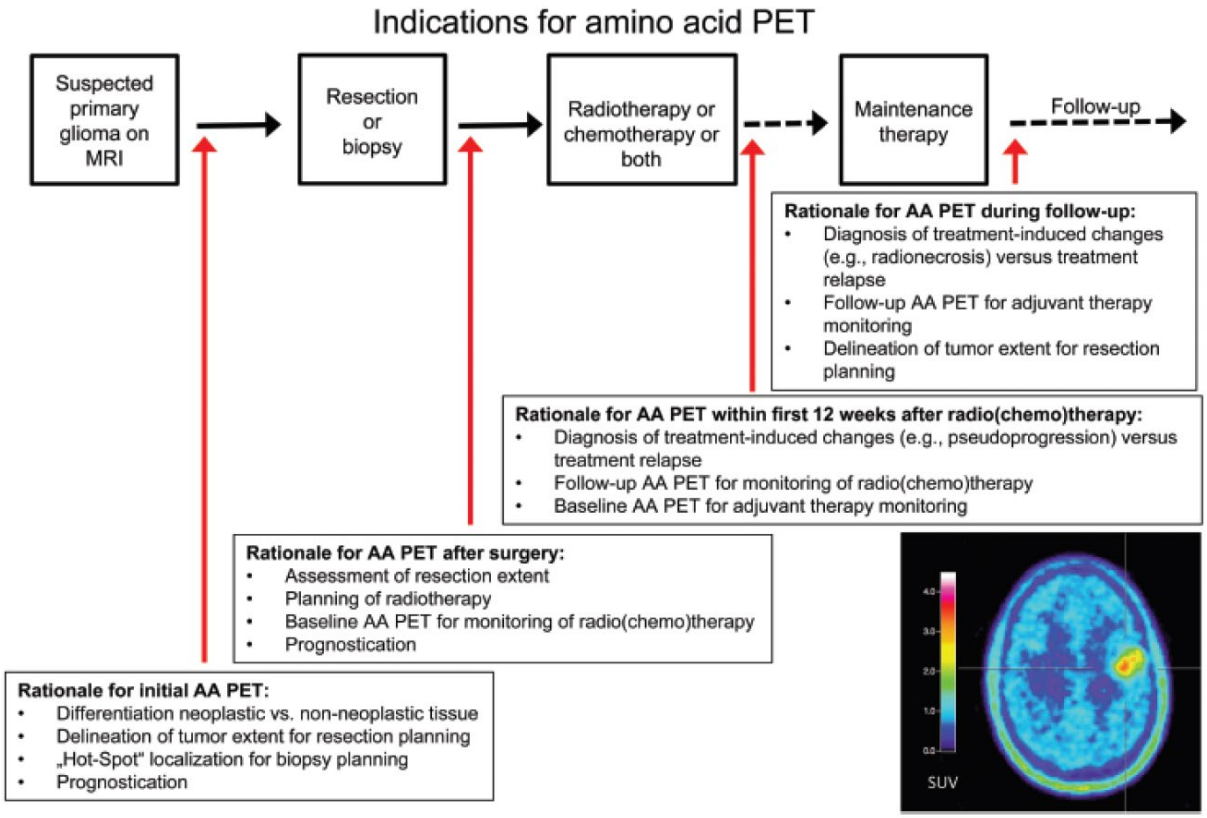
• Prior to surgery to plan biopsy or surgical field

• Prior to radiotherapy to plan radiation field

• After surgery, radiation or systemic treatment to assess response or plan subsequent treatment

• To differentiate between pseudoprogression and true progression

• Prognostication



GCP

The Clinical trials were performed in accordance with GCP according the applicant's statement.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

The product's pharmacokinetics was already characterised during the intial prostate cancer submission (EMEA/H/C/004197) and no further updated seems to be needed for this extension of indication. A summary of the information pertaining to the formulation, manufacture and specification of 18F-fluciclovine is provided below.

The pharmacokinetics, distribution and metabolism of fluciclovine (^{18}F) were evaluated as part of Studies GE-148-001 and NMK36-P1. In Study GE148-001, radioactivity in plasma and urine was assessed using

standard radioactivity counting methods. (For more information regarding Axumin's PK please refer to the initial submission and assessment of EMEA/H/C/004197)

Absorption

The applicant did not submit studies on absorption, which is acceptable as the product is administered.

Food effect

Oka et al showed *in vitro* that 2mM concentrations of certain amino acids, such as serine, glutamine and phenylalanine, could inhibit fluciclovine uptake and accelerate the rate of efflux from target cells[1]. The applicant did not submit studies evaluating food effect on fluciclovine imaging. All studies to date have required at least a 4 hour fast before scanning. Thus, the SmPC recommends that prior to administration of fluciclovine (^{18}F), patients should not eat or drink for at least 4 hours (other than small amounts of water for taking medicinal products) (SmPC section 4.4).

Distribution

Trial GE-148-001 which was evaluated already during the initial assessment evaluated mainly 18F-fluciclovine biodistribution and radiation dosimetry in healthy volunteers. Results from this study have shown that in subjects scanned at intervals for up to 6 hours post-administration, with radioactivity in plasma, urine and organs of interest measured at each timepoint, 18F-fluciclovine is rapidly distributed throughout the body, with initial uptake highest in organs with high levels of AA uptake, particularly the liver (mean, 13.8%), pancreas (4.2%) and bone marrow (11.1%), in all subjects. **Brain uptake is low, at 1.6%.** With increasing time post-injection, uptake in skeletal muscle increases. Limited uterine uptake is noted in women (1.2%). Lung uptake is also apparent (7.1%), but, based on comparison with washout of activity from the whole-blood samples, activity in the lung was likely due to activity in the pulmonary blood pool. No differences considered to be of likely clinical significance were noted between males and females.

Elimination

In Study GE-148-001, a mean of 3.2% of activity was excreted in the urine in over the collection period (mean 4.2 hours). Study NMK36-P1 continued collection for 24 hours, over which time a mean of 5.4% of activity was excreted in the urine. Washout of activity from most organs and tissues (with the exception of the pancreas) is slow. Washout of ^{18}F activity from the blood is such that about half of the maximum ^{18}F concentration in blood is reached by about 1 hour after administration.

Fluciclovine is not incorporated into proteins. Fluciclovine is not metabolised *in vivo*.

Dosimetry in Healthy Volunteers

Data regarding the deosimetry in healthy vounteers were already assessed during the initial assessment; thus only the final dosimetry results are shown here in order to provide an summary of information (Table 2):

Table 2: Absorbed Doses of 18F-fluciclovine by Organ/Tissue

Organ/Tissue	Mean Absorbed Dose (microGy/MBq)
Adrenals	16
Brain	9
Breasts	14
Gallbladder wall	17

[1] Oka S, Okudaira H, Yoshida Y, Schuster DM, Goodman MM, Shirakami Y, Transport mechanisms of trans-1-amino-3-fluoro[1-14C]cyclobutanecarboxylic acid in prostate cancer cells. Nuclear Medicine and Biology 2012. 39: 109-119.

Organ/Tissue	Mean Absorbed Dose (microGy/MBq)
Lower large intestine wall	13
Small intestine wall	13
Stomach wall	14
Upper large intestine wall	13
Heart wall	**52**
Kidneys	14
Liver	34
Lungs	35
Muscle	11
Ovaries	13
Pancreas	**103**
Red marrow	25
Osteogenic cells	23
Skin	8
Spleen	24
Testes	17
Thymus	13
Thyroid	10
Urinary bladder wall	25
Uterus	46

Special populations

The applicant did not submit studies in special populations.

The European Medicines Agency has deferred the obligation to submit the results of studies with Axumin in one or more subsets of the paediatric population in diagnosis of amino acid metabolism in solid tumours (see section 4.2 for information on paediatric use).

Fluciclovine (^{18}F) is not indicated for use in women (SmPC section 4.6).

No studies on fertility have been performed (smPC secrtion 4.6).

Pharmacokinetic interaction studies

No interaction studies have been performed.

Pharmacokinetics using human biomaterials

No pharmacokinetics using human biomaterials studies were submitted (see discussion in pharmacology).

2.3.3. Pharmacodynamics

Mechanism of action

The applicant did not submit studies in humans to elucidate the mechanism of action of fluciclovine (^{18}F) (see discussion in pharmacology).

Primary and secondary pharmacology

Primary Pharmacology

In vitro binding assays have demonstrated that 18F-fluciclovine is actively transported by AA transporters into glioma and prostate cancer cells with high affinity (Okudaira et al, 2011; Ono et al, 2013). 18F-fluciclovine is not metabolised or incorporated into newly synthesised proteins in malignant or normal cells (Okudaira et al, 2011). Cell culture, gene knock-down and heterologous expression studies have identified the sodium-dependent transporter ASCT2 and the sodium-independent system LAT1 as the dominant transporters involved (Oka et al, 2012; Ono et al 2013; Okudaira et al, 2011; Okudaira et al, 2013).

Both ASCT2 and LAT1 are known to be upregulated in cancer cells and have been shown to be associated with a malignant phenotype (Fuchs et al, 2005). The uptake of 18F-fluciclovine is not likely to be affected by the presence of the major related substance OHACBC. It is similarly not likely to be affected by circulating endogenous AAs at the activities administered.

Secondary Pharmacology

There was no metabolism of 18F-fluciclovine *in vitro* when assessed in rat, dog, monkey and human hepatic microsomes. Moreover, there was no clear evidence of metabolism *in vivo*. The potential for pharmacological drug-drug interactions is regarded as low.

2.3.4. PK/PD modelling

PK/PD modelling was not performed for this application

2.3.5. Discussion on clinical pharmacology

Clinical pharmacology was already established during the initial assessment and only a short summary of essential keyfact is given above. The effective half-life of fluciclovine equates to the radioactive half-life of 18F, which is approximately 110 minutes. At the low chemical concentrations of 2 to 10 µg to be administered, fluciclovine (18F) does not have any detectable pharmacological activity. The biodistribution was studied and fluciclovine (18F) was found to be rapidly and extensively distributed to major organs and tissues with uptake being highest in organs with high levels of amino acid uptake, particularly liver, pancreas, bone marrow and skeletal muscle. The critical organ (i.e., the organ with the highest absorbed dose per unit administered activity) was the pancreas. Washout of activity from most organs and tissues (with the exception of the pancreas) is slow. Fluciclovine is not metabolised in vivo. The major route of elimination is via the renal pathway. Urinary excretion is slow, reaching approximately 3% of administered radioactivity within 4 hours and 5% within 24 hours.

Washout of activity from most organs and tissues (with the exception of the pancreas) is slow. Activity in the brain is low. With increasing time post injection, distributed uptake is apparent and is mostly associated with skeletal muscle. Washout of 18F activity from the blood is such that about half of the maximum 18F concentration in blood is reached by about 1 hour after administration.

No data on primary pharmacology of fluciclovine (18F) has been provided in humans with benign brain tumours (e.g meningioma), area of necrosis or inflammatory lesions. This is of concern as in vivo fluciclovine (18F) PET imaging will presumably be tracing the fluciclovine (18F) influx into tumours as well as some other pathologies such as benign brain tumors, area if necrosis or potentially inflammatory lesions. Valid data on this issue is currently missing, but essential in principle to characterise the impact of fluciclovine (18F) in the intended new indication.

Similarly, the quantitative correlation between fluciclovine uptake and enhanced fluciclovine influx into cells was not assessed in vivo neither in healthy volunteers, nor in glioma or prostate cancer patients. This information should be provided.

The dosimetry data from the previous Study GE-148-001 remaining the most comprehensive assessment of the radiation dosimetry of fluciclovine (18F) and are included in the SmPC since the initial MA.

No pharmacodynamic studies or data on secondary pharmacology were submitted. This is acceptable as the administered dose is below the limits of detection in the plasma and hence, no pharmacological activity is expected from this low concentration level. At the chemical concentrations used for diagnostic examinations, fluciclovine (18F) does not appear to have any pharmacodynamic activity also in glioma patients.

Moreover, the impact of food and fluid intake on distribution and uptake of fluciclovine was not studied. From the information during the initial application it was determined that 4 hours of fasting was sufficient to get a low level of amino acids in the plasma in order to prevent any possible interference with the uptake of the active substance. This recommendation as well as the advice for drinking only sips of water within 4 hours prior to the scan is included in the product information.

No interaction studies have been performed. In in vitro studies, fluciclovine (18F) was not taken up by common drug transporters indicating a negligible potential for drug interactions. Therefore, no relevant interactions between fluciclovine and other drugs are expected. However, anti-mitotic agents and colony stimulating factors may have an impact on the uptake of fluciclovine in patients with glioma. No information regarding this issue was provided, which mean that the impact of treatment associated sources of bias remains open. More clarification is required.

The pharmacokinetics in patients with renal or hepatic impairment is still not characterised and data on this issue remains missing (which is reflected in SmPC section 4.2, 4.4 and 5.2). No differences considered to be of likely clinical significance were noted between males and females according the preliminary limited data in glioma patients. No dose adjustment requirements for the elderly population is currently recommended. However, subgroup analyses in glioma patients are not deemed interpretable due to the low number of patients investigated.

2.3.6. Conclusions on clinical pharmacology

The PK of fluciclovine (18F) was in general characterised in several Phase I studies measuring biodistribution and dosimetry presented and assessed already during the initial MAA. The mechanism of action and PK data for fluciclovine (18F) is still adequately described in the SmPC (Section 5.1 and 5.2) and information on the potential in vivo pharmacodynamic drug-drug interactions with a number of compounds that may be frequently used by the intended population was also included in the SmPC section 4.5.

However, with respect to the new applied indication "glioma" the data regarding primary pharmacology of fluciclovine (18F) has not been provided for humans with benign brain tumours (e.g meningioma), area of necrosis or inflammatory lesions. This is of concern as in vivo fluciclovine (18F) PET imaging will presumably be tracing the fluciclovine (18F) influx into tumours as well as some other pathologies such as benign brain tumors, area if necrosis or potentially inflammatory lesions. Valid data on this issue is currently missing, but essential in principle to characterise the impact of fluciclovine (18F) in the intended new indication.

Similarly, the impact of quantitative/semiquantitative measurement of fluciclovine (18F) uptake as an aid to image interpretation cannot be assessed at present which is needed. Furthermore, the impact of anti-mitotic agents and colony stimulating factors on uptake of fluciclovine in patients with glioma is

missing, which mean that the impact of treatment associated sources of bias remains open. More clarification is required.

2.3.7. Clinical efficacy

The clinical program to support this application comprises two studies conducted by Nihon Medi-Physics Co., Ltd (NMP; **Studies NMP-P201, NMP-P202**) and two studies conducted by **BED (Studies BED006 and BED008)**.

Two further studies conducted by NMP, **Studies)-P301 and NMP-P302** (hereafter referred to as Studies NMP-P301 or P301 and NMP-P302 or P302) are also included to provide additional **supportive information** about fluciclovine (18F) in primary glioma patients.

In total, 172 patients with glioma were exposed to the product, including 112 patients with suspected or confirmed high grade glioma and 59 patients with suspected or confirmed low grade glioma. Only 90 of these 172 were investigated prospectively, the other 82 patients included in trial BED-008 were selected from patients investigated during routine diagnostics at 3 sides using 18F-Fluciclovine for PET imaging.

Moreover, reference is made to relevant clinical guidelines and a comprehensive review of the literature to support the use of AA PET tracers in adult patients with glioma.

The following Table 1 provides an overview about the trials claimed as pivotal or supportive for the applied extension of indication "18F-fluciclovine PET Imaging in Adults for the Detection of Glioma".

Table 1: Studies Supporting the Safety of 18F-fluciclovine PET Imaging in Adults for the Detection and Continuing Assessment of Glioma

Study Number	Phase	Treatment	Patients Exposed to 18F-fluciclovine	Safety Assessments
NMP-sponsored Studies				
NMP-P201	2	Single i.v. administration of ^{18}F-fluciclovine (administered activity, 200.0 to 214.9 MBq), with cranial dynamic PET scans obtained 0 to 60 minutes (rebinned into static images at ~10, ~30 and ~50 minutes) after administration.	5 [HG]	AEs, haematology, blood biochemistry, urinalysis, 12-lead ECG, vital signs, physical examination
NMP-P202	2	Single i.v. administration of ^{18}F-fluciclovine (administered activity, 106.0 to 287.1 MBq), with cranial PET scans obtained 10 to 20 minutes and 40 to 50 minutes after administration.	40 (FAS:35) [21 HG; 19 LG]	AEs, haematology, blood biochemistry, urinalysis, 12-lead ECG, vital signs, physical examination
NMP-P301	3	Single i.v. administration of ^{18}F-fluciclovine (administered activity, 64.8 to 303.6 MBq), with 10-minute cranial PET scans started 10 to 50 minutes after	20 [14 HG; 6 LG]	AEs, haematology, blood biochemistry, urinalysis,12-lead ECG, vital signs, physical examination
NMP-P302	3	Single i.v. administration of ^{18}F-fluciclovine (administered activity, 91.9 to 252.4 MBq), with 10-minute cranial PET scans started 10 to 50 minutes after	25 [16 HG; 9 LG]	AEs, haematology, blood biochemistry, urinalysis, 12-lead ECG, vital signs, physical examination

BED-sponsored Study				
BED-008	3	^{18}F-fluciclovine (i.v.) given as part of an IIT or a compassionate use program (administered activity ranging from 51.8 to 451.4 MBq), with some patients receiving multiple administrations (106 administrations for 82 patients). PET scans were performed according to institutional practice.	82	**Retrospective design,** no patient assessed
BED-006	3	BIE-trial designed in order to evaluate the diagnostic performance (i.e., PPV, NPV, sensitivity and specificity) of 18F-fluciclovine PET used in combination with CE-T1W MRI (referred to herein as PET [+ CE-T1W MRI]), for the delineation of the extent of primary brain tumor, in terms of reproducibility of read results and concordance with standard of truth (SoT) data, when read and interpreted by naïve readers	No patients included	**Retrospective blinded image evaluation – trial from data collected in trial NMP-P202**

Clinical Trial Program for the newly applied indication glioma:

Study NMP-P201

Study NMP-P201 was a single site, Phase 2, single administration, prospective open-label **study in 5 patients** aged ≥20 years with a suspected diagnosis of glioma. The study evaluated the safety and efficacy of 18F-fluciclovine when administered as a single intravenous (i.v.) injection performed in a total of six (at the end only five) patients with high-grade glioma. Navigational magnetic resonance imaging (MRI) revealed that three patients had a single tumour, one patient showed multiple tumours, and one patient showed "disseminated" tumours. **This trial intends mainly to establish a dose/posology for the product in the glioma setting.**

(For more information and discussion, please refer to **5.4.1** of this report).

Study NMP-P202 (Data from this trial was used for inter-reader testing in BED002)

Study NMP-P202 was a prospective multicentre (10 centers), Phase 2, single administration, open-label study in patients aged ≥20 years with a suspected diagnosis of glioma. The study evaluated the safety and efficacy of 18F-fluciclovine when administered as a single i.v. injection in a total of 42 of whom 40 received the investigational product. The mean age was 55.0 years (all within the category of 20 to 85 years). A total of 21 (52.5%) patients were clinically diagnosed with suspected high-grade glioma and 19 (47.5%) patients were clinically diagnosed with suspected low-grade glioma. The Karnofsky Performance Scale (KPS) index (evaluation of functional impairment) score was 100% for 17 (42.5%) patients, with the majority of patients (32 [80%]) having a KPS score of ≥80%.

(For more information and discussion, please refer to **5.4.2** of this report)

Study BED-008

Study BED-008 was a **retrospective data extraction** study investigating the effectiveness of 18F-fluciclovine PET scans to detect the presence or recurrence of malignant disease in patients with glioma based on data pooled from three sites where 18F-fluciclovine had been administered to patients as part of an investigator-initiated trial or a compassionate use program.

Data were obtained from historical medical records for patients who had received at least one injection of 18F-fluciclovine for the detection of primary or recurrent glioma and had at least one histopathological report confirming the diagnosis of glioma.

Although this study is presented in support of the safety of 18F-fluciclovine, the limitations of the data collection for this purpose are obvious.

A total of 82 patients were enrolled in the study, all of whom had received 18F-fluciclovine injections. Overall, 106 administrations of 18F-fluciclovine were recorded, with 18 patients receiving more than one injection (two, three and five injections were administered in fourteen patients, three patients and one patient, respectively). A total of 56 (68.3%) patients had histopathologically confirmed high-grade glioma (World Health Organization [WHO] Grade III to IV) and 25 (30.5%) patients had low-grade glioma (WHO Grade II) (unknown in one [1.2%] patient).

(For more information and discussion, please refer to **5.4.2** of this report)

Study BED-006

Study BED-006 was a **blinded image evaluation (BIE) study** of 18F-fluciclovine PET and MRI images to evaluate the efficacy of 18F-fluciclovine PET combined with MRI imaging, compared to MRI alone, in adults with malignant glioma. **The study consisted of a BIE of images from the completed prospective Study NMP-P202; no additional PETs from other patients were included.**

The 35 patients (with 47 biopsy locations) included in the FAS for Study NMP-P202 had a PET scan evaluated and were included in the Efficacy Analysis Set of this BIE study. In line with the 20% of images that were randomly selected for re-read according to the protocol, across both timepoints, Reader 1, Reader 2 and Reader 3 all re-read 14/69 (20.1%) images (Intra-reader Analysis Set).

For each MRI acquisition (CE-T1W and FLAIR [or T2W]), each image dataset was read as an independent MRI acquisition by a reader with appropriate experience in neuro-radiology. The 18F-fluciclovine PET images were read in combination with the CE-T1W MRI, each by three different readers, with appropriate experience in nuclear medicine. Each 18F-fluciclovine PET acquisition consisted of two image datasets, acquired at different timepoints post-injection (i.e., PET starting between 10 and 20 minutes post-injection [Timepoint 1] and PET starting between 40 and 50 minutes post-injection [Timepoint 2]). All readers were naïve to the images, but had undergone training on the read procedures and familiarisation using sample cases (not from Study NMP-P202) prior to conducting the BIE read. Furthermore, readers were blinded to any patient-specific information (i.e., medical history, results of Study NMP-P202 reads of the 18F-fluciclovine PET images, biopsy location, histopathology results, the patient's final diagnosis and the patient's outcome).

(For more information and discussion of this trial, please refer to **5.4.2 section anxilliary analyses** of this report)

Study NMP-P301/Study NMP-P302 (claimed as supportive only)

In both studies, the safety and efficacy of 18F-fluciclovine administered as a single i.v. dose to patients with clinically suspected glioma, based on clinical symptoms, clinical course and MRI examinations, was investigated.

Study NMP-P301 was a Phase 3, multicentre, single-dose, open-label, non-randomised study. A total of 22 patients were enrolled in the study, with 20 patients receiving study drug. The majority of patients were male (13 [65.0%]). A total of 14 (70.0%) patients had suspected high-grade glioma and six (30.0%)

patients had suspected low-grade glioma. The majority of patients had a KPS index score of 100% (six [30.0%] patients) or 90% (11 [55.0%] patients).

Study NMP-P302 was a Phase 3, multicentre, single-dose, open-label, randomised, controlled study. A total of 49 patients were enrolled in the study, including 26 patients in the MRI plus 18F-fluciclovine group and 23 patients in the MRI alone group. Safety data were only analysed for the MRI plus 18F-fluciclovine group. A total of 16 (64.0%) patients had suspected high-grade glioma and nine (36.0%) patients had suspected low-grade glioma.

(For more information and discussion, please refer to **5.4.2 section supportive trials** of this report)

Imaging data from Studies NMP-P301 and NMP-P302 were presented together as a combined analysis and also as individual analyses; but claimed only as supportive.

Assessor's comment:

For the extension of indication for diagnostic of glioma, the applicant has only submitted 4 small studies (NMP) including between 5 and 20 to 40 patients (FAS: max. 35 patients). The only larger trial, BED-008 was a retrospective data analysis from patients investigated in three centers in the US and Norway between 2006 and 2015; however, beside the fact that the data is retrospective, only 18 patients out of 82 were included in the final analysis. The additionally presented inter-reader comparison trial BED-006 utilised data from one of the already listed trial (NMP-P202). With respect to the pivotal claims it has to be considered that trials NMP-P301 and particularly NMP-P302 are only claimed as supportive. This is probably reasoned by the fact that trial NMP-302 failed significantly to reach the primary endpoint, which aims to show a clinical benefit from the additional PET diagnostic with18F-Fluciclovine.

Thus, an adequately sized prospective phase 3 trial that could be seen as a convincing pivotal for this application is missing. Furthermore, there is a lack of bridging data would allow a comparison to results with standard PET imaging agents used for glioma PET imaging in the EU (e.g 18F-FET). Such comparative data were at least available from the Bologna Source for the comparator choline (^{11}C) in the prostate cancer indication. The lack of any comparison to other PET imaging agents makes it also difficult to assess the relevance of the literature data for other PET imaging agents, which is additionally discussed to justify this application.

Moreover, the small prospective NMP trials were all performed in the Japanese population only. Body weight in this population was lower and dose regimes administered seems to differ in comparison to that used for the glioma diagnostic in the retrospective data analysis from US and Norwegian patients in BED-008. This indicates difficulties regarding the acceptance of the proposed posology.

In conclusion, the clinical development program for this application seems rather preliminary and obvious limitations regarding size, design of the trials and overall quality raise major concern whether this data can be really sufficient to justify the broad claim of the intended indication "in adults for the detection and continuing assessment of glioma".

2.3.7.1. Dose response study(ies)

With regards to internal radiation dosimetry, the critical organ (i.e., the organ with the highest absorbed dose per unit administered activity) is the pancreas, with a mean absorbed dose of 102 microGy/MBq (range: 57 to 141) and the heart wall ((Table 2). The mean effective dose per unit administered activity is 22 microSv/MBq (range: 20 to 26) (GE-148-001; McParland et al, 2013).

The final dosimetry results from these studies demonstrated that the total radiation dose from the recommended clinical administered activity of 185 MBq of 18F-fluciclovine is very comparable to that of other 18F radiopharmaceuticals such as 18F-FDG. The proposed recommended administered activity of 18F-fluciclovine in glioma (WHO Grades II to IV) is 185 MBq (5 mCi). The radiation absorbed effective

dose resulting from the administration of the recommended activity of 185 MBq is 4 mSv. The applicant states that cumulative clinical trial experience strongly supports an administered activity of 185 MBq, due to the very high uptake in malignant glioma tissue relative to background in normal brain tissue, combined with acceptable ionising radiation exposure.

Assessor's comment:

Considering the severity of malignant glioma, the additional radiation exposure from an 18F-fluciclovine is not a major risk for this patient population, if a clear benefit can be convincingly demonstrated according the conditions outlined in the relevant EMA GUIDELINE ON CLINICAL EVALUATION OF DIAGNOSTIC AGENTS (CPMP/EWP/1119/98/Rev. 1).

Dynamic Imaging in Patients with Glioma was investigated in **Study NMP-P201**.

Trial NMP-P201 ("OPEN EXPLORATORY STUDY OF THE SAFETY AND EFFICACY OF NMK36 (18F-Fluciclovine) SINGLE ADMINISTRATION (INTRAVENOUS) IN PATIENTS CLINICALLY DIAGNOSED WITH BRAIN TUMOR included" (Study completed 8.7.2011)

This trial was an open exploratory phase 1 trial aimed the exploratory evaluation of the safety and efficacy (glioma demonstration, administered activity, positron emission tomography (PET) scan start time) of 18F-Fluciclovine single intravenous administration in inpatients clinically diagnosed with glioma from the clinical symptoms/course and brain MRI, and scheduled for brain tumor surgery. **A single intravenous administration of the entire contents of 1 vial of NMK36 (2 mL, 185 MBq/2 mL on assay) was investigated in 5 patients.**

The trial investigated primarily glioma demonstration from visual evaluation and exploring semi-quantitative indicators and secondary the administered activity (concordance rates), PET scan start timg of 10, 30 and 50 min after administration in order to idneitfdy the optima PET scan start time and overall safety,

In the population of 5 patients included in NMP-P201

For five of the 31 tissue sample sites there was discordance between the histopathological diagnosis and the result from navigated contrast MRI scans.

For two of these sites there was discordance with the result obtained using 18F-Fluciclovine PET scans (185 MBq administration scans); the other three sites were deemed positive, in agreement with the histopathological diagnosis.

Discordance between the histopathological diagnosis and the 18F-Fluciclovine PET scans (185 MBq administration scans) assessment result was not observed in any other tissue sample site.

With respect to glioma demonstration by visual evaluation the concordance rates between demonstration on fluciclovine (18F) PET scans (185 MBq administration scans) and tissue sample sites with a histopathological diagnosis of "tumor" are reported to be ≥85% in the 5 patients investigated at each time point (around 10 min, 30 min and 50 min after administration); it is claimed that these concordance rates were higher than the 82.8% concordance rate for using navigated contrast MRI scans.

Furthermore, the results suggest in the applicant's view that PET imaging using 18F-Fluciclovine is possible at any time from immediately after to 60 min after 18F-FLUCICLOVINE administration. However, from the variation in SUV over time, the T/N (contralateral, cerebellar) ratios suggest that it is preferable to start PET imaging immediately after 18F-FLUCICLOVINE administration.

The administered activity (measured value) was 200.0 MBq to 214.9 MBq. Similar results were obtained when scans corresponding to 87 MBq administration and 270 MBq administration were simulated using the 185 MBq administration scans as standard. It was concluded that good demonstration of gliomas can be achieved at the dose envisaged for clinical use, namely at 87 MBq to 270 MBq administered activity.

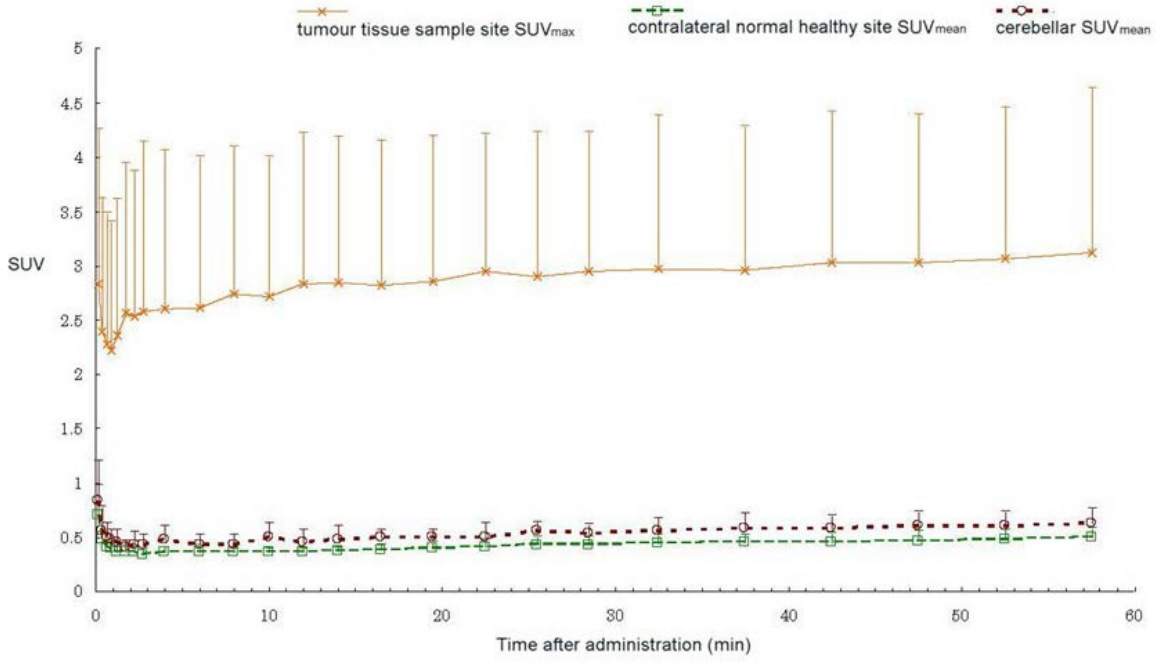
From this exploratory evaluation of the safety and efficacy of a single intravenous administration of fluciclovine (18F) it was concluded that PET scans afford good glioma identification, and may in principle demonstrate the presence and spread of brain tumor that cannot be identified by contrast MRI using 87 MBq to 270 MBq activity, with a PET scan start time of from immediately after 18F-FLUCICLOVINE administration to 60 min after 18F-FLUCICLOVINE administration. Moreover, the safety results show that 18F-FLUCICLOVINE use can be tolerated clinically; thus, it was decided that it is appropriate to proceed to the next phase of clinical trials.

In addition, the study included an activity simulation sub-study whereby, although all patients were administered actual administered activities of radiation of 200.0 to 214.9 MBq, simulated activities were created by rebinning 5, 10 and 15 minutes of PET list mode data at various times post-injection (i.e., 10, 30, 50 minutes) to create simulated image datasets corresponding to actual administered activities of 87 MBq, 185 MBq and 270 MBq, respectively.

For example, a simulation of a 10 minute post-injection of 87 MBq image was reconstructed from the list mode data at 10 minutes±2.5 minutes. The methodology used was similar to published by (Gatidis et al, 2016), but used summed sequential images rather than the randomised under-sampling of PET list mode data. Immediately before 18F-fluciclovine administration, cranial CT scans were obtained using a PET-CT camera for attenuation correction and to obtain anatomical information. Efficacy, in terms of detection of the extent of glioma (by visual evaluation and semi-quantitative indicators), was analysed by administered radioactivity and PET scan start time after dosing in order to optimise the procedures to be used in future studies.

Kinetic data in patients with a suspected diagnosis of high-grade glioma were obtained in Study NMP-P201. Time-activity curves (Figure 2) show rapid uptake of 18F-fluciclovine, with tumour tissue sample site mean maximum standardised uptake value (SUVmax) values increasing immediately after 18F-fluciclovine administration, and remaining high thereafter. Contralateral normal healthy site and cerebellar mean standardised uptake value (SUVmean) values increased immediately after 18F-fluciclovine administration, then gradually decreased until around 3 minutes after 18F-fluciclovine administration, remaining relatively unchanged thereafter. The T/N ratios (tissue sample site SUVmax/normal healthy site [contralateral/cerebellar] SUVmean) peaked approximately 3 minutes after 18F-fluciclovine administration, remaining high thereafter. Thus, consistent T/N ratios were observed across a wide imaging timeframe in this population with high-grade glioma.

Figure 2: Time-activity Curve Comparing the Uptake of 18F-fluciclovine in Tumour Versus Contralateral Normal Healthy and Cerebellar Tissue in Patients with Suspected High-grade Glioma



Source: Figure 11.4-8 (NMP-P201 CSR).

Assessor's comment:

A range of different administered activities was used in the NMP-P201 and P202 trials. It is reported that this was triggered due to practices in Japan, where doses for administration were dispensed at fixed activity and then used to treat several patients throughout the day: Insofar, it is understood why the actual administered activity varied based on the time of administration relative to the time of calibration. The applicant stated that this represents usual practice in Japan where the concept of a fixed injected administered activity at the time of injection is preferred.

Although it is acknowledged that Study NMP-P202 incorporated a comparison of actual administered activities of 106.0 to 287.1 MBq by prospectively assigning patients into either a high or low administered activity group, it needs to be considered that these Japanese patients seemed to have a lower body weight than the Caucasian EU population evaluated. Moreover, there seems to be a significant variability in the doses evaluated.

Moreover, it is noted that for patients reported in the retrospective analysis trial BED-008, conducted at sites outside Japan (US and Norway), significantly higher doses and probably posology according body weight were used. This is not fully evaluable from the information provided. (OC)

Since this data might indicate that in a Caucasian population (with a higher body weight) a different posology was explored and assessed as more adequate for these patients, it seems questionable whether the applied posology is really adequate to be recommended for the EU population.

At present, the posology seems only to be appropriate for the Japanese population. The applicant is requested to clarify the obvious differences and justify the relevance of the currently proposed fixed dose posology for the EU population. (MO)

Considering the limited database derived from a small number of patients investigated, it seems difficult to confirm the validity of the applicant's statement according the currently applied posology.

An adequately sized pivotal trial was not performed in order to demonstrate the reliability of the proposed posology at present.

In addition, it is reported that with respect to glioma demonstration by visual evaluation, the concordance rates between demonstration on fluciclovine (18F) PET scans (185 MBq administration scans) and tissue sample sites with a histopathological diagnosis of "tumor" was ≥85% in the 5 patients investigated at each time point (around 10 min, 30 min and 50 min after administration); these concordance rates were higher than the 82.8% concordance rate for using navigated contrast MRI scans. However, it is not clear from the study report whether this comparison of concordance rate refers also to T2-FLAIR MRI which has a higher sensitivity in this setting. Moreover, the number of patients investigated is very limited.. The applicant is requested to clarify this issue.

Additionally, the applicant describes that study NMP-P201 included an activity simulation sub-study whereby, although all patients were administered actual administered activities of radiation of 200.0 to 214.9 MBq, simulated activities were created by rebinning 5, 10 and 15 minutes of PET list mode data at various times post-injection (i.e., 10, 30, 50 minutes) to create simulated image datasets corresponding to actual administered activities of 87 MBq, 185 MBq and 270 MBq, respectively. This approach is not assessable, since the study report for this data was not submitted. Although the overall relevance of this data seems questionable at all for this application, the applicant is requested to provide this trial report and to explain better this approach in order to understand what was performed. In conclusion, the currently proposed posology is not sufficiently justified by data.

2.3.7.2. Main study(ies) (Diagnostic performance against a standard of truth)

Studies NMP-P201 and NMP-P202 were defined as Phase 2, single administration, open-label studies in patients aged ≥20 years with primary glioma who were scheduled to undergo resection. The studies evaluated the safety and efficacy of 18F-fluciclovine when administered as a single intravenous (i.v.) injection to patients with a suspected diagnosis of malignant glioma based on either clinical symptoms and/or brain MRI.

Study NMP-P201 was a single site Phase 2 study investigating 5 (!) patients and discussed above in the dose justification section, whereas **Study NMP-P202 was a multicentre single arm Phase 2 study in 40 patients with primary glioma, but the FAS includes only 35 who received 18F-fluciclovine.**

Assessor's comment:

Trial NMP-P202 was the largest prospective trial submitted in this application. It includes only (42) 40 patients, but even from this limited number only 35 were included in the final analysis of efficacy. Nevertheless, this data has to be seen as the main source for pivotal claims in this application.

Trial NMP-P202

Objective: The purpose of this study was to assess the efficacy and safety of a single (intravenous) dose of 18F-Fluciclovine in patients with clinically suspected high/low-grade glioma based on clinical symptoms/clinical course and MRI investigations.

Population:

Diagnosis and Main Inclusion Criteria:

Inclusion Criteria:

Patients who satisfied all of the following criteria were selected. It was irrelevant whether they were inpatients or outpatients, or what sex they were.

(1) Patients who were aged 20 years or over on the date of obtaining consent.

(2) Patients with clinically suspected high-grade gliomas or low-grade gliomas, from their clinical symptoms/course and MRI investigations (T1-weighted imaging, contrast T1-weighted imaging and FLAIR [or T2-weighted imaging], who had been scanned within the previous 30 days from the date of obtaining consent at a medical institution participating in the study), and were scheduled for resection.

(3) Patients who provided written informed consent to participate in the study.

Exclusion Criteria adequately excluding patients further increasing heterogeneity in interpretability of PETs or in whom administration of 18F-Fluciclovine is deemed not benficial. PETwith specific also according the Rapporteur's view

Number of Patients: 40 patients for safety / 35 patient FAS for efficacy

Suspected high-grade glioma group: 18 patients; Suspected low-grade glioma group: 17 patients

The numbers of study patients in the high radiation dosage group and the low radiation dosage group were divided to have roughly equal numbers.

(1) High Radiation Dosage Group (166.5 MBq to 297.0 MBq)

Suspected high-grade glioma group: 11 patients
Suspected low-grade glioma group: 9 patients

(2) Low Radiation Dosage Group (78.3 MBq to 139.7 MBq)

Suspected high-grade glioma group: 10 patients
Suspected low-grade glioma group: 10 patients

Assessor's comment:
According the information provided in trial NMP-P202 (as well as in the supportive trials NMP-P301 and P302) only patients with primary glioma were included. Information regarding patients with recurrent disease is only available from the retrospective analysis in BED-008. This approach may be acceptable for an exploratory approach; however, for a pivotal trial the relevant guideline [EMA GUIDELINE ON CLINICAL EVALUATION OF DIAGNOSTIC AGENTS (CPMP/EWP/1119/98/Rev. 1)] recommends explicitly inclusion of a sufficient number of patients representative for the full population in which the diagnostic agent is intended to be used. This means inclusion of patients

- *for screening in asymptomatic patients or those with other intracranial diseases, in patients with suspected but not confirmed disease,*
- *in patients with a confirmed disease for evaluation of its extent (initial staging), severity or prognosis*
- *in patients undergoing treatment to monitor its efficacy*
- *in previously treated patients to search for recurrence and*
- *in patients with a confirmed recurrence for evaluation of its extent (restaging), severity or re-evaluate the prognosis.*

These essential requirements are obviously not fulfilled neither for this trial with 35 patients nor for the other small trials presented to justify the claim. In particular, since all data in the 18 patients with recurrent glioma from BED-008 is only retrospective (MO).

Statistical Methods:

Analysis of the following analytical sets was performed. The FAS was used for the main analyses.

• Enrolled cases (patients from whom consent had been obtained)

• Patients who completed the study

• Safety Analysis Set

• Full Analysis Set (FAS)

• The set to whom the study protocol was applicable (Per Protocol Set, [PPS])

(2) Analyses relating to efficacy

1) Analysis using the main assessment criterion

The percentage of patients; of those whose tissue collected at the site in the 1st. 18F-Fluciclovine Scan were assessed as that from Appraisal Region ①, and confirmed by histopathological methods as tumor, and of the 95% confidence interval were calculated. In addition, a statistical test was performed using the normal approximation under the null hypothesis for a population rate of 0.7, in order to verify whether

there was a statistical excess of the lower threshold of 70% that was used in setting the number of study patients required for the positive predictive value of the 1st. 18F-Fluciclovine Scan.

2) Secondary Assessments

① Calculations of the

- percentage of patients; of those whose tissue collected at the site in the 1st. 18F-Fluciclovine Scan assessed as that from Appraisal Region ②, and confirmed, histopathologically, as tumor;
- and of the 95% confidence interval.

② Calculations of the;

- percentage of patients, of those whose tissue collected at the site in the 1st. 18F-Fluciclovine Scan assessed as that from Appraisal Region ① or Appraisal Region ②, and confirmed, histopathologically, as tumor,
- and of the 95% confidence interval

③ Calculations, by the grade of malignancy at enrollment, of the;

- percentage of patients, of those whose tissue collected at the site in the 1st. 18F-Fluciclovine Scan assessed as that from Appraisal Region ①, and confirmed, histopathologically, as tumor,
- and of the 95% confidence interval.

Full analysis set (FAS): 35 patients (suspected high-grade glioma group, 17 patients; suspected low-grade glioma group, 18 patients)

Per protocol set (PPS): 33 patients (suspected high-grade glioma group, 16 patients; suspected low-grade glioma group, 17 patients).

Efficacy and Safety Endpoint

Only "exploratory" endpoints were defined in this trial as follows:

(1) Main ("Primary"?) Assessment Criterion:

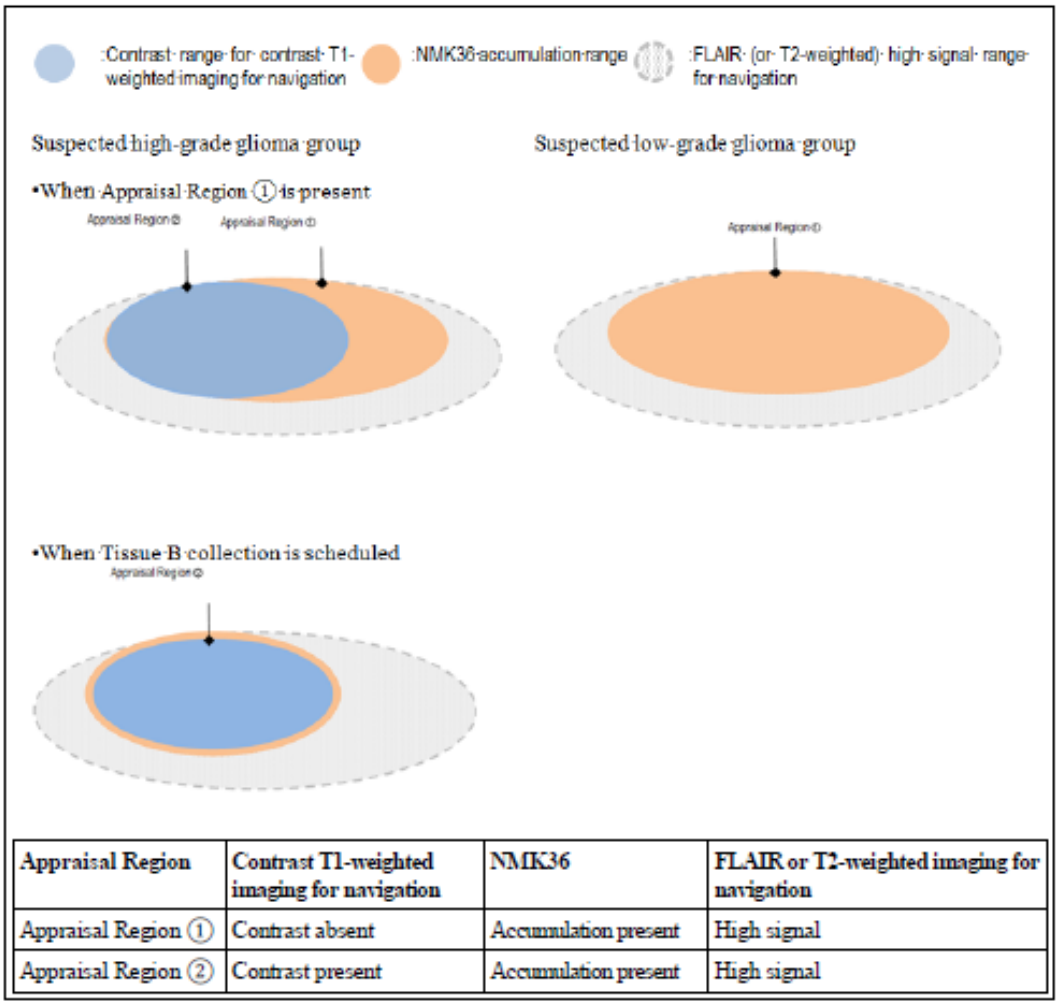
The positive predictive value of Appraisal Region ① in the 1st. 18F-Fluclicovine Scan

(2) Secondary Assessment Criteria:

1) The positive predictive value of Appraisal Region ② in the 1st. 18F-Fluclicovine Scan
2) The positive predictive value of Appraisal Region ① and Appraisal Region ② in the 1st. 18F- Fluclicovine Scan
3) The positive predictive value, by grade of malignancy at enrollment, for Appraisal Region ① in the 1st. 18F-Fluclicovine Scan

Other secondary criteria: Range of dosages administered, Range of PET imaging times, Appraisal of contrast (+) PET(−) regions in the 1st. 18F-Fluclicovine, Appraisal of contrast (−) PET(−) regions in the 1st. 18F-Fluciclovine Scan, Exploration of semi-quantitative indices to enable appropriate visualization of the scope of tumors, Safety assessment endpoints

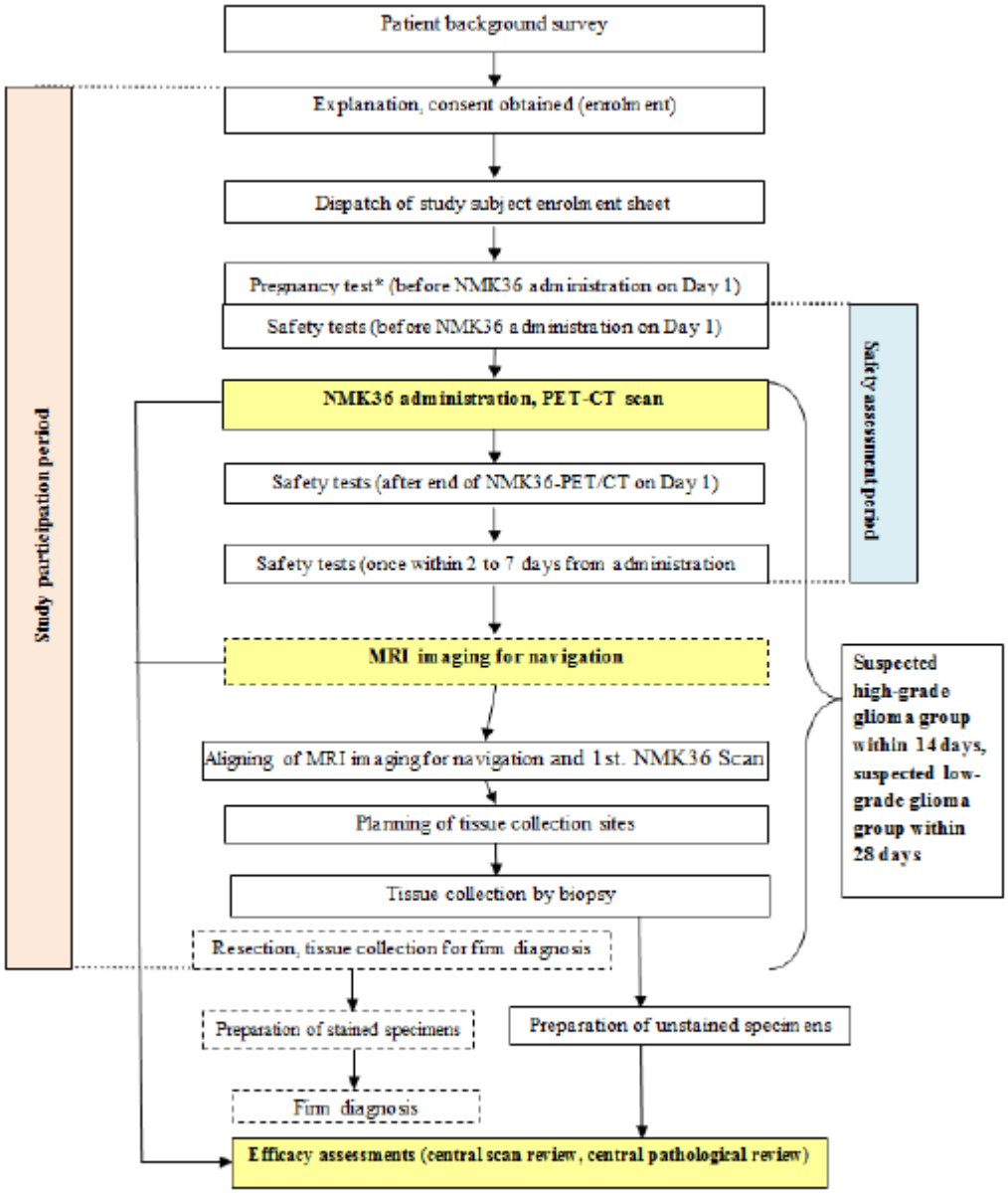
Figure Assessment of Tissue Collected by Biopsy



Appraisal Region	Contrast T1-weighted imaging for navigation	NMK36	FLAIR or T2-weighted imaging for navigation
Appraisal Region ①	Contrast absent	Accumulation present	High signal
Appraisal Region ②	Contrast present	Accumulation present	High signal

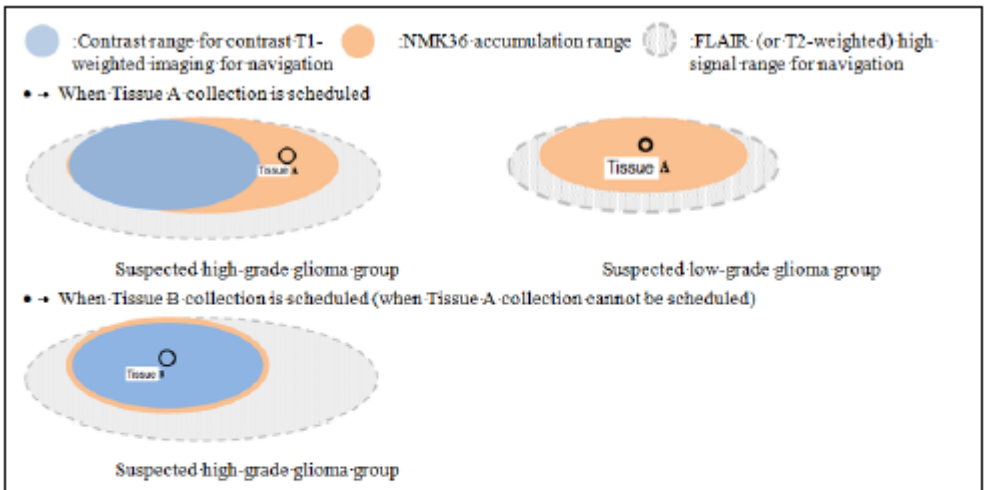
Study Design:

The following Figure provides an overview of the study design and conduct:



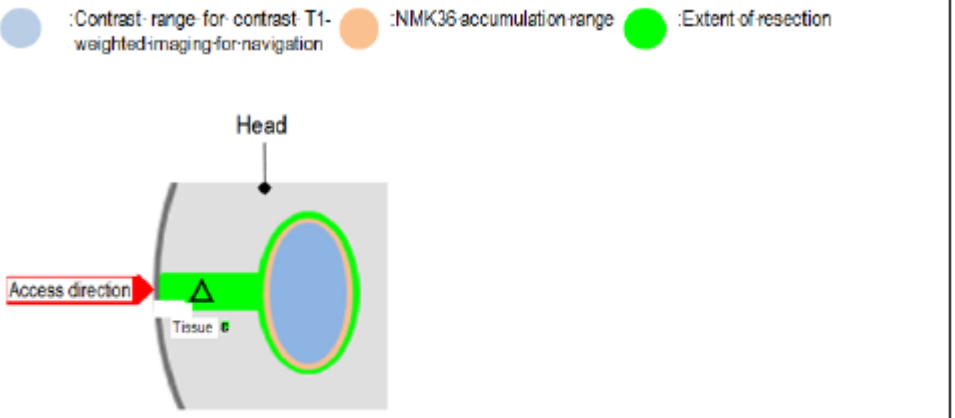
*A pregnancy test was carried out on female patients to verify that they were not pregnant.
The dotted boxes show routine clinical practice

Figure Schedule for Tissue Collection Sites (A and B)



Tissue collection site	Description
Tissue A	Tissue scheduled and collected by the principal investigator etc. which was considered to be contrast (–) PET (+) with the 1st. NMK36 Scan and contrast T1-weighted imaging.
Tissue B	Tissue scheduled and collected by the principal investigator etc. which was considered to be contrast (+) PET (+) with the 1st. NMK36 Scan and contrast T1-weighted imaging for navigation. Only collected in situations where Tissue A collection could not be scheduled.

Figure Tissue C [Contrast (–) PET(–)] Collection



Tissue collection site	Description
Tissue C	Tissue which was collected by the principal investigator etc. which was considered to be contrast (–) PET(–) from the 1st. NMK36 Scan and contrast T1-weighted imaging. Collected only when possible.

Results:

There were 42 patients who consented to participate in this study, all of which were enrolled. Of these, 40 patients received 18F-FLUCICLOVINE. The remaining 2 patients had an eligibility match error, and therefore were withdrawn prior to administration of the investigational product.

Thirty-seven of the 40 patients to whom 18F-FLUCICLOVINE was administered completed the study. Three patients were withdrawn from the study after administration of 18F-FLUCICLOVINE: reasons for

withdrawal included "Withdrawn from tissue collection by biopsy", "Tissue collection could not be scheduled" and "Continuation difficulties".

Conduct: According the study report, there were 14 reported instances of deviations from the protocol in 11 study patients. There were 2 instances, in 2 patients, of serious deviations from the protocol both were recorded as "An image was stored whilst the PET accumulation range display was still being produced, as the tissue collection image (snapshot)". There were 3 reports of an infusion solution containing sugar was used in the time interval from 6 hours or more before laboratory tests (blood collection, urine collection) and this was reported as a deviation, because fasting was not carried out.

There were no deviations from the inclusion criteria, or non-compliance with withdrawal criteria.

Outcome as reported in the study report:

Of the 35 patients in the FAS, the principal investigator etc. collected: Tissue A from 28 patients; Tissue B from 7 patients; and Tissue C from 12 patients.

When assessments were carried out by the Central Scan Review Committee of images for the collection of Tissue A or Tissue B, using the 18F-Fluciclovine scans and 2 types of MRI scan, there were 26 patients whose tissue from the 1st. 18F-Fluciclovine Scan was assessed as from Appraisal Region ①, 8 patients whose tissue was assessed as from Appraisal Region ②, and 1 patient for whom no 18F-Fluciclovine accumulation was found, and was therefore deemed to be outside the appraisal regions.

Since no 2nd. 18F-Fluciclovine Scan could be obtained with 1 patient, there were 34 patients who had 2nd. 18F-Fluciclovine Scans assessed. In the 2nd. 18F-Fluciclovine Scan, there were 23 patients whose tissue was assessed as from Appraisal Region ①, 9 patients whose tissue was assessed as from Appraisal Region ②, and 2 patients for whom no 18F-Fluciclovine accumulation was found, and were therefore deemed to be outside the appraisal regions.

Table Number of Patients by Tissue Collection Sites according to the Principal Investigator etc., and the Number of Patients (FAS) by Appraisal Region Assessments of Tissue Collection Sites According to the Central Scan Review Committee

		No. Patients (%)
Number of Study Patients (FAS)		**35**
Tissue collection sites according to the principal investigator etc.*[1]	Number of patients from whom Tissue A was collected	**28 (80.0%)**
	Number of patients from whom Tissue B was collected	**7 (20.0%)**
	Number of patients from whom Tissue C was collected	**12 (24.3%)**
Appraisal Region Assessment of the 1st. 18F-Fluciclovine Scan by the Central Scan Review Committee for Tissue A and Tissue B*[2]	Number of patients	35
	Number of patients who had regions assessed as Appraisal Region ①	26 (74.3%)
	Number of patients who had regions assessed as Appraisal Region ②	8 (22.9%)
	Number of patients deemed to have no appraisal regions	1 (2.9%)
Appraisal Region assessment of the 2nd. 18F-Fluciclovine Scan by	Number of patients	34
	Number of patients who had regions	23 (65.7%)

the **Central Scan Review Committee for Tissue A and Tissue B*[2]**	assessed as Appraisal Region ①	
	Number of patients who had regions assessed as Appraisal Region ②	9 (25.7%)
	Number of patients deemed to have no appraisal regions	2 (5.7%)

Main ("Primary"?) Assessment Criterion:

The positive predictive value of Appraisal Region ① in the 1st. 18F-Fluclicovine Scan

The positive predictive value for the 26 Appraisal Regions ① in the 1st. 18F-Fluclicovine Scan (number of regions; 95% confidence interval) was 100.0% (26/26 regions; 86.8% to 100.0%).

In addition, the normal approximation under the null hypothesis for the lower limit threshold value (70%) used for setting the required number of patients, was significantly statistically exceeded ($p<0.001$).

There were similar results for the PPS**.**

Secondary Assessment Criteria:

1) *The positive predictive value of Appraisal Region ② in the 1st. 18F-Fluclicovine Scan*

The positive predictive value of Appraisal Region ② in the 2nd. 18F-FLUCICLOVINE Scan was assessed for 8 regions (8 patients; 1 region per patient) by the Central Scan Review Committee. The positive predictive values of the 8 Appraisal Regions ② in the 1st. 18F-FLUCICLOVINE Scan was 87.5% (7 out of 8 regions; 52.9% to 97.8%).

2) *The positive predictive value of Appraisal Region ① and Appraisal Region ② in the 1st. 18F- Fluclicovine Scan*

The positive predictive value of the total of 34 regions from Appraisal Region ① and Appraisal Region ② in the 1st. 18F-FLUCICLOVINE Scan was calculated. The positive predictive value of the total of 34 regions from Appraisal Region ① and Appraisal Region ② in the 1st. 18F-FLUCICLOVINE Scan was 97.1% (33 out of 34 regions; 85.1% to 99.5%).

3) *The positive predictive value, by grade of malignancy at enrollment, for Appraisal Region ① in the 1st. 18F-Fluclicovine Scan*

The positive predictive value by grade of malignancy at enrollment was calculated for 26 Appraisal Regions ① (suspected high-grade glioma group, 10 regions; suspected low-grade glioma group, 16 regions) in the 1st. 18F-FLUCICLOVINE Scan.

The positive predictive values for Appraisal Regions ① in the 1st. 18F-FLUCICLOVINE Scan were 100.0% (10 out of 10 regions; 72.2% to 100.0%) for the high-grade glioma group, and 100.0% (16 out of 16 regions; 80.6% to 100.0%) for the low-grade glioma group.

Other outcome relevant in applicant's view:

- The positive predictive values for Appraisal Regions ① in the 1st. 18F-FLUCICLOVINE Scan were 100.0% (13 out of 13 regions; 77.2% to 100.0%) for both the "high radiation dosage group" and the "low radiation dosage group".
- Concordance of appraisal region assessments between the 1st. and 2nd. 18F-FLUCICLOVINE Scans (number of regions and 95% confidence intervals; similarly below), was calculated as 94.1% concordance (32/34 regions; 80.9% to 98.4%) and the κ coefficient (95% confidence interval) was 0.824 (0.587 to 1.000): therefore high concordance was obtained between the 1st. and 2nd. scans.

- There were no patients who were assessed by the principal investigators etc. as having contrast (+) PET (-) regions in the 1st 18F-FLUCICLOVINE Scan.
- Of 12 tissues collected as Tissue C from 12 patients (suspected high-grade glioma group, 5 tissues; suspected low-grade glioma group, 7 tissues), 8 tissues (suspected high-grade glioma group, 2 tissues; suspected low-grade glioma group, 6 tissues) were assessed by the Central Scan Review Committee as "non-tumor", and 4 tissues (suspected high-grade glioma group, 3 tissues; suspected low-grade glioma group, 1 tissue) as "tumor". The results of histological diagnosis of 4 tissues which were assessed as "tumor", which had a false negative from 18F-FLUCICLOVINE were infiltration of glioblastoma (2 tissues); infiltration of oligodendroglioma (1 tissue); and infiltration of astrocytoma (1 tissue): all of them had "infiltration" which meant that invasive tumor cells were present. The estimated proportion of tumor cells in 2 out of these 4 tissues was 5% or less

Assessor's comment:

In the study protocol and the efficacy summary document the applicant stated that the primary aim of this trial was to take a tissue sample in an area of brain which the investigator considered tumour negative on CE-T1W MRI and tumour positive on 18F-fluciclovine PET (Tissue A). If Tissue A could not be collected, a sample was to be taken from an area which the investigator considered CE-T1W MRI positive and PET positive (Tissue B). Additional samples could be taken from areas of brain which the investigator considered CE-T1W MRI and PET negative (but which could be FLAIR/T2W MRI positive). The CIRC then assessed from which 'Evaluation Region' the tissue sample had been taken (Evaluation Region 1 being CE-T1W MRI negative, PET positive and FLAIR/T2W MRI positive; Evaluation Region 2 being CE-T1W MRI positive, PET positive and FLAIR/T2W MRI positive in the opinion of the CIRC) by superimposition of information from the navigation system used to locate biopsies on MRI/PET scans. Based on these central evaluations, PPV was calculated. Overall, this is a complicated approach addressing potentially one important aspect in glioma patients.

Moreover, seven of the 42 patients (~17%) enrolled were not included in the FAS. Although the reasons for exclusion might be acceptable and in the interest of the patient, this further lowers the reliability in outcome. Moreover, it seems that only 47 biopsies were taken, which means that only in about one third of the patients more than one biopsy was evakuable. Considering the numbers of evaluation strata the sponsor planned [a.) Tissue collection sites(Tissue A, B and C), b.) Evaluation Regions (1, 2 and outside the evaluation region) and two different PET scan start time (10-20 min and of 40-50 min) it seems rather difficult to make any clear conclusions from this finding. In particular, since additionally two different radiation dosage groups (high versus low) and two different glioma gradings (high- and low-grade) were investigated.

In consequence, it seems the applicant has tried to mixed up to many variables without a clear pivotal claim. This is not primarily necessary in a phase 2 trial, as far as the aim is exploratory mainly. Unfortunately, this trial seems no to be the largest trial claimed as pivotal for this application and was also used for the blinded image evaluation for inter-reader comparability exercise (BED-006).

It seems not reliable to calculate diagnostic parameters for the applied indication from this source.

Moreover, CE-T1W MRI negative and FLAIR/T2W MRI was available from the patients in addition to the PET. However, no comparison between results of biopsies only positive in 18F-Fluciclovine PET and FLAIR/T2W MRI was provided. Considering that FLAIR/T2W might have a higher sensitivity this is a shortcoming. At the end data from trial NMP-P202 are rather difficult to be interpreted due to the small number of patients investigated and the complicated study design and the mix-up of MRI and PET in the calculation of the diagnostic parameters (e.g. PPV).

In conclusion, the Rapporteur's is of the opinion that data from trial NMP-P202 seems - at best- to indicate that 18F-Fluciclovine together with CE-T1W MRI and FLAIR/T2W MRI allows to identify glioma. The results presented have not proven any reliable superiority of 18F-Fluciclovine PET at present. Particularly a lack of demonstration of any reliable additional benefit to the MRI diagnostic alone is missing at present. The use of different radiation dosage regimes in acceptable for a phase 2 trial, however, as an additional bias factor lowers the overall pivotal value of this trial.

Considering that this was the largest of the prospective trials claimed as pivotal and differences in the study design of the both supportive trials NMP-P301/302 preclude methodological further pooling of data, it is not possible in the Rapporteur's view to use this data seriously to justify any pivotal claims.

The calculated diagnostic parameters (PPV,NPV and others) are also not seriously reliable from a methodological point of view. Due to the complex study design, the very limited number of biopsies available and the unknown impact of the MRI diagnosis on the 18F-Flucivlovine the data are seen as exploratory at best.

Trial BED 008

Assessor's comment:

BED-008 was a retrospective data extraction study investigating the effectiveness of 18F-fluciclovine PET in patients with glioma based on data from three sites (MSKCC, Emory University and OUH) where 18F-fluciclovine had been administered to patients in either as part of an IIT or a compassionate use programme. Patients with high- and low-grade recurrent glioma are included.In the applicant's view this trial mainly should support the use of 18F-fluciclovine PET in the continuing assessment of glioma and thereby justify the broad indication applied, since all other trials submitted from the Japanese source focused on the assessment of primary glioma population only. Therefore, the majority of patients (50/82 [61%]) collected in BED-008 have recurrent glioma after prior treatment; approximately two-thirds had high-grade disease and one-third had low-grade (WHO Grade II) disease. Again, no patients with WHO Grade I disease is included, which makes it difficult to carry out any analysis on this population. These seems to limit claims regarding all grades of low-grade gliomas.

Data were obtained from historical medical records for patients who had received at least one injection of 18F-fluciclovine for the detection of primary or recurrent glioma and had at least one histopathological report confirming the diagnosis of a glioma (SoT). Also for these patients calculation of the PPV of 18F-fluciclovine PET scanning in conjunction with MRI diagnostic was provide, aiming to describe the results for detection of recurrence in patients previously diagnosed with histologically confirmed glioma (SoT). Again the detection rate and sensitivity were calculated without distinguishing sufficiently between the contribution of MRI and PET in a reliable manner.

- **Study Design/ Study Objectives**

Study BED 008 was a retrospective data extraction study to collect and analyze relevant data collected from three clinical or research sites to confirm efficacy of 18F-fluciclovine given intravenously (i.v.) as a PET imaging agent for the purposes of evaluating the extent of primary (i.e. initial diagnosis) or recurrent brain tumors.

The accuracy of 18F-fluciclovine PET as a diagnostic agent for the detection of primary and recurrent brain tumor was assessed in a pooled analysis of data from patients undergoing investigation for these conditions. In order to calculate diagnostic accuracy statistics, only those patients with histological confirmation were included in the study.

All patients who received at least one injection of 18F-fluciclovine as a PET imaging agent for brain tumor, and for whom histopathological SoT was available, were eligible for inclusion into this study.

The majority of the data were included in but were not to be limited to the following timescales: *Screening*: Medical data related to brain tumor collected prior to injection of 18F-fluciclovine;

- *Baseline/Treatment*: Relevant medical and imaging data collected within 1 month prior to and 1 month following 18F-fluciclovine administration;
- *Follow-up*: Relevant medical and imaging data collected until death/loss to follow up of the patient after 18F-fluciclovine administration; including histopathology results from biopsy or surgery undertaken related to the 18F-fluciclovine scan performed;
- *Digital Imaging and Communications in Medicine (DICOM) image data for PET and MRI scans* (where associated with PET imaging): These data were also to be collected. Other PET

imaging data related to the diagnosis and management of the patient's brain tumor were also to be collected where these were readily available from the institution taking part in the study.

Data were collected from patients treated with 18F-fluciclovine up to 01 July 2017. Data from all sites were pooled. Three sites participated in the study, two from the USA and one from Norway. The 18F-fluciclovine PET scans performed at Site 0101 (Emory) were for research purposes only. There was no clinical interpretation of these scans and they were not used to guide biopsy sampling, which was performed separately.

Assessor's comment:

It needs to be considered that the population here presented was highly selective and constructed due to limitations in the available cases. From the information provided the reasons for performing 18F-Fluciclovine PET in the selected cases remains unclear. Although the general approach for the selection seemed rational and may be sufficient for an exploratory analysis in preparation for generating a hypothesis for a prospective clinical trial, the overall pivotal value for this application is seen as low and not fully reliable since selection bias is obvious.

Sample Size

Planned: Approximately 100 patients

Analyzed: 82 patients were enrolled, of whom 43 patients had a PET scan interpretation.

Assessor's comment:

Obviously, the applicant planned to include 100 patients; however, only 83 patients were enrolled into the trial. Moreover, it seems that only for 42 patients a valid PET scan interpretation was available. This seems to be a significant limitation even for a retrospective analysis and challenges the reliability for the results overall. Moreover, several patients were investigated with 18F-Fluciclovine more than once. This might be probably explained by inclusion of patients with recurrence of disease, but may also indicate a need for PET repetition due to other reasons (e.g. low quality of the PET). The applicant needs to clarify this issue and explain the approach, how PETs from patients who have been investigated more than once this population were selected for inclusion in the calculation of the diagnostic parameters (PPV etc.). In general, this procedure is not fully transparent from the study report and is deemed as not very reliable.

Study participants

All patients who underwent 18F-fluciclovine PET scanning for the detection of brain tumor at a clinical site participating in this study prior to 01 July 2017 who had histopathological data as a diagnostic SoT were included in the study. The study planned to include approximately 100 patients.

Inclusion Criteria

To be eligible, all of the following criteria had to be met:

- Patient historically managed by a site at which ethical committee approval for retrospective data collection under this protocol had been received or was not required.
- Patient had received at least one injection of 18F-fluciclovine for the detection of primary or recurrent brain tumor **prior to 01 July 2017**.
- Patient had had at least one histopathological report confirming the diagnosis of brain tumor.

Exclusion Criteria

Patients were to be excluded from the analyses if any of the following criteria were met:

- Patient had participated in clinical trials or open access programs in countries or sites not participating in this study.

- Patient had undergone 18F-fluciclovine PET for reasons other than primary or recurrent brain tumor.
- Patient was below the age of 18 years at time of imaging with 18F-fluciclovine PET.

Diagnosis and Main Criteria for Inclusion/Exclusion: Patients were eligible if they had at least one histopathological report confirming the diagnosis of brain tumor and had received at least one injection of 18F-fluciclovine for the detection of primary or recurrent brain tumor prior to 01 July 2017. Patients also had to have been historically managed by a site at which ethical committee approval for retrospective data collection under this protocol had been received or was not required.

Patients who had participated in clinical trials or open access programs in countries or sites not participating in this study, had undergone 18F-fluciclovine PET for reasons other than primary or recurrent brain tumor and/or were below the age of 18 years at time of imaging with 18F-fluciclovine PET were to be excluded.

Assessor's comment:

The applicant presented data from patients included between 2004 and 2015/2017(?) in BED-008. Since this seems to be a long period for a clinical trial in which technical/handling details regarding the PET performance and/or within the PET scan instruments may have changed, the applicant is requested to report on all relevant changes at study sides. Additionally a comprehensible overview which allows to evaluate the number of PETs per center and the time of PET performance (month/year) in order to assess on the experience with the PET glioma diagnosis performed in the centers recruiting for the trial.

Treatments

This was a retrospective data extraction study. No protocol directed medical interventions were to be given. There were no patient visits associated with this study. All relevant historical data were extracted from the databases or medical records of patients who had undergone 18F-fluciclovine PET imaging. All relevant data from presentation/diagnosis to the time of death/loss to follow up of the patient were collected.

Objectives

Primary Objective

- The primary effectiveness endpoint is the calculation of the PPV of 18F-fluciclovine PET scanning to detect:

  a) recurrence in patients previously diagnosed with brain tumor

  b) presence of malignant disease in patients undergoing testing for primary brain tumor,

  each in comparison to histopathological SoT.

Secondary Objectives

- Determination of the detection rate (DR), sensitivity, specificity, and negative predictive value (NPV) in both of these populations.
- Comparison was made with standard MRI techniques used alongside PET, and any other amino acid PET imaging (where available) that was performed with which the patient was injected.
- Survival data, where possible, was collected for all patients enrolled.

Endpoints:

Primary endpoint

- The primary effectiveness endpoint was the calculation of the PPV of ^{18}F-fluciclovine PET scanning to detect histologically confirmed primary or recurrent brain tumor.

Secondary Endpoints

- Calculation of DR, sensitivity, specificity, and NPV for both primary and recurrent brain tumor.
- Diagnostic accuracy comparison with MRI, including FLAIR sequences where available.
- Diagnostic accuracy comparison with any other tracer used for PET imaging, e.g. ^{11}C-methionine.
- Survival in the study population compared to expected survival statistics.
- Proportion of patients with clear margins following surgical resection, if performed.

Outcomes

Disposition of Patients

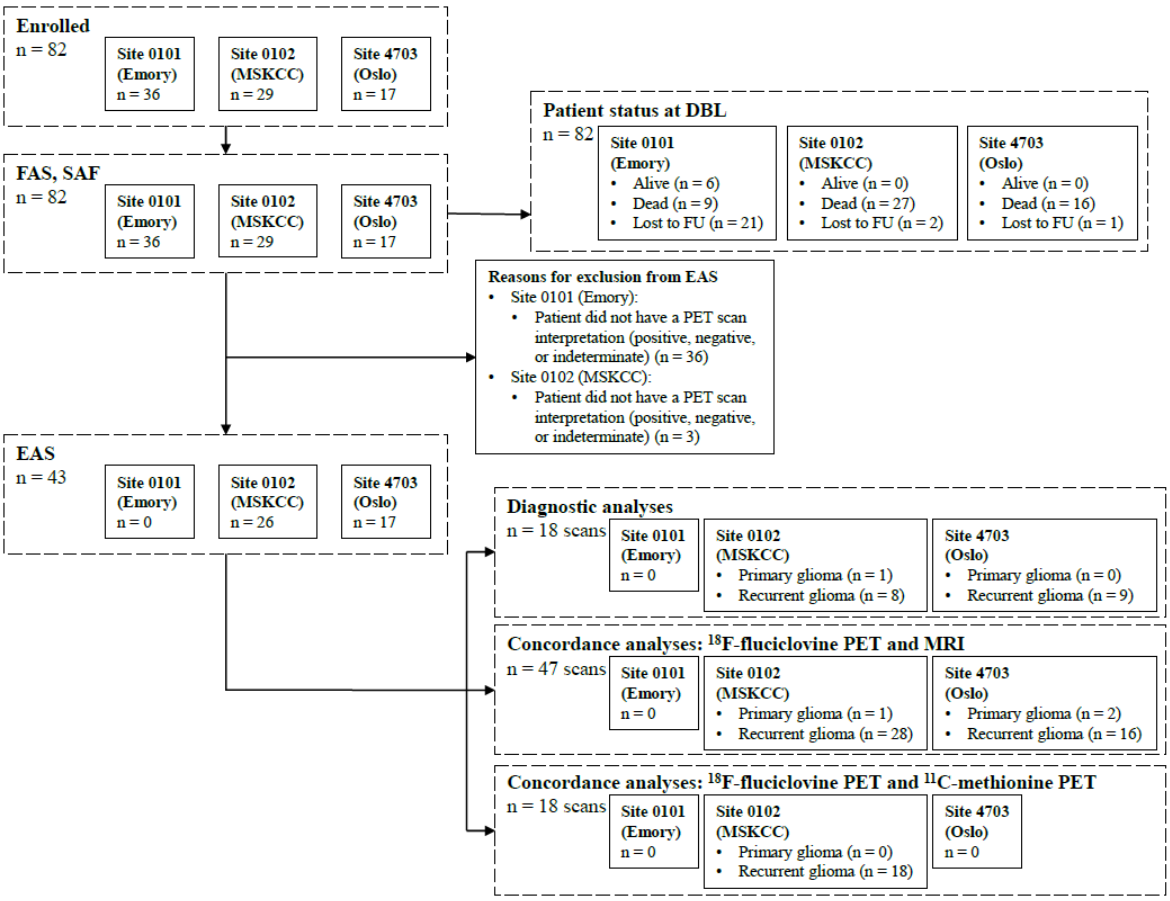
Overall, data were collected for 82 patients, comprising 36 patients from Site 0101 (Emroy), 29 patients from Site 0102 (MSKCC), and 17 patients from Site 4703 (Oslo). **The first included scan was performed in August 2004, and the last included scan was performed in May 2015.** All 82 patients were included in the SAF and the FAS.

Of the 82 patients, 43 were included in the EAS. There was no clinical interpretation of the 18F-fluciclovine PET scans performed at Site 0101 (Emory) and they were not used to guide biopsy sampling, which was performed separately. The patients from Site 0101 were therefore not included in the EAS.

For diagnostic analyses, only records where the date of the 18F-fluciclovine PET scan and the date of the SoT were within 30 days of each other, and the results were positive or negative, were included in the diagnostic performance analysis. **There were 18 scans which met these criteria, specifically one scan in a patient with primary glioma and 17 scans in patients with recurrent glioma.**

For concordance analyses, the 18F-fluciclovine PET scan and the comparative scan had to have been within 60 days of each other. For 18F-fluciclovine PET and MRI, there were 47 scans which met these criteria, specifically three scans in patients with primary glioma and 44 scans in patients with recurrent glioma. For 18F-fluciclovine PET and 11C-methionine PET, there were 18 scans which met these criteria, all in patients with recurrent glioma.

The disposition of patients in this study is shown schematically in Figure 1.



DBL=database lock; EAS=Effectiveness Analysis Set; FAS=Full Analysis Set; FU=follow-up; MRI=magnetic resonance imaging; MSKCC=Memorial Sloan Kettering Cancer Center; PET=positron emission tomography; SAF=Safety Analysis Set.
Source: Table 14.1.1, Table 14.2.1.1, Table 14.2.2.2, Table 14.2.3.2, and Listing 16.2.3.1

Assessor's comment:

One of the inclusion criteria was that "Patient had received at least one injection of 18F-fluciclovine for the detection of primary or recurrent brain tumor prior to 01 July 2017". In this context, it is not understood why the last scan in the patients was performed on 01.May 2015. This seems contradictorily and needs to be clarified.

Moreover, it was stated that of the 82 patients investigated only 43 finally included in the EAS, since there was no clinical interpretation of the 18F-fluciclovine PET scans performed at Site 0101 (Emory) and they were not used to guide biopsy sampling, which was performed separately. However, even from these 42 patients claims as efficacy population only 18 had evaluable PETs according the defined inclusion criteria. Although the exclusion is rational, the applicant needs to justify that results from a trial for which inclusion of 100 patients was assessed as necessary at the beginning, but only 18 met the fully inclusion criteria allows any valid conclusion. It is noted that in all trials of the clinical development program the number of patients planned at the time the trial protocol was developed was significantly higher than the number of patients finally recruited and presented in the analysis. However, the discrepancy observed in BED-008 is outstanding and raised again the question whether the calculated diagnostic characteristics (PPV, DR and NPC etc) can claim reasonably any reliability, even in the absence of the reasoned doubts regarding an additional selection bias.

Statistical methods

The following four populations were considered in the statistical analysis of the study:

- The Enrolled Set consisted of all patients included in the database.

- The Safety Analysis Set (SAF) consisted of all patients who had an injection of 18F-fluciclovine irrespective of whether an image was obtained.
- The Full Analysis Set (FAS) consisted of all patients included in the database who received 18F-fluciclovine and had a PET scan.
- The Effectiveness Analysis Set (EAS) consisted of all patients included in the database who received 18F-fluciclovine and had a PET scan interpretation (positive, negative or indeterminate).

For diagnostic analyses, only records where the date of the 18F-fluciclovine PET scan and the date of the SoT were within 30 days from each other, and the results were positive or negative were included in the diagnostic performance analysis. This was to ensure there was no disease progression between the PET scan and the biopsy, as high grade glioma is rapidly progressive.

For concordance analyses, the 18F-fluciclovine PET scan and the comparative scan (MRI or 11C-methionine PET scan) had to have been within 60 days of each other.

The PPV of 18F-fluciclovine PET scanning used was calculated using histology results as the SoT. The 95% CIs of the PPV estimates were presented. Analysis was presented by previous diagnosis of glioma (primary glioma and recurrent glioma). The point estimate of PPV (expressed as a percentage), and the Clopper-Pearson 95% exact CIs of PPV were presented on the patient level and lesion level.

No adjustments were made for multiple scans or multiple lesions. If there were no distinguishable multiple lesions for any patient this analysis was to be omitted.

In the circumstance that a patient had multiple 18F-fluciclovine PET scans, the patient level analysis was to include a result for each scan performed. The result was positive if any lesion evaluated during the scan was positive; the result was negative if all lesions evaluated during the scan were negative.

Lesions with indeterminate results were excluded from analyses

The DR, sensitivity, specificity, and NPV of 18F-fluciclovine PET scanning were calculated using histopathology results as the SoT. The Clopper-Pearson 95% exact CIs of the estimates were also to be presented.

The PPV, DR, sensitivity, specificity, and NPV of MRI were calculated using histopathology results as the SoT. The Clopper-Pearson 95% exact CIs of the estimates were also to be presented.

The concordance and discordance of 18F-fluciclovine PET scan and MRI imaging were presented, along with the Cohen's Kappa statistic and the two-sided 95% CI.

The PPV, DR, sensitivity, specificity, and NPV of 11C-methionine were calculated using histopathology results as the SoT and the two-sided 95% CI.

The concordance and discordance of 18F-fluciclovine PET scan and 11C-methionine PET scan were presented, along with the Cohen's Kappa statistic. The point estimate and the two-sided 95% exact CI were presented.

Assessor's comment

Also from a biostatisticians perspective it is not clear what claim is actually intended to be supported by this study. According to the primary objective, the aim was to calculate the PPV to detect recurrence of brain tumour or presence of brain tumour for 18F-fluciclovine PET scanning. However, "detection" can be understood in different ways.

Firstly, it could be related to the initial diagnosis of recurrent or primary tumour. However, in this case, the target population would be subjects with suspected recurrent or primary brain tumour while the study population included only patients with histopathological confirmed recurrent or primary brain tumour.

Therefore, the PPV of PET for the initial diagnosis cannot be estimated based on the study population because patients with a positive PET scan whose diagnosis was not histopathological confirmed (i.e. who were false positives) were not included in the study. With regard to initial diagnosis, only the sensitivity of PET could be estimated based on the study population provided it is representative.

The choice of the study population allows only making statements about the diagnostic performance of PET in the population of patients with histopathological confirmed brain tumour. Such statements could still be meaningful if these support using PET for guiding therapeutic decisions. However, it is highly questionable that the results support the conclusion that PET has an additional benefit for patients compared to the current standard. The PPV and sensitivity for PET were not larger than for MRI (whereby sensitivity is of questionable relevance anyway because it only translates to detection of at least one positive lesion for a patient that is known to be positive). Whether PET allows the identification of additional malignant lesions compared to current standard was not evaluated; however, as only 2 out of 140 histopathological evaluated specimens were PET positive only, or PET positive while MRI could not assign, this seems to be highly questionable.

Specificity and NPV are not considered meaningful parameters in this population as all patients are positive according to the histopathological SoT.

As histopathology was the SoT, a patient from the study population cannot be considered to be overall "negative" with regard to SoT. Nevertheless, the applicant considered at least 2 patients to be negative with regard to the SoT, which is not fully understood. It is assumed that these were patients whose PET positive/negative lesions were all negative with regard to the SoT (but positive with regard to at least one additional lesion for which no PET status is available). This is considered meaningful for calculation of PPV because the proportion of patients for which a malignant lesion was correctly identified among all patients with at least one positive PET is indeed of interest. Otherwise, sensitivity should be the proportion of patients for whom a malignant lesion was correctly identified by PET among those patients with at least one positive lesion according to SoT, i.e. the overall study population. Therefore, the sensitivity is not considered 100% but 88%.

The careful selection of the study population and collection of information with regard to the outcomes of interest in the study population is of utmost importance in a retrospective study in order to avoid selection bias. The information provided by the applicant is considered insufficient in this regard for the following reasons:

- *The applicant did not describe what patients were selected for PET scan in the study sites. It is unknown whether PET scan was performed for all patients with suspected or histopathological confirmed brain tumour, systematic criteria were in place to select specific patients for PET scan, or allocation to PET scan was unsystematic.*
- *The patient flow was not sufficiently described. In particular, it is unknown how many patients/reports were screened in the study sites, and reasons for not including patients/reports in the study were not given*
- *It is not clear what guided the decision where to select specimens to determine the histopathological SoT. In particular, it is unknown whether histopathological status is known for all lesions that were PET positive/negative. Likewise, it seems that PET status is not known for all lesions with known histopathological status (otherwise, no patients could be considered as false positive for PET in a population including only patients with histopathological confirmed brain tumour).*
- *It is unknown whether/what additional information was available to the PET scan readers before deciding on PET status.*

Results:

Primary Effectiveness Endpoint: PPV of 18F-fluciclovine PET Scanning to Detect Histologically Confirmed Primary or Recurrent Brain Tumor:

The PPV (95% CIs) for 18F-fluciclovine PET scanning to detect histologically confirmed recurrent brain tumor is reported to be 88.2% (63.6%, 98.5%; Table 11). Only one patient with primary glioma had a scan which met the criteria for inclusion in the diagnostic performance analysis. This patient had a TP 18F-fluciclovine PET scan result.

Secondary Effectiveness Endpoint: DR, Sensitivity, Specificity and NPV for Both Primary and Recurrent Brain Tumor

For patients with recurrent brain tumor, the DR (95% CIs) was 100.0% (80.5%, 100.0%), and the sensitivity (95% CIs) was 100.0% (78.2%, 100.0%; Table 11). The specificity and NPV could not be

calculated as no patients had a negative 18F-fluciclovine PET scan. Only one patient with primary glioma had a scan which met the criteria for inclusion in the diagnostic performance analysis. This patient had a TP 18F-fluciclovine PET scan result.

Category	N	TP n (%)	FP n (%)	TN[a] n (%)	FN[a] n (%)	PPV % (95% CI)	Sensitivity % (95% CI)	DR % (95% CI)
Primary glioma	1	1 (100.0)	0	0	0	100.0 (2.5, 100.0)	100.0 (2.5, 100.0)	100.0 (2.5, 100.0)
Recurrent glioma	17	15 (88.2)	2 (11.8	0	0	88.2 (63.6, 98.5)	100.0 (78.2, 100.0)	100.0 (80.5,

CI=confidence interval; DR=detection rate; FN=false negative; FP=false positive; N=number of patient scans; NPV=negative predictive value; PET=positron emission tomography; PPV=positive predictive value; SoT=standard of truth; TN=true negative; TP=true positive. Source: Table 14.2.1.1 a The NPV and specificity could not be calculated as there were no patients with a negative 18F-fluciclovine PET scan

Assessor's comment:

Almost all of the evaluable 18 patients out of 82 patients with 18F-Fluciclovine PETs have recurrent glioma. Beside the fact that this population is too small for reliable conclusions, the meaning and the clinical relevance of the presented diagnostic parameter remain unclear. As already stated in the comment on the biostatistical method above 18F-Fluciclovine PET seems not to add any additional benefit in the diagnostic approach for the patients in comparison to MRI alone; thus the reliability of the calculated diagnostic parameters above (which include again also the information derived from MRI) is deemed to be low.

In conclusion, a pivotal value from BED-008 data for this application is not seen; at best this data may indicate that 18F-Fluciclovine is able in principle also to detect recurrence of glioma and not only primary glioma. However, the potential benefits discussed for 18F-FET-PET in the RANO/EANO recommendation for the setting of recurrent glioma (e.g. differentiation between glioma and tumor necrosis after radiation treatment etc.) are not demonstrated in BED-008 for the applied 18F-Fluciclovine. Demonstration of any additional diagnostic benefit in addition to MRI in patients with recurrent glioma remains missing in the Rapporteur's view.

Blinded Reader Study BED006

Study Objectives

This study was designed to evaluate the diagnostic performance (i.e., PPV, NPV, sensitivity and specificity) of 18F-fluciclovine PET used in combination with CE-T1W MRI (referred to herein as PET [+ CE-T1W MRI]), for the delineation of the extent of primary brain tumor, in terms of reproducibility of read results and concordance with standard of truth (SoT) data, when read and interpreted by naïve readers (Blinded Reader Study). **The data including SoT consisted of tissue specimens collected at sites of biopsy determined during Study NMK36-BT-P202**.

Sample Size and Study participants

All available datasets (~35 patients) from Study NMK36-BT-P202 (consisting of 69 images, with 47 individual biopsy locations)

Primary endpoints

- Determination of the positive predictive value (PPV) of 18F-fluciclovine positron emission tomography (PET) scanning used as an adjunct to contrast-enhanced-T1-weighted (CE-T1W) magnetic resonance imaging (MRI), compared to the PPV of CE-T1W MRI alonePPV of PET (+ CE-T1W MRI) compared to CE-T1W MRI.

Secondary:

- Determination of the negative predictive value (NPV), sensitivity and specificity of 18F-fluciclovine PET scanning used as an adjunct to CE-T1W MRI, compared to CE-T1W MRI alone.
- Determination of the diagnostic performance of 18F-fluciclovine PET scanning used as an adjunct to CE-T1W MRI, compared to the diagnostic performance of fluid-attenuated inversion recovery (FLAIR [or T2W]) alone.
- Determination of the diagnostic performance of 18F-fluciclovine PET scanning used as an adjunct to CE-T1W MRI, compared to the combined diagnostic performance of FLAIR (or T2W) MRI and CE-T1W MRI.
- **Determination of inter- and intra-reader reproducibility of 18F-fluciclovine PET image evaluation read in conjunction with CE-T1W MRI.**

Exploratory:

- Determination of the extent and intersection of VOIs between imaging modalities (e.g., 18F-fluciclovine PET vs. CE-T1W MRI vs. FLAIR [or T2W]

Randomisation and Blinding

For this BIE study, readers were blinded to the specifics of the clinical evaluations, personal information and patient identification. Specifically, readers were blinded to the patient's medical history, results of the reads from Study NMK36-BT-P202 for the 18F-fluciclovine PET images, biopsy location, histopathology results, the patient's final diagnosis and outcome.

The randomisation was such that individual patient images had different randomization codes for each reader; the randomisation codes dictated the order in which the blinded readers viewed the image datasets during the BIE;

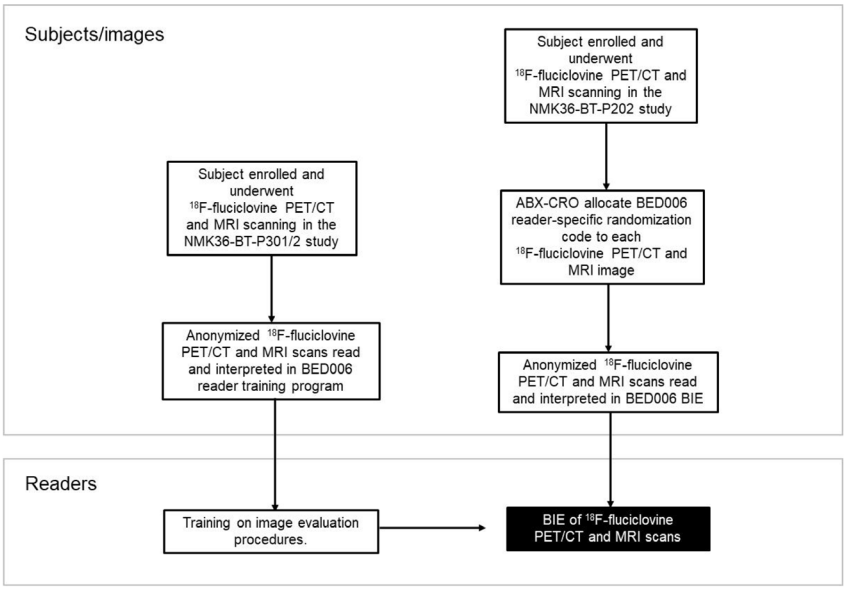
Study conduct

Copies of anonymized 18F-fluciclovine PET patient images were obtained and evaluated in this study by readers blinded to any patient-specific information (i.e., medical history, results of NMK36-BT-P202 reads of the 18F-fluciclovine PET images, biopsy location, histopathology results, the patient's final diagnosis and the patient's outcome).

Prior to conducting the BIE read, all readers had training on the read procedures and familiarization using cases from Studies NMK36-BT-P201 and/or NMK36-BT-P301/2.

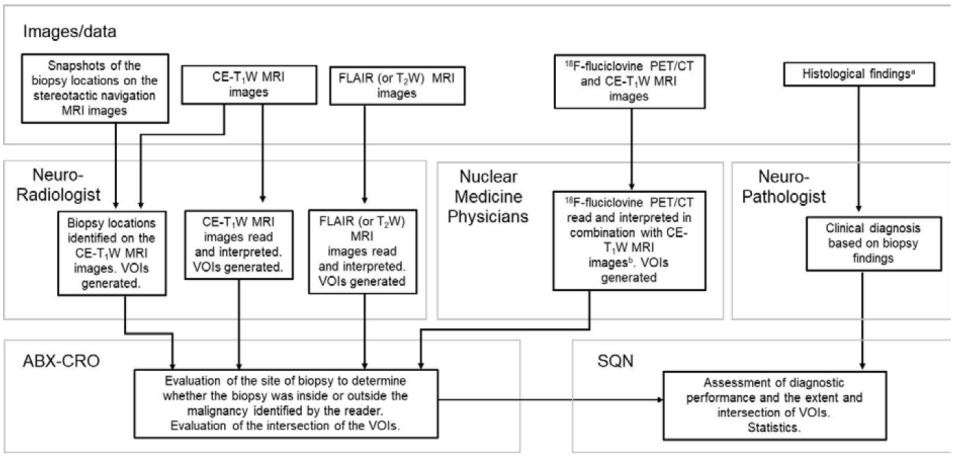
MRI (CE-T1W and FLAIR [or T2W]) image evaluation was performed by one independent blinded reader (neuro-radiologist). PET (+ CE-T1W MRI) image evaluation was performed by three independent blinded readers (nuclear medicine physicians). To ensure the image evaluations of each reader could be compared reliably, all readers were required to perform the image evaluation procedures in an identical manner for each image dataset.

Figure 1: Study Design - Subject Flow and Reading of Scans



BIE=Blinded Image Evaluation; CT=computed tomography; MRI=magnetic resonance imaging; PET=Positron emission tomography.

Figure 2: Study Design - Data Review



CE-T_1W=contrast-enhanced-T_1-weighted; CT=computed tomography; FLAIR=fluid-attenuated inversion recovery; MRI=magnetic resonance imaging; PET=Positron emission tomography; SQN=Syne Qua Non; T_2W=T_2-weighted; VOI=volume of interest.

[a] Central Pathology Review Committee histology assessment of biopsies obtained in Study NMK36-BT-P202.

[b] Random 20% of images were re-read.

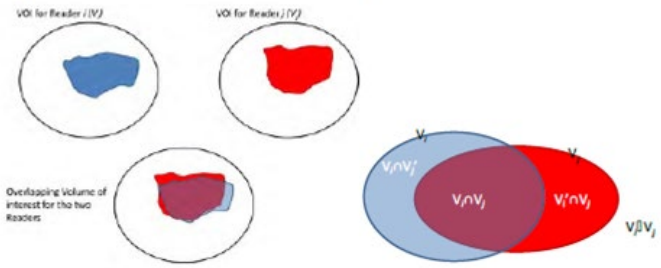
Statistical analysis:

Fleiss' Kappa statistics were used to assess the overall inter-reader reliability of binary interpretation of 18F-fluciclovine PET scan images at the site of biopsy (i.e., inter-reader agreement was based on the binary analysis of whether there was agreement between readers on whether the biopsy location was within the PET positive region). The confidence intervals for the Kappa statistics were calculated.

Pairwise inter-reader agreement was also assessed using Cohen's Kappa statistics. The VOIs of 18F-fluciclovine PET for each individual reader, and the intersection of VOIs and the VOI similarity metrics DC and Concordance Index (CI) between any two readers were summarized descriptively.

A graphic representation and the formulae used to calculate the VOI similarity metrics is provided in Figure 4.

Figure 4: Calculation of VOI Similarity Metrics



$$DC = \frac{2V_i \cap V_j}{V_i + V_j}$$

$$CI = \frac{V_i \cap V_j}{V_i \cup V_j}$$

where V_x is the VOI for reader *x*

$V_i \cap V_j$ is the intersection of the VOI for reader *i* and reader *j*

and $V_i \cup V_j = V_i + V_j - V_i \cap V_j$

CI=Concordance Index; DC=Dice Coefficient; VOI=volume of interest.

Outcomes

The applicant reports that for the overall analysis, irrespective of whether images were positive or negative on MRI, in terms of diagnostic performance, the PPV for PET (+ CE-T1W MRI) was high for all three readers at both timepoints (range, 93.1% to 96.4%).

In comparison, the PPV for CE-T1W MRI alone was 94.1% and the PPV for FLAIR (or T2W) MRI alone was slightly lower at 84.6%. The NPV for PET (+ CE-T1W MRI) ranged from 38.1% to 43.8% for the three readers at both timepoints. In comparison, the NPV for CE-T1W MRI alone was 26.7% and the NPV for FLAIR (or T2W) MRI alone was 37.5%. The data demonstrate the higher sensitivity of PET (+ CE-T1W MRI) compared to CE-T1W MRI alone, as well as the higher specificity of PET (+ CE-T1W MRI) compared to FLAIR (or T2W) MRI alone.

Specifically, the sensitivity of PET (+ CE-T1W MRI) ranged from 64.9% to 75.7% for the three readers at both timepoints, whereas the sensitivity was lower for CE-T1W MRI alone (42.1%) but slightly higher for FLAIR (or T2W) MRI alone (86.8%). The specificity of PET (+ CE-T1W MRI) ranged from 77.8% to 88.9% for the three readers at both timepoints, whereas the specificity was comparable for CE-T1W MRI alone (88.9%) but lower for FLAIR (or T2W) MRI alone (33.3%).

For biopsies that were taken from negative areas on CE-T1W MRI (n=30), the sensitivity of 18F-fluciclovine PET scanning used in combination with CE-T1W MRI ranged from 45.5% to 61.9%.

Of these 30 biopsies, 10 to 13 were True Positives identified by PET (+ CE-T1W MRI) when they were negative on CE-T1W MRI alone. For biopsies that were that were within a region positive for FLAIR (or T2W) (n=39), the specificity of 18F-fluciclovine PET scanning used in combination with CE-T1W MRI ranged from 66.7% to 83.3%. Of these 39 biopsies, four or five were True Negatives identified by PET (+ CE-T1W MRI) when they were False Positive on FLAIR (or T2W) MRI.

Diagnostic performance data for PET (+ CE-T1W MRI) at Timepoint 1 (i.e., PET starting between 10 and 20 minutes post-injection) and Timepoint 2 (i.e., PET starting between 40 and 50 minutes post-injection) were generally consistent:

- PPV ranged from 96.2% to 96.4% at Timepoint 1 and from 93.1% to 96.0% at Timepoint 2.
- NPV ranged from 38.1% to 42.1% at Timepoint 1 and from 38.1% to 43.8% at Timepoint 2.
- Sensitivity ranged from 65.8% to 71.1% at Timepoint 1 and from 64.9% to 75.7% at Timepoint 2.
- Specificity ranged was 88.9% for all three readers at Timepoint 1 and ranged from 77.8% to 88.9% at Timepoint 2.

Analyses of inter-reader agreement of PET (+ CE-T1W MRI) reads based on the binary interpretation of the data (i.e., whether there was agreement between the readers on whether the biopsy location was within the PET positive region) indicated that concordance was high for all three readers overall and for pairwise inter-reader comparisons (Reader 1 vs. Reader 2, Reader 1 vs. Reader 3 and Reader 2 vs. Reader 3). Specifically, overall, 89.4% and 87.0% of scans were in agreement by all three readers at Timepoint 1 and Timepoint 2, respectively (Fleiss' Kappa, 0.86 and 0.82, respectively) based on binary interpretation of the data. At both timepoints, concordance was ~90% or higher for each pairwise inter-reader comparison (Cohen's Kappa, 0.78 to 0.91) (binary interpretation). Inter-reader agreement in terms of the VOI was also high, with the median DC ranging from 0.783 to 0.894 and the median CI ranging from 0.643 to 0.808 between the comparisons at Timepoint 1 and Timepoint 2. As for diagnostic performance, no notable differences were noted between timepoints.

Binary analyses of intra-reader agreement of PET (+ CE-T1W MRI) reads when re-read a second time by the same reader indicated that concordance was high for all three readers. Specifically, overall, concordance ranged from 83.3% to 100%, with Cohen's Kappa ranging from 0.66 to 1.00 (depending on reader and timepoint). Intra-reader agreement with the initial read vs. the re-read in terms of the VOI was also high, with the median DC ranging from 0.887 to 0.911 and the median CI ranging from 0.797 to 0.840 between the comparisons at Timepoint 1 and Timepoint 2. Again, no notable differences were noted between timepoints.

Analyses of the extent and intersection of VOIs between imaging modalities demonstrate the significant added volume of the VOI that was identified on PET (+ CE-T1W MRI) vs. CE-T1W MRI alone. In addition, data demonstrate the additional volume identified on FLAIR (or T2W) MRI alone vs. PET (+ CE-T1W MRI). The median additional volume identified using PET (+ CE-T1W MRI) that was outside the volume identified with CE-T1W MRI alone represents a median 28% to 63% increase from the volume of CE-T1W MRI.

The median additional volume identified on FLAIR (or T2W) MRI, but not with PET (+ CE-T1W MRI), was 66% to 68% of the total volume identified by FLAIR (or T2W) MRI although, as previously described, the specificity of FLAIR (or T2W) was lower.

Table 7: Summary of Diagnostic Performance for all Imaging Modalities (Efficacy Analysis Set)

Parameter [% (95% confidence interval)]	18F-Fluciclovine PET (+ CE-T1W MRI)						MRI		
	Reader 1		Reader 2		Reader 3		CE-T1W MRI	FLAIR (or T2W) MRI	FLAIR (or T2W) and CE-T1W MRI
	Timepoint 1	Timepoint 2	Timepoint 1	Timepoint 2	Timepoint 1	Timepoint 2			
PPV	96.2% (80.4%, 99.9%)	96.0% (79.6%, 99.9%)	96.2% (80.4%, 99.9%)	93.1% (77.2%, 99.2%)	96.4% (81.7%, 99.9%)	93.3% (77.9%, 99.2%)	94.1% (71.3%, 99.9%)	84.6% (69.5%, 94.1%)	85.4% (70.8%, 94.4%)
NPV	38.1% (18.1%, 61.6%)	38.1% (18.1%, 61.6%)	38.1% (18.1%, 61.6%)	41.2% (18.4%, 67.1%)	42.1% (20.3%, 66.5%)	43.8% (19.8%, 70.1%)	26.7% (12.3%, 45.9%)	37.5% (8.5%, 75.5%)	50.0% (11.8%, 88.2%)
Sensitivity	65.8% (48.6%, 80.4%)	64.9% (47.5%, 79.8%)	65.8% (48.6%, 80.4%)	73.0% (55.9%, 86.2%)	71.1% (54.1%, 84.6%)	75.7% (58.8%, 88.2%)	42.1% (26.3%, 59.2%)	86.8% (71.9%, 95.6%)	92.1% (78.6%, 98.3%)
Specificity	88.9% (51.8%, 99.7%)	88.9% (51.8%, 99.7%)	88.9% (51.8%, 99.7%)	77.8% (40.0%, 97.2%)	88.9% (51.8%, 99.7%)	77.8% (40.0%, 97.2%)	88.9% (51.8%, 99.7%)	33.3% (7.5%, 70.1%)	33.3% (7.5%, 70.1%)

CE-T_1W=contrast- CE-T1W=contrast-enhanced-T1-weighted; FLAIR=fluid-attenuated inversion recovery; MRI=magnetic resonance imaging; NPV=negative predictive value; PET=positron emission tomography; PPV=positive predictive value.

Source: Table 14.2.1.1 and Table 14.2.2.1

Assessor's comment:
BED-006 was designed to evaluate the technical performance of 18F-fluciclovine PET in combination with CE-T1W MRI for the delineation of the extent of primary brain tumour, in terms of reproducibility of read results and concordance with SoT data, when Study NMP-P202 scans were re-read and interpreted by naïve readers. The SoT consisted of tissue specimens collected at sites of biopsy determined during Study NMP-P202 (using histology results determined by the histopathologist for Study NMP-P202 in Japan). Considering the limited number of PETs available, the applicant's decision to restrict the source for analysis only on the evaluable PETs from NMP-P202 is not understood. Addition of available PETs from the both other trials NMP-P301 and 301 would have resulted in a higher degree of reliability regarding the findings of this analysis. (OC).

The applicant summarises that of the 47 biopsies taken in Study NMP -P202 (38 positive, nine negative; based on histopathological results), 39 were within a region positive for FLAIR (or T2W) MRI and eight fell outside FLAIR (or T2W) regions. Of the eight biopsies that fell outside FLAIR (or T2W) regions, six were negative on PET (+ CE-T1W MRI) (except for Reader 3 at Timepoint 2, where only five were negative). This comprised three True Negatives and three False Negatives (or two False Negatives for Reader 3 at Timepoint 2). The remaining 2/8 (or 3/8 for Reader 3 at Timepoint 2) biopsies that fell outside FLAIR (or T2W) regions were positive on PET (+ CE-T1W MRI), and were, thus, were claimed as True Positives. No False Positives were identified (i.e., there are no cases that had a negative biopsy, but were positive on PET [+ CE-T1W MRI] and negative on FLAIR [or T2W] MRI). In the Rapporteur's view, this small differences are not sufficient to prove convincing a benefit from the additional PET procedure. It seems that the true negatives and the three false negative regions are balanced, which makes it impossible to define a clear benefit. Considering the small number of patients and biopsies involved, in our view chance findings may also explain the outcome. In the Rapporteur's view, the data do not suggest reliably any added benefit of PET scanning used in combination with CE-T1W MRI compared to FLAIR (or T2W) MRI alone. Moreover, it was not demonstrated that the small differences discussed had any impact on the surgery or the patients outcome.

It is agreed that the reported image interpretation across readers and timepoints investigated in trial BED-006 may demonstrate an acceptable reproducibility across readers and when images were re-read by the same reader for a second time. This seems to be demonstrated by an agreement of 89.4% and 87.0% of scan-interpretation by all three readers at Timepoint 1 and Timepoint 2, respectively (Fleiss' Kappa, 0.86 and 0.82, respectively). At both timepoints, concordance was observed as ~90% or higher for each pairwise inter-reader comparison (Cohen's Kappa, 0.78 to 0.91) (binary interpretation).
However, since the outcome of a PET read is an area that is declared to be PET positive, it is not obvious what is the best way to analyse reader agreement because the most frequently applied measures for reader agreement are based on binary outcomes.
Fleiss' kappa statistics and Cohen's Kappa statistics were calculated based on binary agreement with regard to the PET status of biopsies that were obtained in study 202. The applicant does not explain the rationale why the obtained biopsies are an adequate basis for analysis of reader agreement, and what conclusions that can be made regarding overall reader agreement based on this limited set of biopsies. A possible rationale could be that reader agreement with regard to these biopsies is considered representative for overall reader agreement (i.e. that reader agreement for other sites where no biopsy was taken is on average the same), or that agreement with regard to the selected biopsies is of particular importance. However, the representativeness of the findings based on the selected biopsies could be questioned, taking into account that these biopsies were preferably taken from areas that were considered to be PET positive in the original study 202, and it may be assumed that biopsies were not randomly taken but at sites that were unambiguously PET positive. This should be discussed by the applicant (OC).
Furthermore, as more than one biopsy was obtained from some subjects, the underlying assumption of independency for calculation of the confidence intervals for the kappa statistics is not fulfilled (OC).
In addition, pairwise inter-reader agreement was analysed based on intersection of VOIs using DC and CI (thereby, it needs to be considered that CI can be converted to DC by CI = DC/(2-DC) such that using one of these measures is sufficient as the second one does not provide new information regarding agreement). These are considered relevant as they provide a continuous measure that take the complete PET positive areas into account rather than single biopsies. (OC)
The main issue in this application remains also considering the results of BED-006 and the blinded interreader testing: A clear, reliable clinical benefit from performing an 18F-flociclovine PET in addition to FLAIR-MRI was not demonstrated in glioma patients, which is confirmed by the negative outcome of trial NMP-P302.

Subgroup analyses:

For the primary effectiveness endpoint (PPV of 18F-fluciclovine PET scanning to detect histologically confirmed primary or recurrent brain tumor) and one of the secondary endpoints (DR, sensitivity, specificity and NPV for both primary and recurrent brain tumor), data were summarized overall and according to subgroups by sex, age, race, WHO grade, histological type, and 18F-fluciclovine radioactivity dose.

Assessor's comment:

The applicant concedes that data available is insufficient for any subgroup analysis neither for primary glioma nor even for recurrent glioma patients in the EAS. This is illustrated by the finding e.g that there was only one scan for a patient aged ≥65 years and one scan for a patient who had previously been administered 18F-fluciclovine, which met the criteria for inclusion in the diagnostic performance analysis. Moreover, as this could be expected already from the small number of subjects included in BED 008 as discussed above the applicant reports that subgroup analyses were only planned in subjects with recurrent glioma in the study protocol, however, even this analyses are not interpretable due to the very limited population included.

Summary of main study(ies)

The following tables summarise the efficacy results from the two main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial NMP-P202

Title: AN OPEN-LABEL STUDY TO ASSESS THE EFFICACY AND SAFETY OF A SINGLE (INTRAVENOUS) DOSE OF NMK36 TO PATIENTS WITH CLINICALLY SUSPECTED HIGH/LOW GRADE GLIOMA		
Study identifier	NMP-P202 ((NMK36-BT-P202)	
Design	Multi-center open-label trial, carried out with NMK36 single-dose intravenous administration (prospective trial)	
	Duration of main phase:	October 2013 (date of obtaining consent from first study patient) until July 2014 (Final date of observations, including follow-up investigations, of study patients)
	Duration of Run-in phase:	N/A
	Duration of Extension phase:	N/A
Hypothesis	Exploratory: To assess the efficacy and safety of single (intravenous) dose of NMK36 in patients with clinically suspected high/low-grade glioma, based on clinical symptoms, clinical course and MRI investigations.	
Treatments groups	42 (FAS: 35) Patients aged 20 years or older on the day of obtaining consent, with clinically suspected high-grade gliomas or low-grade gliomas, from their clinical symptoms/course and MRI investigations, and who were scheduled for resection.	
Endpoints and definitions	**Primary exploratory assessment criteria**	The positive predictive value of Appraisal Region ① in the 1st. NMK36 Scan
	Secondary exploratory assessment criteria 1	The positive predictive value of Appraisal Region ② in the 1st. NMK36 Scan

	Secondary exploratory assessment criteria 2	The positive predictive value of Appraisal Region ① and Appraisal Region ② in the 1st. NMK36 Scan
	Secondary exploratory assessment criteria	The positive predictive value, by grade of malignancy at enrollment, for Appraisal Region ① in the 1st. NMK36 Scan
	Secondary exploratory assessment criteria	Range of dosages administered (and other sec. assessment criteria)
Database lock	24 June 2014	
Results and Analysis		

Analysis description	**Primary Analysis**	
Analysis population and time point description	Per protocol	
Descriptive statistics and estimate variability	Treatment group	Final analysis set
	Number of subject	35
	The positive predictive value of Appraisal Region ① in the 1st. NMK36 Scan	The positive predictive value of 26 Appraisal Regions ① in the 1st. NMK36 Scan was 100.0% for the FAS (26 out of 26 regions; 95% confidence intervals, 86.8% to 100.0%), and the lower threshold of 70% was significantly exceeded (p <0.001). There were similar results for the PPS.
	The positive predictive value of Appraisal Region ② in the 1st. NMK36 Scan	The positive predictive value of 8 Appraisal Regions ② in the 1st. NMK36 Scan was 87.5% (7 out of 8 regions).
	The positive predictive value of Appraisal Region ① and Appraisal Region ② in the 1st. NMK36 Scan	The positive predictive value of 34 Appraisal Regions ① and Appraisal Regions ② in the 1st. NMK36 Scan was 97.1% (33 out of 34 regions).
	The positive predictive value, by grade of malignancy at enrollment, for Appraisal Region ① in the 1st. NMK36 Scan	The positive predictive values, by grade of malignancy at enrollment, for Appraisal Region ① in the 1st. NMK36 Scan were 100% (10 out of 10 regions) in the "suspected high-grade malignancy group", and 100% (16 out of 16 regions) in the "suspected low-grade malignancy group".
	Range of dosages administered	The positive predictive value, by radiation dosage administered at enrollment, for Appraisal Region ① in the 1st. NMK36 Scan was 100% (13 out of 13 regions) for the "high radiation dosage group", and 100% (16 out of 16 regions) the "low radiation dosage group".

	Other secondary efficacy assessment criteria	**4.) Range of PET Imaging Times** The concordance between the 1st. and 2nd. NMK36 Scans of the results of assessments of the appraisal regions was 94.1% (32 out of 34 regions), and the κ coefficient was high, at 0.824. 5.) **The positive predictive value of 23 Appraisal Regions ① in the 2nd. NMK36 Scan** was 100.0% (23 out of 23 regions), the same result as for the 1st. NMK36 Scan. **6.) No regions corresponding to contrast(+) PET(−) ** were observed in the 1st. NMK36 Scan. **7.)Eight of the 12 tissue samples collected from the contrast(−) PET(−) regions in the 1st. NMK36 Scan were judged to be "non-tumor", and 4 of the samples were judged to be "tumor".** 8) The mean values of the indices, SUVmax, T/N (contralateral) ratio, T/N (cerebellar) ratio and %SUVmax for tissue collection sites were all higher for "tumor" than for "non-tumor" .
Note / Analysis description	**This was an exploratory trial claimed as pivotal. The study design includes many different strata in two dose regimes administered and only 35 patients could be analysed at the end. The pivotal value remain indeterminated, since the number of patients included is too lowp and particularly the diagnostic impact of MRI in the reported results is not sufficiently evaluable. The calculated diagnostic parameters are therefore assessed as invalid.**	

Table 2 : Summary of Efficacy for trial BED-008 (retrospective data analysis)

Title: A Retrospective Observational Study Investigating the Effectiveness of 18F-fluciclovine PET in Human Subjects with Brain Tumor		
Study identifier	BED-008	
Design	This was a retrospective data extraction study. Data were collected from three sites where 18F-fluciclovine had been administered to patients with primary (i.e. initial diagnosis) and recurrent brain tumors. There were no patient visits; all data were extracted from the databases or medical records of patients who had undergone 18F-fluciclovine PET imaging.	
	First scan performed	August 2004
	Last scan performed	May 2015
Hypothesis	Exploratory: To assess retrospectively the efficacy and safety of single (intravenous) dose of 18F-Fluciclovine in patients with recurrent brain tumours	
Treatments groups	N/A	

Endpoints and definitions	**Primary objective**	The primary effectiveness endpoint is the calculation of the positive predictive value (PPV) of 18F-fluciclovine positron emission tomography (PET) scanning to detect: a) recurrence in patients previously diagnosed with brain tumor b) presence of malignant disease in patients undergoing testing for primary brain tumor, each in comparison to histopathological standard of truth (SoT).
	Secondary objective 1	Determination of the detection rate (DR), sensitivity, specificity, and negative predictive value (NPV) in both of these populations.
	Secondary objective 2	Comparison was made with standard magnetic resonance imaging (MRI) techniques used alongside PET, and any other amino acid PET imaging (where available) that was performed with which the patient was injected.
	Secondary objective 3	Survival data, where possible, was collected for all patients enrolled
Database lock	1. July 2017 / Date of Report: Final, 24 August 2018	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	From the 82 included patients in the retrospective analysis 18 patients were selected for the "final anaylsis set"(FAS) , 17 of these 18 patients had recurrent glioma, only one patient suffered from primary glioma, MRI findings were available for the selection of the biopsy region. There were 140 biopsy or surgery specimens for the 82 patients in the Full Analysis Set (FAS), of which the majority (135 [96.4%]) were classified as malignant. For 85 (60.7%) specimens, the site of the biopsy or surgery was guided by imaging. However, for 52 (37.1%) specimens, it is described that it was unknown whether the site of biopsy or surgery was guided by imaging. Overall, a positive MRI is described to have contributed to the collection of 81 (57.9%) specimens and a positive PET scan may have contributed to the collection of 11 (7.9%) specimens. The site of biopsy or surgery was guided by both positive MRI and positive PET imaging for nine (6.4%) specimens.	
Descriptive statistics and estimate variability	Treatment group	Final analysis set
	Number of subject	Included: 82 Analysed: 18

	The primary effectiveness endpoint is the calculation of the positive predictive value (PPV) of 18F-fluciclovine positron emission tomography (PET) scanning to detect: **a) recurrence in patients previously diagnosed with brain tumor** **b) presence of malignant disease in patients undergoing testing for primary brain tumor, each in comparison to histopathological standard of truth (SoT).**	a.) The PPV (n, 95% CIs) for 18F-fluciclovine PET scanning to detect histologically confirmed recurrent brain tumor was 88.2% (n=17, 63.6%, 98.5%). b.) Only 1 patient had a primary glioma in the analysis.
	Secondary objective 1: Determination of the detection rate (DR), sensitivity, specificity, and negative predictive value (NPV) in both of these populations.	The DR (n, 95% CIs) was 100.0% (17, 80.5%, 100.0%), and the sensitivity (n, 95% CIs) was 100.0% (17, 78.2%, 100.0%).The NPV and specificity could not be calculated as there were no patients with a negative 18F-fluciclovine PET scan.
	Secondary objective 2: Comparison was made with standard magnetic resonance imaging (MRI) techniques used alongside PET, and any other amino acid PET imaging (where available) that was performed with which the patient was injected.	The PPV (n, 95% CIs) for MRI to detect histologically confirmed recurrent brain tumor was 88.2% (17, 63.6%, 98.5%), the DR (n, 95% CIs) was 100.0% (17, 80.5%, 100.0%), and the sensitivity (n, 95% CIs) was 100.0% (17, 78.2%, 100.0%). The specificity and NPV could not be calculated as there were no patients with a negative MRI scan.
	Secondary objective 3 Survival data, where possible, was collected for all patients enrolled	Survival in the 82 patients included was nine (28.1%) patients with primary glioma and 43 (86.0%) patients with recurrent glioma were known to have died, giving a total of 52 (63.4%) patients. Median time to death (95% CIs) was not reached for primary glioma, and was 9.8 months (6.8 months, 13.4 months) for recurrent glioma.

Note / Analysis description	**This trial was a retrospective analysis of data available from three centers using 18F-Fluciclovine in some patients for glioma patients also. As indicated by the inclusion of overall 82 patients (originally planned 100) and analysing on 18 of these patients, the reliability of this trial regarding any diagnostic parameter as here present is very low and not acceptable for pivotal claims. Again, the diagnostic impact of MRI in the reported results is not sufficiently demonstrated. The calculated diagnostic parameters are therefore assessed as not reliable.**

Analysis performed across trials (pooled analyses and meta-analysis)

There were no pooled analyses or meta-analyses presented.

Clinical studies in special populations

There were no studies performed in renal or hepatic impaired patients.

The absence of clinical studies performed in renal or hepatic impaired patients since the initial approval should be justified.

2.3.7.3. Supportive study(ies)

In the applicant's view, studies **NMP-P301** and **NMP-P302** seemed to be claimed mainly as **supportive** Phase 3, single administration studies designed to evaluate the safety and efficacy of 18F-fluciclovine administered as a single i.v. injection to patients with suspected malignant glioma, based on their clinical symptoms, clinical course and MRI examinations, who were scheduled for resection via craniotomy.

The methodology for image evaluation was essentially the same for the two studies and is discussed below in Section 2.5.4.1.2.

Imaging data from the two studies were combined into the Study NMP-P301/P302 CSR. In both studies, patients (n=20 [Study NMP-P301] and n=25 [Study NMP-P302]) received 18F-fluciclovine, with 10-minute cranial PET scans started 10 to 50 minutes after administration.

Studies NMP-P301 and NMP-P302 also included an assessment of how patient management was impacted by the results of the 18F-fluciclovine PET imaging (i.e., whether the extent of resection planned using the navigational MRI images changed [increased, decreased or was unchanged] after incorporation of data from 18F-fluciclovine PET).

Study NMP-P301 was a Phase 3, multicentre, single-dose, open-label, non-randomised study. A total of 22 Japanese patients were enrolled in the study, with 20 patients receiving study drug.

The majority of patients were male (13 [65.0%]). The mean age was 55.4 years (all within the category of 20 to 80 years). A total of 14 (70.0%) patients had suspected high-grade glioma and six (30.0%) patients had suspected low-grade glioma. The majority of patients had a KPS index score of 100% (six [30.0%] patients) or 90% (11 [55.0%] patients).

Open-label study to assess efficacy (diagnosability) and safety of a single dose (i.v.) of 18F FLUCICLOVINE in patients with clinically-suspected high/low-grade glioma.

Objective: To confirmatorily evaluate efficacy (diagnosability) and safety of a single dose (i.v.) of 18F FLUCICLOVINE in patients with clinically-suspected high/low-grade glioma based on clinical symptoms, course, and MRI examination, and who are scheduled for resection.

Population:

Inclusion criteria:

Select patients who satisfy all requirements listed below. The in-patient/outpatient status and sex differences shall not be considered.

(1) Patients at least 20 years of age on the date of consent.

(2) Patients with suspected high/low-grade glioma based on clinical symptoms, course, and MRI examination (T1-weighted image, contrast T1-weighted image, or FLAIR (or T1-weighted) image performed at the study site within the past 30 days from the date of consent), and for whom tumourectomy by craniotomy is scheduled.

Definition of suspected high-grade glioma group: "A group of patients with indistinct contrast findings based on T1-weighted images and contrast T1-weighted images with MRIs used for subject enrolment"

Definition of suspected low-grade glioma group: "A group of patients with indistinct contrast findings based on T1-weighted images and contrast T1-weighted images with MRIs used for subject enrolment."

(3) Patients who gave written consent themselves.

Exclusion criteria

Patients who meet any of the following criteria shall be excluded from this clinical trial.

(1) Patients who have received or who are receiving treatment for glioma (tumourectomy by craniotomy, chemotherapy, or radiation therapy). However, exclude patients who are receiving symptomatic treatment for neurological symptoms associated with brain tumour.

(2) Patients who have received chemotherapy for malignant tumours within the previous 5 years.

(3) Patients who are pregnant, breastfeeding, or may be pregnant.

(4) Patients whose most recent test results conducted within the last 30 days after obtaining consent meet pre-defined criteria of liver or renal dysfunction.

(5) Patients with a Karnofsky Performance Status (KPS) of 50 or less.

(6) Patients with a history of serious hypersensitivity to medication.

(7) Patients who have been administered 18F FLUCICLOVINE prior to participating in this clinical trial or patients who have been administered other investigational new drugs within the last 180 days after obtaining consent.

(8) Patients who are deemed ineligible to participate in this clinical trial by the principal investigator or subinvestigator (hereafter, investigators) for other reasons.

Conduct:

(1) IMP administration: After intravenously administering a full-dose vial of 18F FLUCICLOVINE into a vein in the arm, flush with physiological saline. Set the administered radioactivity to between 78.3 MBq (87.0 MBq - 10%) and 297.0 MBq (270 MBq + 10%) adjusted for administration time.

(2) 18F FLUCICLOVINE-PET/CT imaging: Perform 10-minute cranial PET imaging between 10 and 60 minutes after administering 18F FLUCICLOVINE.

(3) MRI imaging for navigation: Perform MRI imaging for navigation after completing safety examination on 18F FLUCICLOVINE administration Days 2 to 7 and before tumourectomy. Perform 3 types of MRI

imaging for navigation: 3D or 2D gapless for the T1-weighted image for navigation and contrast T1-weighted image for navigation.

1) T1-weighted image for navigation (slice thickness ≤2 mm)*
2) Contrast T1-weighted image for navigation (slice thickness ≤2 mm)*
3) FLAIR (or T2-weighted) image for navigation (slice thickness ≤5 mm)
* Use identical imaging conditions before and after contrast.

(4) Plan for tissue collection sites to collect tissues for evaluating the diagnostic performance

Investigators plan tissue sampling sites in accordance with the following procedures.

1) Position the 18F FLUCICLOVINE image, T1-weighted image for navigation, and FLAIR (or T2-weighted) image for navigation using the contrast T1-weighted image for navigation as reference.
2) Visually determine the extent of 18F FLUCICLOVINE accumulation.
3) Visually referring to the contrast T1-weighted image for navigation and FLAIR (or T2-weighted) image for navigation, plan A tissue sampling site in an area that meets the conditions ① to ③ below.

Number of Subjects (Planned and Analyzed):

(1) Planned : NMP-P301 trial: 21 subjects / NMP-P302 trial: 26 subjects

(2) Enrolled: NMP-P301 trial: 22 subjects / NMP-P302 trial: 26 subjects

Combined assessment: 48 subjects

(3) Analyzed

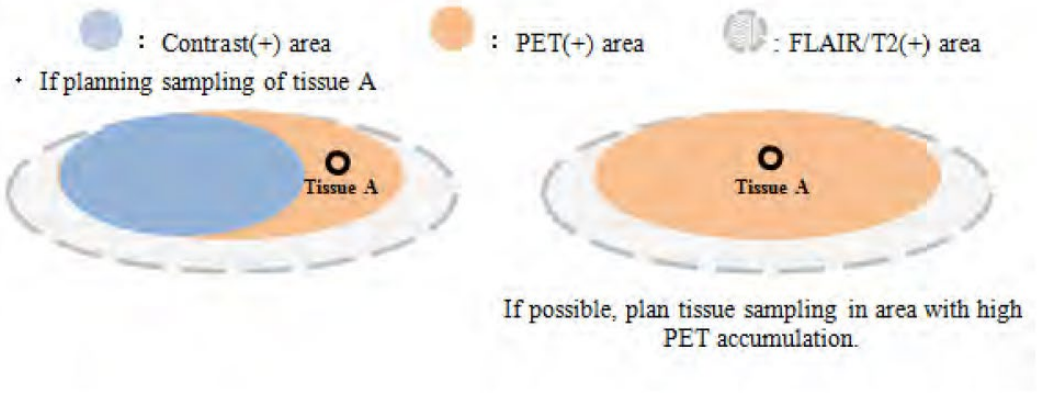
NMP-P301 trial: 20 safety analysis subjects, 15 full analysis set (FAS) subjects, 13 per protocol set (PPS) subjects

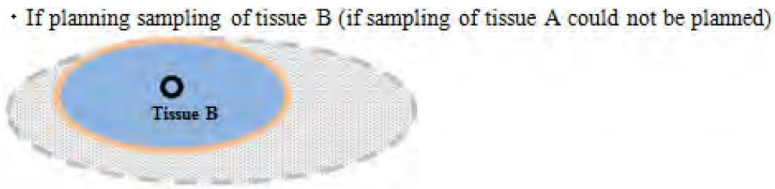
NMP-P302 trial (additional NMK36 administration group only): 25 safety analysis subjects, 21 FAS subjects, 19 PPS subjects

Combined assessment: 45 safety analysis subjects, 36 FAS subjects, 32 PPS subjects

① Contrast(-) PET(+) area* (* If enrolled in the suspected low-grade glioma group, if possible plan tissue sampling in areas with high PET accumulation.
② FLAIR/T2(+) area
③ Area from which tissue can be safely sampled from a medical perspective If sampling of Tissue A could not be planned, plan one tissue sampling site [Tissue B: contrast(+) PET(+)] in an area that meets conditions ① to ③ below.
① Contrast(+)PET(+) area
② FLAIR/T2(+) area
③ Area from which tissue can be safely sampled from a medical perspective

Figure : Predefined Areas of interest





4) Plan one tissue sampling site [Tissue C: contrast(-) PET(-)] with the same procedures as 3) above if there are areas that meet the following conditions. [First priority area]
① Contrast(-) PET(-) FLAIR/T2(+) area ＊(* If enrolled in the suspected low-grade glioma group, if possible plan tissue sampling from the centre of a FLAIR/T2(+) area (Figure 1). If the centre of a FLAIR/T2(+) area overlaps with a PET(+) area, plan tissue sampling from a PET(-) FLAIR/T2(+) area (Figure 2).
②Area from which tissue can be safely sampled from a medical perspective

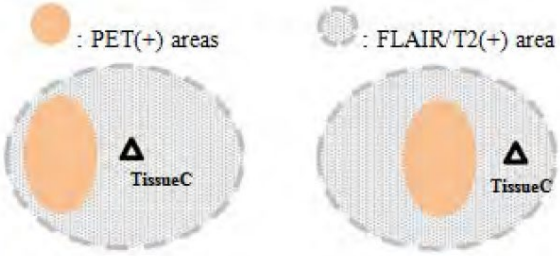
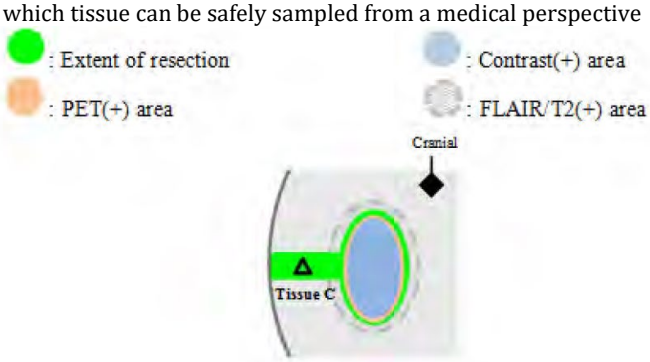


Figure 1 Figure 2

【Second priority areas】
① Contrast(-) PET(-) FLAIR/T2(-) area
② Area scheduled to be excised by tumourectomy
③ Area from which tissue can be safely sampled from a medical perspective



(5) Planning the extent of resection Investigators plan the extent of tumourectomy determined to be appropriate from a medical viewpoint while referring to the MRI image for navigation and 18F FLUCICLOVINE image. When doing so, use the snapshot function to electronically save representative slices which show the visualisation class of the MRI image for navigation and the 18F FLUCICLOVINE image, in order to evaluate the contribution of the 18F FLUCICLOVINE image to determining the extent of tumourectomy [see (9)2) below] (save the MRI image for navigation and the 18F FLUCICLOVINE image as a fused image).
(6) Collection of tissue to evaluate diagnostic performance

The investigators shall collect the tissues for evaluating diagnostic performance during biopsy according to the following procedure, which is similar to the resections via craniotomy.
1) A microincision shall be made in the dura mater in the area where the craniotomy shall be performed for resection.
2) Under neuronavigation, perform biopsy through a microincision and sample a slice of Tissue A (or Tissue C). Sample Tissues A and C in random order.
3) When sampling tissue, display the position of Tissue A (or Tissue C) on the triaxially-displayed contrast T1-weighted image for navigation using the neuronavigation system, and save this image electronically using the snapshot function (it is inadvisable to display the extent of PET accumulation as this will bias central image determination).
4) Then, under neuronavigation, perform biopsy through a microincision towards Tissue C (or Tissue A) planned for sampling, then sample 1 or more slices of tissue.
5) When sampling tissue, electronically save a snapshot image of the tissue sampling site similar to 3) above.
If sampling of Tissue A could not be planned, perform the same procedures as above for Tissue B.
6) The collected tissues shall be placed in cold storage in formalin solutions.
(7) Preparation of stained specimens for central pathology diagnosis
1) Investigators, a study collaborator, or external contract organisation (contracted company) transfers tissues preserved in formalin solution to a 70% alcohol solution the day after tumourectomy.
2) External contract trial centres (contract companies) shall prepare unstained samples.
3) The institutions to which the clinical trial is outsourced (contract companies) shall stain the unstained samples.
(8) Confirmation of the pathological diagnosis results at the clinical trial centres (definitive diagnoses)
Investigators or study collaborators confirm pathological diagnostic results (definitive diagnosis) based on WHO classifications, which are conducted at study sites along with tumourectomy, and record in the case report.

(9) Evaluation by clinical trial centres

Investigators perform evaluations 1) and 2) below.

1) Evaluation of contrast (+)PET(-) areas

2) Evaluation of changes to the extent of tumourectomy by adding the 18F FLUCICLOVINE image

(10) Evaluation by the central pathology review committee

The central pathology review committee members shall determine which of the following evaluation areas the tissues, which were collected by the clinical trial centres, belong to and measure semi-quantitative indices.

Evaluation area	**Contrast T1-weighted image for navigation**	**18F FLUCICLOVINE**
Evaluation area ①	Unclear	Accumulation present
Assessment region ②	Clear	Accumulation present

(11) Evaluation by the central pathology diagnosis committee. The central pathology diagnosis committee shall diagnose the stained specimens

(1) Primary endpoint

Positive predictive values of evaluation area ①

(2) Secondary evaluation items

1) Positive predictive value of evaluation area ②
2) Positive predictive value of PET(+) areas
3) Positive predictive values in evaluation area ① by suspected degree of malignancy upon enrolment
4) Positive predictive values for each PET imaging time range
5) Sensitivity and specificity of 18F FLUCICLOVINE images for all sampled tissue
6) Investigation of semi-quantitative indices that can suitably delineate the tumour extent
7) Concordance of 18F FLUCICLOVINE image determination results between readers

8) Evaluation of contrast(+)PET(−) areas
9) Percentage that 18F FLUCICLOVINE images contributed to setting and changing extent of tumourectomy
10) Comparison of histopathological findings of tissues sampled from PET(+) areas and PET(−) areas
11) Percentage of subjects enrolled as suspected low-grade glioma group whose tissue sampled from PET(+) areas was a high-grade glioma
13. Safety evaluation

Sample size
NMK36-BT-P301: Subjects in this clinical trial included 21 patients with suspected gliomas, based on their clinical symptoms, clinical course, and MRI examinations, who were scheduled for resection via craniotomy. In addition, 8 patients with suspected high- and low-grade gliomas were enrolled as subjects in this trial and received NMK36 in the NMK36-BT-P302 trial.

NMK36-BT-P302: The target sample size during this clinical trial was set at 52 patients (suspected high-grade glioma group: 32 patients, suspected low-grade glioma group: 20 patients), which was the number of patients that were estimated to be included within the required period of time and would include the number of patients required to evaluate the primary endpoint (PPV in evaluation area ①) of the NMK36-BT-P301 trial (29 patients in the suspected high-grade glioma group and 18 patients in the suspected low-grade glioma group, when the patients in the NMK36-BT-P301 trial and this trial were combined). Patients were evenly distributed into the control group and NMK36 administration group.

Furthermore, when a total of 29 subjects in NMK36-BT-P302 and the NMK36-BT-P302 trial satisfied the criteria below, the sponsor could conclude enrolment.
• Subjects from whom Tissue A could be planned and collected
• Subjects for whom the diagnosis of the tissue collection sites was confirmed by the central pathology diagnosis
• Subjects for whom the pathological diagnosis in the clinical trial centers (definitive diagnosis) was glioma.

The applicant calculated the number of cases after combining both studies required for evaluating the primary evaluation items (number of cases from whom tissue was able to be sampled from evaluation area ①) to be 23 to reject the null hypothesis of PPV ≤ 0.7 for α(one-tailed)=0.025 with statistical power of 0.9. Adding up both studies and incorporating 29 subjects from the suspected high-grade glioma group and 18 subjects from the suspected low-grade glioma group (total 47 subjects), the applicant believed to be able to sample Tissue A from 13 subjects in the suspected high-grade glioma group and 16 subjects from the suspected low-grade glioma group for a total of 29 subjects, and would be able to secure the necessary 23 subjects required to evaluate the primary evaluation items.

Assessor's comment
The sponsor should usually not be given the possibility to conclude enrolment on an optional basis in an open-label study. However, the targeted number of patients were included in both studies without concluding enrolment.

Statistical methods
The DPE (DPE) was performed using three analysis sets, namely the combined population made up of NMK36-BT-P301 trial subjects and the additional NMK36 administration group in the NMK36-BT-P302 trial, the NMK36-BT-P301 trial subjects, and the additional NMK36 administration group in the NMK36-BT-P302 trial.
The safety analysis set (SAS) included the population of subjects who received NMK36 during this clinical trial.
The full analysis set (FAS) included the safety analysis population, excluding the subjects who were unsuitable or ineligible for inclusion in the safety evaluation, and with no recognized scientific suitability.
The per protocol set (PPS) was defined as the population within the FAS that excluded trial subjects with known deviations from the clinical trial protocol.

Subjects who withdrew before administration of NMK were excluded from the SAS, while subjects who withdrew before resection were excluded from the FAS. Whether subjects were included or not included in the analysis was decided by the sponsor, based on scientific and ethical points of view, and with reference to the opinions of medical specialists, before the start of the efficacy analysis.

Failed and missing data were treated as "no data."Anomalous data were treated as true data when the causes were investigated and were unknown. When the causes were clear, they were treated as rejected data. The handling of the rejected data was decided by the sponsor, based on scientific and ethical points of view and with reference to the opinions of medical specialists, before the start of the analysis of efficacy. Moreover, the rejected data and the included data were analyzed as part of the discussion, and the variations in the results that were due to adding the rejected data to the analysis were examined.

The analysis of efficacy in this trial was performed by making a final decision on the results determined by the majority decision of three CPRC members (responsible for PET) [presence of imaging of contrast T1-weighted images for navigation, presence accumulation of NMK36, and signal intensities of FLAIR (or T2-weighted) images for navigation]. Furthermore, the semiquantitative indices were analyzed by using the mean values from three CPRC members (responsible for PET).

The PPV in evaluation area ① (primary endpoint) was the percentage of subjects whose tissues were tumors, based on histopathological examination, calculated from the group of subjects whose tissue collection sites were evaluation area ① and using a 95% CI (Clopper-Pearson and Wilson methods). Moreover, a test by normal approximation using the null hypothesis with a population ratio of 0.7 with one-sided α=0.025 was performed in order to verify whether these values exceeded the lower limit of 70% of diagnoses when the PPV was used to determine the required sample size for the PPV.

The 95% CI (Wilson method) was also calculated for the secondary endpoints.

Groups of two radiologists were created from three CPRC members (responsible for PET), and the concordance rate and κ coefficient for each image interpreter pair (total of 3 pairs) was calculated using outcomes of decisions taken on the presence of PET accumulation in all of the collected tissues and each collected tissue.

Assessor's comment

A majority decision of three CPRC members does not correspond to clinical practice. The diagnostic performance of a majority decision could be larger compared to a single reader.

The FAS should usually include all patients that were included in the study. If it is nevertheless intended to exclude patients from analysis, a justification is required and exclusion needs to be based on pre-specified, objective criteria. In this trial, in addition to exclusion due to non-administration of study drug or withdrawal before resection which is acceptable, decision to exclude subjects was made by the sponsor based on 'scientific and ethical points of view' which were not further defined. Making the decision on exclusion of patients before start of efficacy analysis does not protect from bias in an uncontrolled study. Main reasons for excluding subjects from the FAS were non-collection of tissue (n=4) or no tissue collection site information (n=3). It needs to be discussed whether bias due to exclusion of these patients can be excluded (i.e. why the reason that no tissue was collected, or site information was missing can be considered independent from the PET status and histopathological status effect). Sensitivity analyses should be provided for the primary analysis assuming that patients without tissue collection site were collected in evaluation area ①, and a worst-case analysis for subjects where no tissue was collected (i.e. considering as area 1 and a false positive diagnosis). (OC)

The primary analysis was not based on the FAS but on the group of subjects whose tissue collection sites were evaluation area ① because the aim of the study was to show the additional value of PET. An additional effect measure of interest could be the proportion of patients with a (potential) additional benefit among all treated patients, i.e. 22/45 patients.

The threshold of 0.7 for the hypothesis test for PPV was justified by the positive diagnosis rate of 5-ALA (65.8%) as a reference. Testing the null hypothesis of a PPV ≤ 0.7 using a normal approximation assumption may not be the optimal approach taking the small number of patients considered for primary analysis (n=25) into account. Therefore, consistency with results from additional analyses (i.e. exclusion of 0.7 from the 95% CI) is of particular importance and requested. (OC)

Although formally the sample size may be seen as sufficient to reject the null hypothesis, it is challenged that the small sample size is adequate for a valid assessment of the outcome for the secondary endpoints. In particular, the issue whether patient management was impacted by the results of the 18F-fluciclovine PET imaging remains open. These needs to be clarified. (OC)

Study NMP-P302 was a Phase 3, multicentre, single-dose, open-label, randomised, controlled study. A total of 49 patients were enrolled in the study, including 26 patients in the MRI plus 18F-fluciclovine group and 23 patients in the MRI alone group. (Safety data were only analysed for the MRI plus 18F-fluciclovine group.)

Of those patients dosed with 18F-fluciclovine, the majority were male (18 [72.0%]). The mean age was 54.3 years (all within the category of 30 to 90 years). A total of 16 (64.0%) patients had suspected high-grade glioma and nine (36.0%) patients had suspected low-grade glioma. The majority of patients had a KPS index score of 100% (seven [28.0%] patients) or 90% (nine [36.0%] patients), with the remaining patients having a score between 60% and 80%.

Objective: To evaluate and verify the efficacy (diagnostic performance and outcomes) and safety of a single intravenous administration of NMK36 to subjects with clinically suspected gliomas based on their clinical symptoms, clinical course, and magnetic resonance imaging (MRI) examinations who are scheduled for resection via craniotomy.

Primary Endpoint: Primary endpoint (control group and NMK36 administration group):

Comparison (direct method) of the 9-month progression-free survival rate (hereafter, % 9mo-PFS)

Secondary Endpoints:

i) **Positive predictive values (PPV) in evaluation area ①**

ii) **PPV in evaluation area ②**

iii) PPV in PET (+) areas

iv) PPV in evaluation area ① by suspected degree of malignancy at the time of enrollment

v) PPV for each PET scan time range

vi) Sensitivity and specificity of 18F FLUCICLOVINE images in all collected tissues

vii) Search for semiquantitative indices that can appropriately visualize the extent of the tumor

viii) Inter-reader concordance rate for the reading of 18F FLUCICLOVINE images

ix) Evaluation of contrast (+) PET (-) areas

x) Comparison of histopathological findings in tissues collected from PET (+) and PET (-) areas

xi) Percentage of patients with high-grade glioma in tissue samples taken from PET (+) areas in patients enrolled in the suspected low-grade glioma group

Population: Patients with suspected gliomas, based on their clinical symptoms, clinical course, and MRI examinations, who were scheduled for a resection via craniotomy.

Inclusion criteria

Patients meeting all of the following criteria were selected. The in-patient/outpatient status and sex were not considered.

(1) Patients aged ≥20 years on the date of consent.

(2) Patients with suspected gliomas, based on their clinical symptoms, clinical course, and MRI examinations [T1-weighted images, contrast-enhanced T1-weighted images, FLAIR (or T2-weighted)

images within 30 days before the date on which consent was obtained], and who were scheduled for a resection via craniotomy.

(3) Patients who gave written consent themselves

Exclusion criteria

Patients to whom any of the following applied were excluded from participation in this study:

(1) Patients who received treatment or were currently being treated for gliomas (resection via craniotomy, chemotherapy, or radiotherapy), and patients who underwent diagnostic needle biopsies. However, symptomatic treatments for neurological symptoms accompanying cerebral tumors were excluded from this criterion.

(2) Patients who received chemotherapy for malignant tumors in the past 5 years.

(3) Patients who were pregnant, breastfeeding, or may be pregnant.

(4) Patients whose most recent test values, obtained no more than 30 days before the date of consent, met any of the following criteria:

- Liver function disorders: Total bilirubin (≥3.0 mg/dL), AST (≥2.5 times the hospital reference value), ALT (≥2.5 times the hospital reference value)
- Renal dysfunction: eGFR (<30 mL/min/1.73 m2)

(5) Patients with a Karnofsky Performance Status (KPS) ≤50.

(6) Patients with a history of severe drug hypersensitivity.

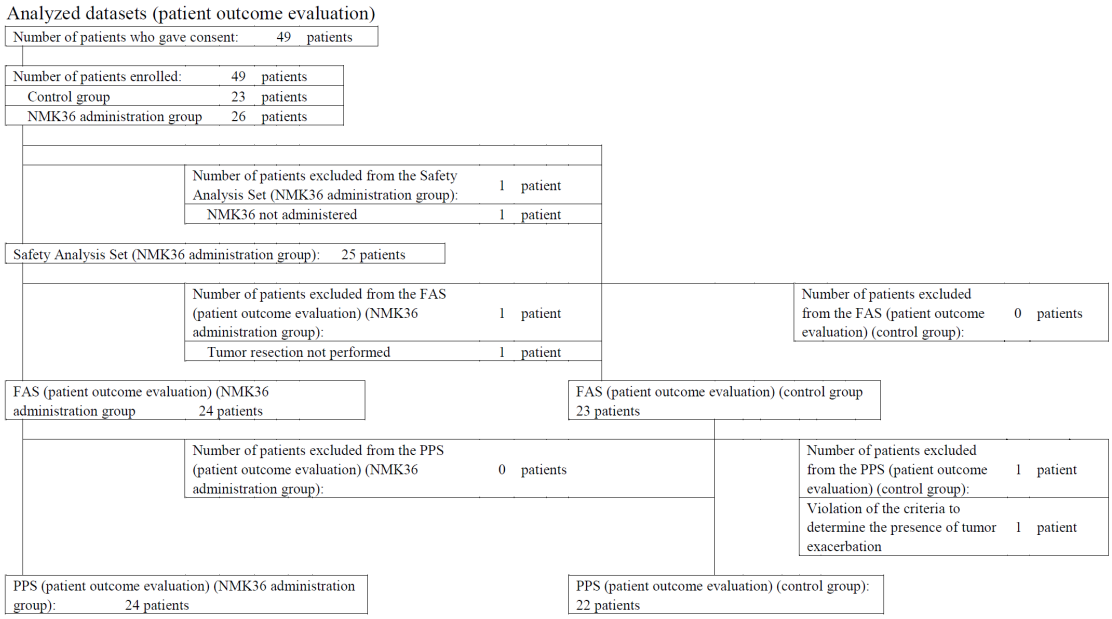
(7) Patients who received administrations of 18F FLUCICLOVINE before they were enrolled in this study or patients who received other study drugs within 180 days before the date of consent.

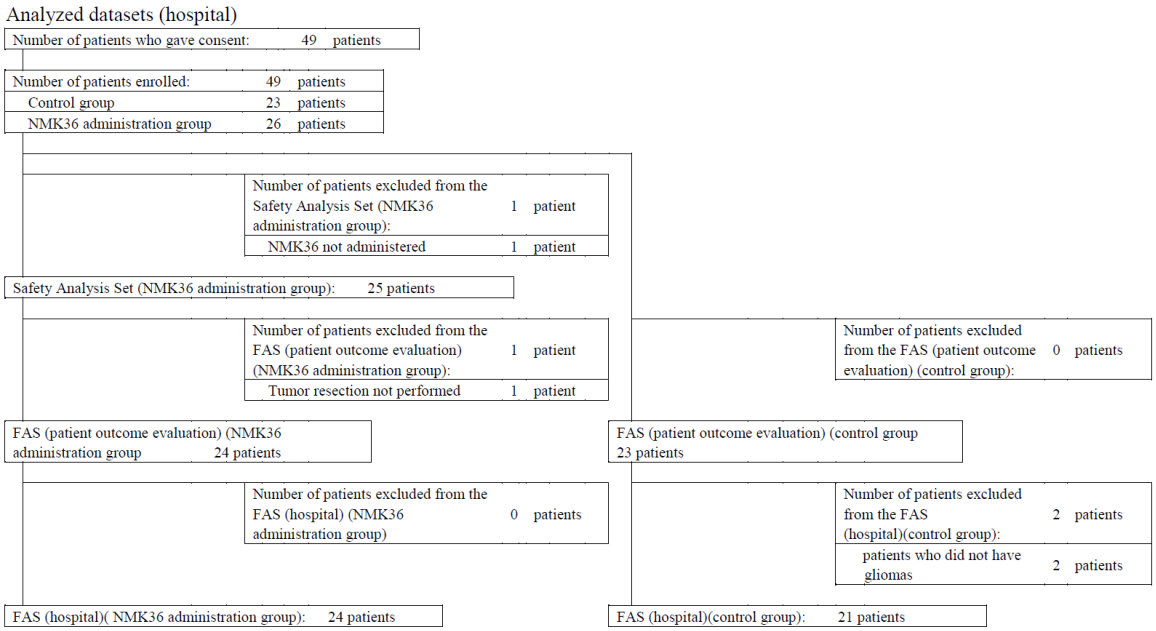
(8) Patients who underwent 11C-MET testing within 180 days before the date of consent, and patients scheduled to undergo 11C-MET testing between the date of consent and MRI imaging 270 days (±14 days) after tumor resection.

(9) Patients who were judged to be ineligible for participation in this study for other reasons by the Investigators

Results:

The 49 patients enrolled into this clinical trial underwent randomized allocation; 26 patients were allocated to the 18F FLUCICLOVINE administration group and 23 patients were allocated into the control group.





The analysis target sample size was 24 patients each in the FAS (patient outcome evaluation), PPS (patient outcome evaluation), and FAS (hospital) among the 26 patients in the 18F FLUCICLOVINE administration group, and all 23 patients in the FAS (patient outcome evaluation), 22 patients in the PPS (patient outcome evaluation) and 21 patients in the FAS (hospital) among the 23 patients in the control group.

The FAS (patient outcome evaluation) was defined as the primary analysis set, and analysis was also performed on the PPS (patient outcome evaluation) for the primary endpoint only.

Primary Endpoint outcome: (**Comparison of the % of 9months-PFS)**

a.) Suspected high-grade glioma group

1 Direct method: Primary endpoint

The %9 mo-PFS [number of patients, 95% confidence interval (Clopper-Pearson method), same hereafter] in the FAS (patient outcome evaluation) was 33.3% in the 18F FLUCICLOVINE administration group (4/12 patients, 9.9% to 65.1%) and 46.7% in the control group (7/15 patients, 21.3% to 73.4%), and the difference between the groups [18F FLUCICLOVINE administration group - control group (%), 95% CI (Clopper-Pearson method), same hereafter] was -13.3% (-49.0% to 25.0%) and was lower in the 18F FLUCICLOVINE administration group than in the control group. Even in the PPS (patient outcome evaluation), the difference in %9mo-PFS between the groups was -16.7% and was lower in the 18F FLUCICLOVINE administration group than in the control group, which was similar to the result in the FAS (patient outcome evaluation).

Secondary Endpoint outcome:

2 Kaplan-Meier method: Secondary endpoints

In the FAS (patient outcome evaluation), the difference in % of 9 months-PFS between the groups was -12.1%, and as with the direct method, was lower in the 18F FLUCICLOVINE administration group than in the control group.

(Regarding the outcome of the other secondary endpoints please refer to study report in M5-5.5.5.1; since they seemed not to have any further impact for this application; no separate analysis on the prespecified PPV endpoints were submitted in the study report. The applicant stated that the diagnostic performance evaluation in the 18F FLUCICLOVINE administration group in this clinical trial are discussed in the clinical trial report for the NMP-P301 trial, where the 18F FLUCICLOVINE administration groups from the NMP-P301 trial and this clinical trial were combined and evaluated)

…

(6) Percentage of 18F FLUCICLOVINE images that contributed to the determination and modification of the extent of resections: Secondary endpoints

1) Evaluation of changes to the extent of resection after the incorporation of 18F FLUCICLOVINE images

When the extent of tumor resection was evaluated during tumor resection planning and after tumor resection in the 24 patients in the 18F FLUCICLOVINE administration group [FAS (patient outcome evaluation)], the results were the same during planning and after resection in 23 patients. The results that differed during planning and after resection involved one patient in the suspected high-grade glioma group whose grade was IIIA during planning, but was evaluated as IIIB after resection.

2) Percentage of 18F FLUCICLOVINE images that contributed to the determination and modification of the extent of resection

The percentage of 18F FLUCICLOVINE images (number of patients, same hereafter) that contributed to the determination and modification of the extent of resections [enlarged or reduced (hereafter, E or R)] during tumor resection planning in the 18F FLUCICLOVINE administration group [FAS (patient outcome evaluation)] was 37.5% (9/24 patients), and among these, E occurred in 29.2% (7/24 patients) and R occurred in 8.3% (2/24 patients). When examined by suspected degree of malignancy group, E or R occurred in 53.3% (8/15 patients) in the suspected high-grade glioma group; among these, E occurred in 46.7% (7/15 patients) and R occurred in 6.7% (1/15 patients). E or R occurred in 11.1% (1/9 patients) in the suspected low-grade glioma group; among these, E occurred in 0.0% (0/9 patients) and R occurred in 11.1% (1/9 patients). **The results were the same as during tumor resection planning when evaluation was performed after tumor resection.**

(7) Correlation between prognosis and the degree of PET accumulation in the tumor: Secondary endpoints

Assessor's comment:

Trial NMP-P302 is described as a Phase 3, multicentre, single-dose, open-label, randomised, controlled study which enrolled 49 patients. Since it is one of 4 small clinical trials investigating the applied product in glioma and together with NMP-P301 the only trial which includes a control group it is hereby shortly reviewed and summarised, although the trial failed.

Again only a small number of 26 patients were investigated with MRI plus 18F-fluciclovine group while 23 patients received MRI alone for glioma diagnostic. In the 18F-fluciclovine group 16 (64.0%) patients had suspected high-grade glioma and nine (36.0%) patients had suspected low-grade glioma.

*The trial's objective was to evaluate and verify the efficacy (diagnostic performance **and outcomes**) and safety of a single intravenous administration of 18F-fluciclovine to subjects with clinically suspected gliomas based on their clinical symptoms, clinical course, and magnetic resonance imaging (MRI) examinations who are scheduled for resection via craniotomy.*

The primary endpoint was chosen to show the impact of additional PET diagnostic on clinical outcome in terms of a comparison (direct method) of the 9-month progression-free survival rate (hereafter, %9mo-PFS). Main secondary endpoints aiming to evaluate the Positive predictive values (PPV) in evaluation area and in PET (+) areas, as well PPV in evaluation area ① and ② by suspected degree of malignancy at the time of enrolment. Moreover, the diagnostic accuracy in terms of sensitivity and specificity of 18F-fluciclovine images in all collected tissues was investigated.

All patients included had suspected gliomas, based on their clinical symptoms, clinical course, and MRI examinations and were scheduled for a resection via craniotomy. Other inclusion and exclusion criteria are assessed as adequate to characterize the target population and to exclude potential risks or sources of bias for data interpretation.

The analysis target sample size was 24 patients each in the FAS (patient outcome evaluation), PPS (patient outcome evaluation), and FAS (hospital) among the 26 patients in the 18F-fluciclovine administration group, and all 23 patients in the FAS (patient outcome evaluation), 22 patients in the PPS (patient outcome evaluation) and 21 patients in the FAS (hospital) among the 23 patients in the control group. Reasons for exclusion of patients from the analysis are acceptable (no operation, patient does not receive the IVD).

The trial failed to show the expected benefit from additional 18F-fluciclovine PET diagnostic since the outcome for the primary endpoint was negative: The %9 mo-PFS [number of patients, 95% confidence interval (Clopper-Pearson method), same hereafter] in the FAS (patient outcome evaluation) was lower in the 18F-fluciclovine PET group (33.3%4/12 patients, 9.9% to 65.1%) in comparison with 46.7% in the MRI alone control group (7/15 patients, 21.3% to 73.4%). The difference between the groups (administration group - control group (%), 95% CI (Clopper-Pearson method) was -13.3% (-49.0% to 25.0%) and thereby also lower in the 18F FLUCICLOVINE administration group than in the control group. Even in the PPS the difference in %9mo-PFS between the groups was lower (-16.7%) in the 18F-fluciclovine group.

The applicant concludes correctly that the predefined criteria for success were not achieved and speculates that the primary cause may be due to bias in the poor prognostic factors.

From a regulatory point of view it seems relevant that the trial was not able to show any benefit from performing 18F-fluciclovine PET diagnostic in addition to MRI in the target population with respect to the clinical outcome. It remains not conclusive why this trial is claimed as supportive for this application. The only relevant value of this trial seems to be that it may confirm that 18F-fluciclovine PET is able to display glioma, which seems not very helpful. The applicant clarified that the PET results regarding the extent of tumor resection, which was evaluated during tumor resection planning and after tumor resection in the 24 patients in the 18F-fluciclovine group [FAS (patient outcome evaluation)], were the same during planning and after resection in 23 patients. The results that differed during planning and after resection involved one patient in the suspected high-grade glioma group whose grade was IIIA during planning, but was evaluated by histology as IIIB after resection.

Moreover, the separate outcome regarding the pre-specified secondary endpoints according PPV from trial NMP-P302 is missing. Only pooled results are provided. Thus, the applicant is requested to show the outcome regarding the secondary endpoints (i-vi) in order to clarify the PPV in comparison to MRI alone from this trial and to discuss differences regarding the pooled P301 and P302 outcome.

Nevertheless, it is fully acknowledged that in the small population investigated the company's primary aim might have been over-optimistic. However, it confirms the view that studies in adequately large populations are necessary to evaluate the full impact of additional PET diagnostic in the glioma setting.

The applicant describes that in trials NMP-P301 and P302 30.6% (11/36 patients) had an increase in the volume of tumour resected and 16.7% (6/36 patients) had a decrease as a result of addition of PET scanning. This finding is claimed as a clear clinical benefit of the addition of 18F-Flociclovine PET scan to standard of care MRI. Of the 17 patients with a change in volume of resection after addition of 18F-fluciclovine PET, 14 had suspected high-grade disease (11 with an increase in resection volume and three with a decrease) and three had suspected low-grade disease (all three with a decrease in resection volume). This is claimed as a clear clinical benefit from the addition of 18F-fluciclovine PET scanning to standard of care MRI, because more complete glioma resection is believed to improve prognosis while any measure which can safely preserve intact brain is beneficial to patients. Although this statement may be correct in principle, no data was provided to prove this claim. In contrast, the decreased 9 months PFS rate in the PET observed in trial NMP-P302 may be seen as demonstration of inferiority of 18F-Fluciclovine in comparison to MRI regarding the clinical outcome.

2.3.8. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant claims that taken collectively, data from the submitted trials NMP-P201, NMP-P202, NMP-P301/P302, BED-006 and BED-008 provide sufficient data on the technical (reproducibility of image reads across readers and when re-read by the same reader a second time) and/or diagnostic performance (sensitivity and specificity) of 18F-fluciclovine PET imaging in combination with MRI, as well as the impact on diagnostic thinking (positive and negative predictive values) to **justify approval of 18F-Fluciclovine in the intended indication "for the detection and continuing assessment of glioma".**

The Rapporteur does not share this view.

An adequately powered and designed pivotal phase 3 trial performed in a sufficient number of patients essential to justify the applied broad indication is currently missing.

The applicant seeks approval based on four **small prospective open trials** NMP-P201, NMP-P202 and P301/302 which include each only a few patients (between 5 and 35 patients) all with primary glioma only. They were all performed in the Japanese population by another sponsor (Nihon Medi-Physics Co., Ltd.).

In addition, the applicant has added **retrospective data** from further 18 patients (Finally analysed set) evaluated in **trial BED-008**. This analysis was planned to be conducted in 100 Caucasian patients, 82 were enrolled, but only 18 could be evaluated. Data is derived from three centers in the US and Norway. All but one of these patients suffered from recurrent glioma.

Studies NMP-P201 and **NMP-P202** were Phase 1/2, single administration, open-label studies designed to evaluate the safety and efficacy of 18F-fluciclovine administered as a single i.v. injection to patients with a suspected diagnosis of malignant glioma based on either clinical symptoms and/or brain MRI. In both studies, patients (n=5 [Study NMP-P201] and n=40 [Study NMP-P202]) received 18F-fluciclovine. Cranial dynamic PET scans were performed at 0 to 60 minutes after administration (rebinned at 10, 30, 50 minutes after administration using 5, 10 and 15 minutes of PET list mode data to create image datasets simulating 87 MBq, 185 MBq and 270 MBq administered activity, respectively) in Study NMP-P201, and 10 to 20 minutes and 40 to 50 minutes after administration in Study NMP-P202.

Data from trial NMP-P201 is seen as a first proof of principle and was used to establish the currently applied fixed-dose posology for the other trials in Japanese patients. Since it seems that higher doses were administered in the Caucasian population according the retrospective anaylsis presentedin BED-008, major concerns are raised whether the applied fixed dose posology is applicable also for the EU population. While it is acknowledged that fixed dose posologies are established in Japan, it remains open

whether such a posology is also adequate for the application in the EU population, since the Japanese population in general has a significant lower and more homogenous bodyweight distribution in comparison to the European. This reasoned that normally a body-weight adapted posology is preferred and used for PET imaging agents in the EU. (MO)

Furthermore, the design of the largest trial **NMP-P202** (as well as that of the smaller trials NMP-P301 and NMP-P302) is highly complex and not fully comprehensible. With respect to endpoint assessment the applicant has selected and analysed three different biopsy regions (Tissue A, B, and C) according performance in PET and T1 as well as T2W FLAIR MRI in order to define two Appraisal Regions and used additionally two different 18F-Fluciclovine dose levels (high and low dose). In a population of 35 patients analysed this approach ended up in many variables. In such a small population the success of the trial depends from the outcome in a few biopsies only. Considering that all patients included had suspected gliomas, based on their clinical symptoms, clinical course, and previous MRI examinations, the population was preselected in order to assess tumour delineation mainly. Thus, in all patients the probability for a positive glioma detection (PPV) was already very high at inclusion. Tissue sample from regions who are likely to be negative, were only collected in a minority of the patient and an adequate assessment of NPV was not included in the trial. Since this approach precludes a valid evaluation of diagnostic accuracy in terms of specifity and sensitivity, the overall reliability of this data for pivotal claims remains low. In particular, since the trials success depends only from the outcome in very few samples in the trial. At the end, the selected endpoint assessment, which was similar in all the prospective trials, was only exploratory and it is deemed difficult to justify pivotal claims on data generated from such an approach.

Since the PET images from this trial, which was the largest trial in the clinical development claimed as pivotal for this application, were also used for the blinded image evaluation for inter-reader comparability exercise (BED-006) this secondary evaluation has to be seen also as confounded by similar bias.

A rather identical approach for endpoint assessment was also used in the two other trials NMP-P301 and P302. Thus, similarly methodological concerns are raised regarding the relevance of the reported outcome from these trials.

With respect to the claimed indication it is critical from a methodological point of view that the data presented do not allow any valid assessment of outcome from 18F-Fluciclovine PET in glioma diagnosis independent from MRI diagnostic, which has per se a high diagnostic accuracy. All patients included had PET and MRI. According the study reports, selection of biopsy location, essential for the endpoint outcome, was based on findings of both methods in open trials. This means that the overwhelming majority of biopsies were taken in regions identified already with T1 or T2 FLAIR MRI alone. Therefore, the reported diagnostic performance parameters for 18F-Fluciclovine PET are significantly confounded by the MRI outcome alone.

Even in the case that the use of PET would be only applied in combination with MRI, an additional benefit for performing the 18F-Fluciclovine PET diagnostic in addition to MRI needs to be proven. However, for such claims MRI has to evaluated separately and MRI + PET separately, in blinded fashion; the localisation of biopsies have to be determinated independent from the diagnostic method used. This was not performed in the trials and since the trials were performed without blinded reading as open, non-comparative trials and the synopsis of MRI and PET findings was used to define the localization for biopsies even such claim cannot be justified with the data available. Due to overlap of positive findings in both diagnostic methods and the limited number of biopsies available in the small trials, the data submitted is not sufficiently reliable.

Trial NMP-P301 and **NMP-P302** were declared as Phase 3, single administration studies designed to evaluate the safety and efficacy of 18F-fluciclovine administered as a single i.v. injection to patients with suspected malignant primary glioma, based on their clinical symptoms, clinical course and MRI examinations, who were scheduled for resection via craniotomy.

The methodology for image evaluation was essentially the same for the two studies, thus imaging data from the two studies were also combined analysed in the Study NMP-P301/P302 CSR. In both studies, patients (n=20 [Study NMP-P301] and n=25 [Study NMP-P302]) received 18F-fluciclovine, with 10-minute cranial PET scans started 10 to 50 minutes after administration. Studies NMP-P301 and NMP-P302 included additionally an attempt to assess how patient management was impacted by the results of the 18F-fluciclovine PET imaging (i.e., whether the extent of resection planned using the navigational MRI images changed [increased, decreased or was unchanged] after incorporation of data from 18F-fluciclovine PET).

Moreover, trial NMP-P302 was primarily designed to show the presumed impact of 18F-Fluciclovine on the clinical outcome in terms of PFS at 9 months after resection in patients with primary glioma, but failed to show any favourable impact of the PET diagnostic included. (However, it seems to be the only trial in the program which might allow a sort of comparison of the impact of MRI alone.) In consequence, both studies are mainly seen as supportive for this application. Taking collective all prospective trials, the analysed population included 85 patients with primary glioma. Thus, the population available for assessment is deemed rather small to be pivotal even taken collectively.

Beside the principle critics in the trial design of the NMP trials (which apply also for these trials) in needs to be considered that biopsies were collected nearly exclusively in the T1 MRI and/or PET positive areas. However, T2 FLAIR MRI and/or PET negative areas were not adequately represented in the dataset making the assessments of diagnostic performance (sensitivity, specificity, and NPV) for joint MRI/PET imaging incorrect.

Study BED-008 was a **retrospective data extraction study** investigating the effectiveness of 18F-fluciclovine PET scans to detect the presence or recurrence of malignant disease in patients with glioma, based on data analysed from three sites (Memorial Sloan Kettering Cancer Center [MSKCC], NY, US; Emory University, GA, US; Oslo University Hospital [OUH], Oslo, Norway) where 18F-fluciclovine had been administered to patients as part of investigator-initiated trials (IIT) for the two former, or a compassionate use programme for the latter, prior to July 2017. At one of these sites (Emory), 18F-fluciclovine PET scanning had been performed for research purposes only; imaging was not clinically interpreted at the time it was performed, results were not used to guide biopsy sampling and were thus not eligible for inclusion in the full efficacy analysis. All the other studies above included only patients with suspected primary glioma, whereas Study BED-008 included a majority of patients with recurrent glioma (50/82 [61%]). However, at the end only 18 patients (17 with recurrent and 1 with primary glioma) could be included in the final analysis set. Therefore, again data from a highly pre-selected population was analysed retrospectively, which might be acceptable for an exploratory approach, but hardly justify pivotal claims in this indication.

In addition, it is described in the study protocol that the selected PETs were scanned between 2004 and 2016. However, the applied fixed dose posology was first established in a clinical trial starting in 2011. It seems implausible that PETs included in BED-008 share the same technical performance of the PETs as those generated in the prospective trial. Moreover, it is challenged that over such a long period the technical performance of the PETs was not changed. Insofar, the data from BED-008 are seen as exploratory only. Any confirmatory claims can be hardly accepted from this trial. (OC)

In addition, the applicant has also submitted results from a retrospective Phase 3, Blinded Image Evaluation (BIE) study **(BED-006)** using 18F-fluciclovine PET images derived from Study NMP-P202. This trial was intended to evaluate the efficacy of 18F-fluciclovine PET combined with MRI imaging, compared to MRI alone, in adults with glioma retrospectively. The study aimed to assess the inter- and intra-reader reproducibility of image reads when interpreted by naïve readers. Study BED-006 is claimed to provide data to support the technical and diagnostic performance, as well as impact on diagnostic thinking, of 18F-fluciclovine PET imaging in combination with MRI, compared to MRI alone. It is also claimed to

illustrate the potential additive clinical value of 18F-fluciclovine PET in terms of increased tumour volume identified compared to MRI alone. In the Rapporteur's view, this trial may only allow some conclusions regarding the the inter- and intra reader reproducibility; however, the mentioned broad claims are deemed not plausible and thus, not justified at all.

No data was submitted to compare the results for 18F-Fluciclovine PET with that of other PET methods, e.g. 18F-FET PET, which is at least in the EU well established, widely used and recommended in several national guidelines. Since published literature for this PET standard is plenty, any bridging of data seems impossible.

In the Rapporteur's view, an adequately power comparative phase 3 trial in a sufficient number of patients covering all relevant aspects of glioma diagnosis is needed for approval. This is currently missing.

The relevant guideline [EMA GUIDELINE ON CLINICAL EVALUATION OF DIAGNOSTIC AGENTS (CPMP/EWP/1119/98/Rev. 1)] recommends explicitly for a pivotal trial the inclusion of a sufficient number of patients representative for the full population in which the diagnostic agent is intended to be used. This means with respect to the applied indication inclusion of patients:

- for screening in asymptomatic patients or those with other intracranial diseases, in patients with suspected but not confirmed disease,
- in patients with a confirmed disease for evaluation of its extent (initial staging), severity or prognosis
- in patients undergoing treatment to monitor its efficacy
- in previously treated patients to search for recurrence and
- in patients with a confirmed recurrence for evaluation of its extent (restaging), severity or re-evaluate the prognosis.

These essential requirements for a clinical development program intended to seek approval for the applied broad indication are obviously not fulfilled by any of the trials discussed. Even taken the collective population (80-85 patients) as evidence, the reliability of the applicant's efficacy conclusions is significantly challenged and not shared at all. (MO)

The applicant claims that the endpoints evaluated in the 18F-fluciclovine PET clinical program are in line with those outlined in the EMA Guideline on Clinical Evaluation of Diagnostic Agents (CPMP/EWP/1119/98/Rev.1), with the technical and diagnostic performance of 18F-fluciclovine PET, and its impact on diagnostic thinking and patient management established across the clinical studies are not acceptable for the Rapporteur.

Formally results are reported for appropriate primary endpoints for diagnostic performance based on the predictive value of PPV. However, the NPV was not adequately assessed in the clinical trials. The results were confounded by a highly selected population in which the primary aim of the biopsies taken was to get a histopathological prove of glioma. Only patient in whom the diagnosis of glioma was already very likely were included. No patients with inflammatory or other non-malignant or malignant lesions were included to assess the diagnostic accuracy. During response the applicant confirmed that 18F-fluciclovine is not sufficiently characterised in non-malignant brain tumours, necrosis and inflammatory brain lesions. Considering the low number of negative biopsies evaluable, sensitivity and specificity is challenged also with respect to the insufficient characterization of benign brain lesions.

In such a setting aiming to show superiority of adding PET to MRI versus MRI diagnostic performance alone, the PPV and NPV should be determinated by a comparison of biopsy results in a PET+MRI arm with those in a MRI alone arm. To be valid, this comparison has to be performed in an adequately power and sized population in which the favourable outcome does not depend from a few patients only.

Thus, the provided calculations in the small populations and the limited number of biopsies included to prove the presence of glioma are less reliable for an adequate assessment of PPV and NPV. In particular,

considering the complex trial design without sufficient blinded reading of images and the fact that most information regarding the correct glioma diagnosis was already available from MRI alone.

In addition, according the information provided in the study reports, the study protocols of all trials were significantly changed several times during the conduct and - probably more important - even after the open trial data was generated. Since these changes partially also affect the mode of statistical efficacy evaluation, this seems further to lower the reliability of the data shown and needs further clarification since the changes may have biased the reported outcome.

In conclusion, the clinical trial program is neither sufficient to justify the applied broad indication nor adequate to substantiate approval in the EU in the Rapporteur's view.

Efficacy data and additional analyses

Due to the applicant's claim to take the data collectively as pivotal, the assessment of the efficacy is very complicated and remained partially inconclusive and confusing.

The trials had slightly different objectives and endpoints. Although the mode endpoint evaluation was similar, the assessable outcome was biased from the biopsies taken in the different regions and Appraisal Regions defined. In general, the planned approach was more an exploratory than really a pivotal one. Moreover, different glioma grades and the use of a high and low dose of 18F-Fluciclovine for PET imaging complicate the assessment.

It seems that the main efficacy benefit claimed to be proved by the applicant is a superiority in delineating tumour from non-tumor in patients receiving 18F-Fluciclovine PET in addition to baseline diagnostic with T1 and/or T2W MRI. In the applicant's view, the clinical development program has demonstrated this sufficiently for patients with primary as well as recurrent glioma and independently whether the glioma is low or high graded. However, this view is not shared by the Rapporteur as already highlighted in the section above.

Across Studies NMP-P202, NMP-P301/P302, the PPV and NPV for 18F-fluciclovine PET in both CE-T1W MRI positive and negative areas are described to be high (ranging from 87.5% to 100.0% and 78.6% to 100.0%, respectively). However, it remains difficult to identify from the study reports valid PPV (and NPV) for T1 and T2 FLAIR MRIs to compare and identify a reliable added diagnostic benefit from the data.

Similar results for PPV were reported from the retrospective Blinded-Image Evaluation (BIE) Study BED-006 in which 18F-fluciclovine PET images from Study NMP-P202 were again assessed by three blinded trained reader. The PPV for PET plus CE-T1W MRI was reported even higher (ranging from 93.1% to 96.4% across three readers and for two 10-minute PET scans per patient starting between 10 and 20 minutes post-injection and between 40 and 50 minutes post-injection). However, in the same study, the PPV for CE-T1W MRI alone was similar 94.1% and the PPV for FLAIR (or T2W) MRI alone was slightly lower at 84.6% (one reader only for MRI scans). The comparison between PET and FLAIR (or T2W) MRI alone was added as an additional analysis and was not part of the Study NMP-P202 analysis.

The reported PPV for PET plus CE T1W MRI in BED-006 was nearly identical to that of CE-T1W MRI alone and the 95% CIs of the reported PPVs and NPVs of all three diagnostic methods are rather similar and significantly overlapping. Therefore, a clinical benefit for the additional 18F-Fluciclovine PET on top of T1W-MRI seemed not adequately demonstrated from these findings.

Results regarding the NPV are mainly referring to the analysis provided from the BIE re-reading trial BED-006. The NPV for PET plus CE-T1W MRI is described to range from 38.1% to 43.8% for the three readers across both timepoints, which is similar to the NPV of 37.5 % reported for FLAIR (or T2W) MRI alone. As could expected the NPV for CE-T1W MRI alone was lower at 26.7%.

It needs to be considered that the NPV was not adequately addressed in the design of the prospective clinical trials NMP-P202, P301 and P302 due to the overall low number of negative. Since 18F-fluciclovine uptake is not specific for glioma and may occur with other types of malignancy in and around the brain, e.g. in other inflammatory conditions, such as active multiple sclerosis and brain abscesses, the specificity is not reliable assessable. Since location of biopsy was mainly determinated by the intention to prove the tumour histology, the number of biopsies available in potential negative regions was not representative, particularly in trial NMP-P301 and 302. It seems that even assessment of NPV was not included in the largest trial (NMP-P202). Therefore, the provided calculations for diagnostic accuracy in terms of specifity and sensitivity seems also less reliable.

Considering that in the small trials with 20 to 35 patients demonstration of favourable outcome of the trial may depends on very few patients (e.g 1 to 3) the reported outcome for efficacy remains not reliable.

The contribution of T1 or T2 FLAIR MRI alone is not sufficiently evaluable, since no independent blinded assessment in order to define biopsy locations based on results of MRI alone or MRI together with PET was performed.

Considering that trial NMP-P302 showed an inferior outcome for the primary endpoint "9 months PFS" in patients pre-operatively assessed by PET/MRI in comparison to those assessed with MRI alone, no beneficial impact of adding 18F-Fluciclovine PET on patients management or outcome can be concluded compared to standard MRI diagnostics.

This seems to be in line with the results form trial BED-008 in 18 patients with recurrent glioma. In this trial the PPV (n, 95% CIs) for 18F-fluciclovine PET scanning to detect histologically confirmed recurrent brain tumor was 88.2% (n=17, 63.6%, 98.5%). The NPV and specificity could not be calculated as there were no patients with a negative 18F-fluciclovine PET scan. The PPV (n, 95% CIs) for MRI to detect histologically confirmed recurrent brain tumor was the identical with 88.2% (17, 63.6%, 98.5%). Apart from the methodological concerns due to the inacceptable trial design and the provided calculations, it is again noted that also in this trial no additional benefit from adding 18F-Fluciclovine PET to MRI was demonstrated even in the probably more complicated population with recurrent disease.

From trial BED-006 a higher sensitivity of 18F-fluciclovine PET plus CE-T1W MRI compared to CE-T1W MRI alone, as well as the higher specificity of 18F-fluciclovine PET plus CE-T1W MRI compared to FLAIR (or T2W) MRI alone is claimed. This statement is derived from a re-analysis of 30 biopsies from areas which were CE-T1W MRI negative and PET positive. In this re-analysis 10 to 13 of these biopsies (depending on reader and timepoint), were true positives identified by PET plus CE-T1W MRI when they were negative on CE-T1W MRI alone. It is concluded that thus, PET in combination with CE-T1W MRI was able to detect positive lesions that CE-T1W MRI alone did not. However, since it is not reported how many of these 13 lesions were positive in T2-FLAIR MRI also, the clinical relevance of these result of this re-analysis in 30 biopsies is challenged. Similarily 39 biopsies that were within a region positive on FLAIR (or T2W), four or five (again depending on reader and timepoint) were true negatives identified by PET plus CE-T1W MRI when they were false positive on FLAIR (or T2W) MRI. Thus, it is concluded by the applicant that PET in combination with CE-T1W MRI may provide additional discriminatory information compared to FLAIR (or T2W) MRI alone. However, again it is not reported whether these lesions were also negative in CE-T1W MRI alone.

Additionally it is claimed as a favourable effect that analyses of the extent and intersection of VOIs (i.e., tumour volumes) between imaging modalities in BED-006 demonstrate an significant added VOI using PET plus CE-T1W MRI vs. CE-T1W MRI alone. However, the VOIs in FLAIR (or T2W) MRI alone are not adequately assessable compared to PET plus CE-T1W MRI. Therefore, it seems difficult to prove sufficiently a relevant clinical benefit for the patients.

Results from BIE Trial BED-006 seemed to indicate that image interpretation across readers and timepoints may be in agreement, demonstrating reproducibility across readers and when images were re-read by the same reader for a second time. Analyses of inter-reader agreement of PET plus CE-T1W MRI reads based on the binary interpretation of the data (i.e., whether the biopsy location was within the PET positive region or not) indicated that concordance was high for all three readers overall and for pairwise inter-reader comparisons (Reader 1 vs. Reader 2, Reader 1 vs. Reader 3 and Reader 2 vs. Reader 3). Specifically, overall, 89.4% and 87.0% of scans were in agreement by all three readers at Timepoint 1 and Timepoint 2, respectively (Fleiss' Kappa, 0.86 and 0.82, respectively). At both timepoints, concordance was ~90% or higher for each pairwise inter-reader comparison (Cohen's Kappa, 0.78 to 0.91) (binary interpretation). However, the clinical relevance of this analysis remains inconclusive considering that in the data base selected from l trial NMP-P202 the number of negative biopsies was significantly smaller than that of the positive biopsie. This may have had also confounded the outcome for Kappa evaluation.

Sensitivity and specificity (diagnostic performance) of 18F-fluciclovine PET is claimed only from the retrospective analysis performed in trial BED-006. Since NPV was not calculated in the prospective trials this retrospective data analysis is the only source for determination of diagnostic performance. It seems challenging to accept this approach of defining the most important diagnostic parameters; moreover, as no comparison was provided for T1 and/or T2 FLAIR MRI alone.

Moreover, intraoperative administration of 5-aminolevulinic acid (5-ALA) (Gliolan®) is available to define in-vivo delineation of malignant glioma during resection and data was used to define the sample size in the clinical trials. Since approval in 2007 in the EU this method is now seen as clinical standard for best tumour delineation during the surgical procedure, since administration of Gliolan has been proven to better outcome and prognosis also in glioma patients after resection. There is no comparative data showing that outcome of 18F-Fluciclovine PET diagnostic has any additional benefit in comparison to MRI and Gliolan for the patients. The outcome of trial NMP-P302 even seems to indicate an inferior outcome in the 18F-Fluciclovine arm incomparison to patients assessed with MRI alone regarding the 9-months PFS (primary endpoint of the trial).

Around one-third of WHO Grade II gliomas and a majority of Grade I gliomas do not show increased uptake of AA PET tracers. However, no date for WHO grade I glioma patients is available specific for 18F-Fluciclovine from the clinical trials. Therefore, all results regarding low-grade Glioma can only be discussed for grade II glioma due to the restrictions resulting from the small number of patients investigated in the trials.

Based on these not convincing data, the applicant applies to extrapolate the results also for all other clinical settings in which the utility of AA PET has been demonstrated in the published literature. This claim for a broad indication is based on considerations published in the RANO/EANO group publication (Albert et al, 2016) which discussed clinical settings in which addition of AA PET might add potential clinical benefits in glioma patients. Use of AA PET prior to surgery to plan biopsy or surgical field or radiotherapy as well as the assessment of response and planning of subsequent treatment after surgery are mentioned in this recommendation. Additionally, the potential impact on differentiation between pseudoprogression and true progression as well as prognostication in general is also addressed referring to the published evidence for other AA PET agents.

Currently, 18F-FET PET is well-established for glioma diagnosis in Europe and a lot of publications and even the RANO guideline recommends this diagnostic agent as standard in clinical practice. However, no bridging data which would allow any comparison between 18F-FET PET and 18F-Fluciclovine imaging results in glioma was provided. As a surrogate for the missing bridging data the applicant has included several case descriptions only in order provide further evidence for the potential usefulness of 18F-Fluciclovine PET in patients with glioma. However, this can hardly be accepted as convincing pivotal

evidence for the applied extrapolation to the broad indication applied. In particular, as even the claim in the investigated population is not adequately substantiated. In consequence, the applied indication has to be rejected completely.

Additional expert consultation: Not at present

Assessment of paediatric data on clinical efficacy: N/A

2.3.9. Conclusions on the clinical efficacy

The applied fixed-dose posology was established in Japanese patients only. From data in the retrospective analysis BED-008 it seems that higher doses were administered in Caucasian patients outside Japan. Therefore, it remains currently not clear whether the applied fixed dose posology can be extrapolated adequately to the EU population. In particular, since no bridging data is available which would allow to compare the imaging quality and outcome. Therefore, the proposed posology is not sufficiently validated for the applied use in the EU population.

No adequately sized and designed pivotal phase 3 trial was submitted for this application. Instead of that pivotal evidence is claimed from the results of 4 small prospective open clinical trials conducted in Japan including 5 to 35 patients (FAS in total ~ 80 patients) with primary glioma. In order to provide evidence for patients with recurrent glioma a retrospective analysis (BED-008) in a evaluable population of 18 patients was added. In the Rapporteur's view, this very restricted data base is not sufficient to justify adequately any pivotal claim for the broad indication applied.

Since the diagnostic impact of 18F-Fluciclovine PET for detection of glioma in the clinical trials was always confounded by the availability of concomitant MRI imaging (T1 and T2W FLAIR MRI) and all claims are based on diagnostic differences in very few biopsies only, the reported outcome for all diagnostic parameters as PPV, NPV, sensitivity and specifity is not reliable at all and remain inconclusive at the end.

Even taken collectively the data of all trials, the data available is seen as too limited and confounded by selection bias and other methodological pitfalls to justify adequate pivotal claims for the applied indication. Considering the additional uncertainty from the small population investigated, no convincing additional benefit from addition of 18F-Fluciclovine PET to MRI diagnostic was proven in the Rapporteur's view from this data.

Based on this not convincing data, the applicant applies to extrapolate the results also for all other clinical settings in which the utility of AA PET has been demonstrated in the published literature as reflected in applied a broad indication. Since no bridging data to other AA PETs is available and only several case reports were submitted to conclude, the claim for the applied indication needs to be rejected.

In conclusion, a sufficiently powered and adequately designed pivotal phase III trial in the intended patient population is needed, but currently missing. Moreover, bridging data, which would allow a valid comparison with other PET imaging agents that are well established in glioma diagnosis (e.g. 18F-FET PET) is needed to justify the applied broad indication.

2.4. Clinical safety

Introduction

No new non-clinical data compared with the initial MAA were submitted for this application. However, non-clinical data available revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Exposure to ionising radiation is linked with

cancer induction and a potential for development of hereditary defects. However, long-term carcinogenicity studies have not been carried out.

This medicinal product is not intended for regular or continuous administration. At the chemical concentrations used for diagnostic examinations, fluciclovine (18F) does not appear to have any pharmacodynamic activity.

Safety data available for the initial application, derived from the **approved prostate cancer indication**, includes a total of **837 subjects** across the previous studies, including 12 healthy volunteers, 596 patients with recurrent prostate cancer, 201 patients with primary prostate cancer and 28 patients with other cancers. Among the 28 patients with other cancers, there were also 14 patients with glioma, including the five patients from Study NMP-P201 (whose data are included in this application).

In the prostate cancer trial population AEs were reported in very low proportions of patients in each study (5.9% to 13.6% of patients). However, in smaller studies including only six and 10 subjects/patients AE rate reported were significantly higher (between 20.0% and 33.3% of patients with AEs) which may raise concerns regarding differences in safety assessment in the submitted trial populations, probably reflecting a potential underestimation of AEs and dilution of event reporting in the larger retrospective trials.

Overall, treatment-related AEs were reported in 16/832 (1.9%) patients across the studies in prostate cancer (PCa) patients. The only treatment-related AEs in the PCa population, by PT, reported in more than one patient were injection site extravasation (seven [0.8%] patients) and dysgeusia and injection site erythema (two [0.2%] patients each).

The remaining treatment-related AEs, reported in one (0.1%) patient each, were decreased blood fibrinogen, blood fibrinogen increased, malaise, pain, constipation, haemoglobin decreased and blood creatinine increased. This is in line with the experience from other F-18 based radiopharmaceuticals for which no drug related serious adverse reactions have been observed to date.

Table S1: Overview about the safety events in prostate cancer indication

Study Number	**GE-148-001**	**NMK36-P1**	**GE-148-002**	**NMK36-PC-201**	**NMK36-PC-202**	**BED-001**
(N=Prostate Cancer Patients/Healthy Volunteers)	**(N=6/6)**	**(N=0/6)**	**(N=22/0)**	**(N=10/0)**	**(N=68/0)**	**(N=714[a]/0)**
Number (%) of Patients with at Least 1:						
AE	4 (33.3)	2 (33.3)	3 (13.6)	2 (20.0)	7 (10.3)	42 (5.9)
Treatment-related AE	1 (8.3)	2 (33.3)	2 (9.1)	0	1 (1.5)	10 (1.4)
SAE	0	0	0	0	0	2 (0.3)
Severe AE	0	0	0	0	0	3 (0.4)
AE with an outcome of death	0	0	0	0	0	0

AE leading to discontinuation	0	0	0	0	0	0

In general, the most important risk as in all PET diagnostic agents is the potential for misinterpretation of the PET images acquired following administration of fluciclovine (18F), since such interpretation errors may result in inappropriate treatment. This risk increases if diagnostic accuracy is not sufficiently evaluated, e.g. conclusions are derived from too small population.

This risk is already included as an important potential risk in the RMP for fluciclovine (18F) for the prostate cancer indication. However, since the proposed poplation for PET in glioma patients is significantly smaller, this risk is considerably higher for the now applied indication.

Similarly, there is the potential for the product to be used for other diagnostic situations beyond the precise indication applied, which is also already included to be an important potential risk in the RMP.

As the effective dose of fluciclovine (18F) is 4 mSv when the maximal recommended activity of 185 MBq is administered, adverse reactions due to radiation are expected to occur with even with lower probability than with the 8.2 mSv/370 MBq in prostate cancer.

Safety (as well as efficacy) data for the glioma indication is based on a significantly smaller population (Glioma: claimed 172/ Prostate cancer: 837), but even for this limited population for safety assessment, only at most 90 patients seems to be derived from the prospective Japanese trials. In addition, is needs to be excluded that some patients were included in more than one trial.

Table S2: Studies Supporting the Safety of 18F-fluciclovine PET Imaging in Adults for the Detection and Continuing Assessment of Glioma

Study Number	Phase	Treatment	Patients Exposed to 18F-fluciclovine	Safety Assessments
NMP-sponsored Studies				
NMP-P201	2	Single i.v. administration of ^{18}F-fluciclovine (administered activity, 200.0 to 214.9 MBq), with cranial dynamic PET scans obtained	5 [HG]	AEs, haematology, blood biochemistry, urinalysis, 12-lead ECG, vital signs, physical examination
NMP-P202	2	Single i.v. administration of ^{18}F-fluciclovine (administered activity, 106.0 to 287.1 MBq), with cranial PET scans obtained 10 to 20	40 [21 HG; 19 LG]	AEs, haematology, blood biochemistry, urinalysis, 12-lead ECG, vital signs,
NMP-P301	3	Single i.v. administration of ^{18}F-fluciclovine (administered activity, 64.8 to 303.6 MBq), with 10-minute cranial PET scans started	20 [14 HG; 6 LG]	AEs, haematology, blood biochemistry, urinalysis, 12-lead ECG, vital signs, physical examination
NMP-P302	3	Single i.v. administration of ^{18}F-fluciclovine (administered activity, 91.9 to 252.4 MBq), with 10-minute cranial PET scans started	25 [16 HG; 9 LG]	AEs, haematology, blood biochemistry, urinalysis, 12-lead ECG, vital signs, physical examination
BED-sponsored Study				

BED-008	3	^{18}F-fluciclovine (i.v.) given as part of an IIT or a compassionate use program (administered activity ranging from 51.8 to 451.4 MBq), with some patients receiving multiple administrations (106		

Assessor's comment:

The additional safety population from the trial in glioma patient is overall small and is restricted on about 65 patients investigated prospectively and not already included in the initial safety population (NMP-P201/202).In conclusion, the population is too small to assess any minor safety difference in the applied new target population.

The following safety assessments were performed in Studies **NMP-P201, NMP-P202, NMP-P301** and **NMP-P302**:

Adverse event (AE) recording: AEs were recorded during the safety evaluation period from the day of 18F-fluciclovine administration until 1 week post 18F-fluciclovine PET scan in NMP-P202, NMP-P301 and NMP-301. Serious adverse events (SAEs) were defined as those events that met any of the following criteria: the event was fatal, life-threatening, required hospitalisation or prolongation of hospitalisation, resulted in permanent or severe disability or dysfunction, caused congenital anomaly/birth defects, or was any other medically important condition.

Causality of AEs was assessed by the investigator, with events categorised as either "related" or "unrelated" to 18F-fluciclovine according to the definitions specified in the protocols.

Clinical laboratory investigations (haematology, blood biochemistry and urinalysis), 12-lead electrocardiograms (ECGs) and other safety assessments (vital signs, physical examinations) were performed prior administration on day 1 and on day 2 or once between Day 2 and 7.

In the BED-sponsored retrospective Study BED-008 it is described that the main difference in assessment was that SAEs were observed up to 35 days and Grade 2 AEs only when they related to vital organs, e.g. cardiovascular, respiratory and central nervous systems.

However, since the safety assessment approach used for all trials is not fully comprehensible from the submitted documents, the applicant needs to illustrate the safety assessment approach more comprehensible (OC).

Assessor's comment:

No safety data analysis is meaningful from the BED-sponsored Study 006 which includes only patients from NMK-P202. This trial performs a re-evaluation of the data intending to determinate the positive predictive value (PPV) of 18F-fluciclovine positron emission tomography (PET) scanning used as an adjunct to contrast-enhanced-T1-weighted (CE-T1W) magnetic resonance imaging (MRI), compared to the PPV of CE-T1W MRI alone. Secondary, determination of inter- and intra-reader reproducibility of 18F-fluciclovine PET image evaluation read in conjunction with CE-T1W MRI was planned as recommended in the EU guideline.

Patient exposure

According the applicant's statement, a total of 172 patients with suspected/confirmed glioma is claimed to have been exposed to 18F-fluciclovine in the clinical study program, including 112 patients with suspected/confirmed high-grade glioma and 59 patients with suspected/confirmed low-grade glioma (Table S1).

In the NMP-sponsored studies, 18F-fluciclovine was administered as a single injection. In Study BED-008, 106 administrations of 18F-fluciclovine were recorded among 82 patients, with 18 patients receiving greater than one injection. For patients in Study BED-008 who received more than one administration, the mean (±SD) interval between administrations was 106.0 (±86.5) days (range 6 to 405 days).

The mean±SD administered activity per administration was 207.4±6.2 MBq, 186.1±67.0 MBq, 173.4±81.3 MBq, 180.3±44.6 MBq and 339.2±80.8 MBq in Studies NMP-P201, NMP-P202, NMP-P301, NMP-P302 and BED-008, respectively, with a range of 51.8 to 451.4 MBq administered to individual patients across the studies.

Table S3: Key Demographic and Baseline Characteristics Across Studies

Characteristic	NMP-P201 (N=5)	NMP-P202 (N=40)	NMP-P301 (N=20)	NMP-P302 (N=25)	BED-008 (N=82)
Age, years					
Mean±SD	53.6±1	55.0±15.8	55.4±14	54.3±1	52.2±
Range category	30-75	20-85	20-80	30-90	20-80
Sex					
Male, n (%)	2	31 (77.5)	13	18	51 (62.2)
Female, n	3	9 (22.5)	7 (35.0)	7	31 (37.8)
WHO Glioma Grade					
High-grade (III or IV), n (%)	5 (100)	21 (52.5)	14 (70.0)	16 (64.0)	56 (68.3)
Low-grade (I or II), n	0	19 (47.5)	6 (30.0)	9 (36.0)	25 (30.5)
Unknown	0	0	0	0	1 (1.2)
KPS					
100%, n	-	17 (42.5)	6 (30.0)	7 (28.0)	-
90%, n (%)	-	9 (22.5)	11	9 (36.0)	-
80%, n (%)	-	6 (15.0)	0	4 (16.0)	-
70%, n (%)	-	3 (7.5)	2 (10.0)	2 (8.0)	-
60%, n (%)	-	3 (7.5)	1 (5.0)	3 (12.0)	-
50%, n (%)	-	2	0	0	-
≤40%, n	-	0	0	0	-
Not collected	5	-	-	-	82

Abbreviations: CSR=clinical study report; KPS=Karnofsky Performance Scale; MRI=magnetic resonance imaging; SD=standard deviation; WHO=World Health Organization

a For Studies NMP-P201, NMP-P202, NMP-P301 and NMP-P302, glioma grades are based on the suspected grades according to MRI findings. For Study BED-008, WHO grade was based on relevant medical history, including histopathology. All studies used WHO 2007 Classification of Tumours of the Central Nervous System (Louis et al, 2007).

Source: Table 11.2-1 (Study NMP-P201 CSR), Table 11.2-1 (Study NMP-P202 CSR), Table 11.2-1 (Study NMP-P301/P302 CSR), Table 11.2-1 (Study NMP-P302 CSR), Table 7 and Table 9 (BED-008 CSR)

Demographic and baseline characteristics were comparable across the studies and may reflect the demographic . The mean age across all studies was 52 to 55 years (range, 21 to 89). All studies (except NMP-P201 with five patients) included more males than females (62% to 80% males vs. 20% to 38% females). In accordance with the inclusion criteria, KPS score was ≥50% in all studies, where available, with 42.5%, 30.0% and 28.0% of patients in Studies NMP-P202, NMP-P301 and NMP-P302, respectively, having a score of 100%. Typically, the studies included a higher proportion of patients with high-grade glioma (WHO Grades III to IV) than low-grade glioma (WHO Grade II) (NMP-P201, NMP-P301, NMP-P302, BED-006 and BED-008), but the split was approximately even in Study NMP-P202.

Assessor's comment:

All prospective studies relevant for this application were conducted at sites in Japan. It seems that most or all patient were Japanese. The only notable exception in demographics between Study BED-008 and the Japanese studies was in weight (BED-008: mean weight was 83.5 kg vs NMP-P201: 58.5 kg in Study NMP-P201) which may indicate some weakness of the intial dose finding (OC). This needs clarification.

Adverse events

The following table provides an overview on the safety events observed in the clinical development in the glioma indication (for similar tabularised overview in prostate cancer population approved please refer to Table S2 in the introduction of this AR):

Study Number	**NMP-P201 (N=5)**	**NMP-P202 (N=40)**	**NMP-P301 (N=20)**	**NMP-P302 (N=25)**	**BED-008 (N=82)**
Number (%) of Patients with at Least 1:					
AE	2 (40.0)	7 (17.5)	1 (5.0)	1 (4.0)	3 (3.7)
Treatment-related AE	1 (20.0)	5 (12.5)	1 (5.0)	0	0
SAE	0	0	0	0	1 (1.2)
Severe AE	0	1 (2.5)	0	0	0
AE with an outcome of death	0	0	0	0	1 (1.2)
AE leading to discontinuation	0	0	0	0	0

<u>Common adverse events</u>

Table : Summary of AEs by SOC and PT

SOC/PT	**NMP-P201 (N=5)**	**NMP-P202 (N=40)**	**NMP-P301 (N=20)**	**NMP-P302 (N=25)**	**BED-008 (N=82)**
	N(%)				
Blood and lymphatic system disorders	0	0	0	0	1 (1.2)
Thrombocytopenia	0	0	0	0	1 (1.2)

Cardiac disorders	0	1 (2.5)	0	0	0
Ventricular extrasystoles	0	1 (2.5)	0	0	0
Gastrointestinal disorders	0	0	0	0	1 (1.2)
Nausea	0	0	0	0	1 (1.2)
Vomiting	0	0	0	0	1 (1.2)
General disorders and administration site conditions	1 (20.0)	0	1 (5.0)	1 (4.0)	0
Dry mouth	0	0	1 (5.0)	0	0
Malaise	1 (20.0)	0	0	0	0
Puncture site swelling	0	0	0	1 (4.0)	0
Infections and infestations	0	0	0	0	1 (1.2)
Oral herpes	0	0	0	0	1 (1.2)
Investigations	0	4 (10.0)	0	0	0
Blood glucose increased	0	1 (2.5)	0	0	0
Blood pressure increased	0	1 (2.5)	0	0	0
Glucose urine present	0	1 (2.5)	0	0	0
Neutrophil count decreased	0	1 (2.5)	0	0	0
White blood cell count increased	0	1 (2.5)	0	0	0
Protein urine present	0	1 (2.5)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (1.2)
Glioblastoma	0	0	0	0	1 (1.2)
Nervous system disorders	1 (20.0)	1 (2.5)	0	0	1 (1.2)
Cerebral disorder	0	1 (2.5)	0	0	0
Headache	1 (20.0)	0	0	0	1 (1.2)
Hemiparesis	0	0	0	0	1 (1.2)
Hemiplegia	0	1 (2.5)	0	0	0
Psychiatric disorders	0	0	0	0	1 (1.2)
Affect lability	0	0	0	0	1 (1.2)
Respiratory, thoracic and mediastinal disorders	0	2 (5.0)	0	0	0
Parosmia	0	1 (2.5)	0	0	0
Upper respiratory tract inflammation	0	1 (2.5)	0	0	0
Skin and subcutaneous tissue disorders	0	1 (2.5)	0	0	0
Skin exfoliation	0	1 (2.5)	0	0	0

Abbreviations: AE=adverse event; CSR=clinical study report; PT=preferred term; SOC=system organ class Source: Table 12.2-1 (Study NMP-P201 CSR), Table 12.2-1 (Study NMP-P202 CSR), Table 12.2-1 (Study NMP-P301/P302 CSR), Table 12.2-1 (Study NMP-P302 CSR), Table 14.3.1.2 (BED-008 CSR) Note: Data presented are number (%) of patients.

As shown by the data adverse events were reported in very low proportions of patients in each study (3.7% to 17.5% of patients), with the exception of the small Study NMP-P201 in which AEs were reported in 2/5 (40.0%) patients. Treatment-related AEs were reported in one (20.0%) patient in Study NMP-P201, five (12.5%) patients in Study NMP-P202, one (5.0%) patient in Study NMP-P301, and no patients in Studies NMP-P302 and BED-008. A single SAE was reported throughout the studies, in a patient in Study BED-008; this was an event of worsening glioblastoma (reported term) which had an outcome of death and was considered unrelated to 18F-fluciclovine (see Section 2.7.4.2.1.2). A single severe AE was reported throughout the studies, in a patient in Study NMP-P202 (event of blood pressure increased that was considered unrelated to 18F-fluciclovine and was reported 1.5 hours after 18F-fluciclovine administration in a patient with pre-existing hypertension. No AEs leading to discontinuation were reported in any study

Moreover, there was no meaningful pattern of AEs, with events in the majority of SOCs and all event PTs reported in individual patients in each study. The SOCs in which events were reported in more than one patient in a single study were observed in Study NMP-P202 for the SOCs of Investigations (four [10.0%] patients) and Respiratory, thoracic and mediastinal disorders (two [5.0%] patients). For Investigations, these AEs comprised the PTs of blood glucose increased, blood pressure increased, glucose urine present, neutrophil count decreased, white blood cell count increased and protein urine present, each reported in one (2.5%) patient. For Respiratory, thoracic and mediastinal disorders, the AEs comprised the PTs of parosmia and upper respiratory tract inflammation, each reported in one (2.5%) patient.

The only AE, by PT, reported in more than one study, was headache, which was reported in one (20.0%) patient in Study NMP-P201 and one (1.2%) patient in Study BED-008.

Assessor's comment:

We agree that according the information provided the majority of reported AEs above are highly likely to be tumour related events (including all events in the SOC of Nervous system disorders, events under the PTs of nausea, vomiting, parosmia, blood pressure increased and affect lability). Others may be associated with tumour treatment (including reduced white blood cell and platelet counts, and all blood/urine glucose abnormalities). It seems rather unlikely that these events reflect a product specific adverse event in the assessor's view.

According the data presented and confirmed by an comparison with the previous data in prostate cancer patients it seems that the profile of AE reporting was similar across the safety datasets presented in support of the previous prostate cancer submission and the current submission AEs occurred only in very low proportions of patients overall, and very few patients reporting severe AEs and SAEs. No meaningful pattern of treatment-related AEs is apparent across the two safety datasets. None of the treatment-related AEs reported in the prostate cancer safety dataset, by PT, was also observed as a treatment-related AE in the current glioma safety dataset.

In summary, the data available might indicate for both, the prostate cancer and glioma datasets, a similar and consistent safety profile, with no new or significant safety concerns noted and, as such, 18F-fluciclovine continues to be well tolerated and poses no clinically significant safety issues. This may be reasoned because the product at the chemical concentrations used for diagnostic examinations does not appear to have any pharmacodynamic activity.

Treatment-related Adverse Event

There was no meaningful pattern of treatment-related AEs, with events in the majority of SOCs and all event PTs reported in individual patients in each study. Overall, the majority of treatment-related AEs were reported in a single study (NMP-P202).

The only treatment-related AEs, by SOC, reported in more than one patient in a single study, were observed in Study NMP-P202 for the SOC of Investigations (three [7.5%] patients). These comprised the PTs of glucose urine present, white blood cell count increased and protein urine present, each reported in one (2.5%) patient. The remaining treatment-related AEs were events of ventricular extrasystoles and parosmia (one [2.5%] patient each in Study NMP-P202), headache (one [20.0%] patient in Study NMP-P201) and dry mouth (one [5.0%] patient in Study NMP-P301).

Assessor's comment:

The majority of treatment-related AEs were reported only from study NMP-P202; this might again indicate differences in safety assessment approach and increase doubts in consistency of safety assessment during the trials.

Serious adverse event/deaths/other significant events

Serious adverse events

Nearly all AEs reported across the studies were classified as mild or moderate in intensity. Throughout the program of studies, only one severe AE was reported, in a patient in Study NMP-P202. This non-serious event of blood pressure increased reported on the afternoon of the day of 18F-fluciclovine administration in a patient with pre-existing hypertension, was considered unrelated to 18F-fluciclovine.

Deaths

A single AE with an outcome of death due to worsening glioblastoma (reported term) was reported throughout the studies, in a patient in Study BED-008 (this was the only death reported during the safety monitoring period of up to 35 days following 18F-fluciclovine administration in this study). This event was judged as unrelated to 18F-fluciclovine.

Assessor's comment:

Moreover, only one severe AE (worsening of glioma) was reported from in a patient in Study NMP-P202 and single AE with an outcome of death due to worsening glioblastoma (reported term) was reported throughout the studies occurred in a patient in Study BED-008 (this was the only death reported during the safety monitoring period of up to 35 days following 18F-fluciclovine administration in this study). Both events were judged as unrelated to 18F-fluciclovine.

Laboratory findings

Laboratory measurements were conducted in the NMP-sponsored studies (NMP-P201, NMP-P202, NMP-P301 and NMP-P302), comprising haematology, blood biochemistry and urinalysis.

No clinically significant population changes in laboratory parameters were observed across the studies. Statistically significant changes were observed between the pre- and post-administration values for fibrinogen concentration in Studies NMP-P201 and NMP-P202, and for several blood biochemistry parameters in Study NMP-P202. For fibrinogen concentration, the mean±SD change from the pre-administration value was 13.60±5.68 mg/dL in Study NMP-P201 and -10.63±31.16 mg/dL in Study NMP-P202. For blood biochemistry in Study NMP-P202, mean±SD changes from the pre-administration value were reported for albumin (-0.12±0.25 g/dL) alkaline phosphatase (–8.8±18.0 U/L), lactate dehydrogenase (-8.5±20.7 U/L), urea nitrogen (0.82±2.24 mg/dL), total creatine phosphokinase (-11.24±23.55 U/L), total protein (-0.20±0.37 g/dL), triglycerides (–15.3±34.9 mg/dL) and calcium (-0.11±0.30 mg/dL). However, none of these changes was considered to be clinically relevant or significant.

Abnormalities in clinical laboratory measurements were reported as AEs in Study NMP-P202 only, comprising events of protein urine present, white blood cell count increased, glucose urine present, neutrophil count decreased and blood glucose increased, each reported in one (2.5%) patient. All of the AEs associated with these changes were mild in intensity, with the exception of a moderate event of blood glucose increased. The outcome for all the events was resolved, with the exception of the event of blood glucose increased for which a follow-up assessment was not performed.

Assessor's comment:

Since pharmacodynamic at the concerntrations administered are expected, it is not surprising that no clinically significant population changes in laboratory parameters were observed across the studies. Minor changes reported are not clinical relevant and are overall not very likely to be caused by 18F-fluciclovine.

Safety in special populations

Age

18F-fluciclovine has not been investigated in the paediatric population. The mean age across all studies was 52 to 55 years: Given the very low number of AEs reported across the studies and the limited number of patients included in the clinical trials, no trends in the reporting of AEs by age group have been elucidated.

Gender

All studies (except NMP-P201 with five patients) included more males than females (62% to 78% males vs. 23% to 38% females). Given the very low number of AEs reported across the studies and the limited number of patients included in the clinical trials, no trends in the reporting of AEs by gender group have been elucidated.

Race

While race information was not collected in the NMP-sponsored studies (NMP-P201, NMP-P202, NMP-P301 and NMP-P302), all of these studies were conducted in Japan and would have included predominately Japanese patients. Study BED-008 was conducted retrospectively using data from centres in the US and Norway, where the majority of patients were White (76.8%; Table 7 [Study BED-008 CSR]). Considering the very low number of AEs reported across the studies and the small number of patients included in the development programme, there were no notable differences in AE reporting between the NMP-sponsored studies and Study BED-008.

Renal and Hepatic Impairment

18F-fluciclovine has not been studied in patients with renal or hepatic impairment. Thus, careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. This issue is already adequately mentioned in the product information.

Use in Pregnancy and Lactation

There are necessarily no studies with 18F-fluciclovine in pregnant women to inform any drug-associated risks; however, all radiopharmaceuticals, including 18F-fluciclovine, have the potential to cause foetal harm. Before the use of 18F-fluciclovine, pregnancy should be excluded using an adequate/validated test.

No studies on animal reproductive function have been conducted with 18F-fluciclovine. Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus.

It is unknown whether 18F-fluciclovine is excreted in breast milk. A risk to the suckling child associated with ionising radiation cannot be excluded. If the administration of 18F-fluciclovine is considered necessary, breast-feeding should be interrupted for 24 hours and the expressed feeds discarded.

Safety related to drug-drug interactions and other interactions

No interaction studies have been performed with 18F-fluciclovine. 18F-fluciclovine is not subject to metabolism and is not a substrate for renal drug transporters; therefore, drug interactions are not anticipated.

The applicant informs that the use of concomitant medications was recorded in the NMP-sponsored studies (NMP-P201, NMP-P202, NMP-P301 and NMP-P302), and prior and concomitant glioma therapies were recorded in Study BED-008. No suggestion of drug interactions has been detected in the clinical studies with 18F-fluciclovine. However, the very low number of AEs reported across the studies in an overall small population makes it difficult to discern any potential trends in the reporting of AEs by concomitant medication.

Assessor's comment:

DDI and other interactions are already sufficiently included in the product information no additional changes are necessary.

Discontinuation due to adverse events

No AEs leading to discontinuation were reported in any study submitted for the new glioma indication.

Post marketing experience

18F-fluciclovine is approved in Europe and the US under the brand name Axumin for PET imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen levels following prior treatment. Post-marketing data have been summarised in the latest Periodic Safety Update Report (PSUR) for Axumin, covering the period from 22 November 2017 to 27 May 2018. The cumulative exposure to Axumin in ongoing and completed BED-sponsored clinical studies is 1299 patients. Cumulatively up until 27 May 2018, a total of 20,368 patients had been exposed to Axumin outside of sponsored studies.

Based on the post-marketing data, fluciclovine (18F) Axumin continues to be well tolerated, with no new or significant safety concerns noted and, as such, poses no clinically significant safety issues. In the PSUR period from 22 November 2017 to 27 May 2018, the benefit-risk balance for Axumin in the approved prostate cancer indication remained unchanged; no changes were made to the reference safety information and no additional risk minimisation activities were considered warranted.

Assessor's comment:

2.4.1. Discussion on clinical safety

Although it suspected from the mode action and the known pharmacology of 18F-fluciclovine differences regarding safety events between the population of patients with prostate cancer and glioma may mainly reflect the underlying disease than specific signals general and safety risks, the approach to evaluate safety in the trials needs further clarification.(OC)

The principle concern regarding demonstration of efficacy due to the insufficient quality of the data submitted applies also for the assessment of safety aspects: Neither the mode of safety assessment nor the validity of the results reported can be confirmed.

A safety comparison between the submitted trial results raises concerns whether the approach to assess safety in general is fully reliable, since AE frequencies between the small prospective trials (NMP-P201, NMP-P202, NMP-P301, NMP-P302) and the retrospective analysis of single cases treated in 3 centers in BED 008 differ significantly. Since 18F-fluciclovine is used at very low concentrations without any

secondary pharmacological effects, the product's toxicity beside the radiation is seen as negligible. In consequence, this issue is marked as an "other concern" only.

In the glioma population adverse events were reported in low proportions of patients in each study (3.7% to 17.5% of patients), with the exception of the small Study NMP-P201 in which AEs were reported in 2/5 (40.0%) patients.

Treatment-related AEs were reported in 0% to 20.0% of patients across the studies. There was no meaningful pattern of treatment-related AEs, with events in the majority of SOCs and all event PTs reported in individual patients in each study.

Known ADRs of fluciclovine (18F) include: transient dysgeusia, injection site reactions (pain, redness at injection site), nausea, malaise, constipation and headache. Overall, these events are rare, occurring in ≤0.2% of patients exposed to fluciclovine (18F).

No new safety signals were detected from a comparison of the safety in glioma and prostate cancer trial patients investigated with 18F-fluciclovine.

A single SAE was reported throughout the prospective trials studies (. This was an event of worsening glioblastoma which had an outcome of death and was considered unrelated to 18F-fluciclovine. A second non-related death due to worsening of glioima was reported from the retrospective case analysis in trial BED-008. A single severe AE was reported throughout the studies. This was a non-serious event of blood pressure increased, reported on the afternoon of the day of 18F-fluciclovine administration in a patient with pre-existing hypertension. The event of blood pressure increased was considered unrelated to 18F-fluciclovine administration and resolved following medical treatment. No AEs leading to discontinuation were reported in any study.

There were small changes in lab parameters and vital signs, but most appeared non-detrimental and of no clinical relevance.

The mean (± SD) dose of fluciclovine (18F) in the clinical trials was between ~180 and 420 MBq whereas the recommended activity for an adult is 185MBq fluciclovine. This activity is well in the range of a diagnostic radiopharmaceutical and no dose-effects are expected. However, the large difference between the trials and particularly between the Japanese and US/European BED 008 trial need to be clarified.

Specifications related to radiation protection in the context of manipulation and elimination of the radiopharmaceutical by healthcare professionals, and radiation protection for the family, as appearing in the SmPC in section 6.6 were considered appropriate and in accordance with those approved for other fluorine (18F) radiopharmaceuticals.

Safety information for repeated injections is limited (up to 5); however, no worsening of adverse event of other signal for increase of toxicity was reported.

Fluciclovine (18F) has not been studied in patients with renal or hepatic impairment and no specific safety data in patients with impaired renal function or impaired hepatic function have been provided. In these cases, the higher irradiation in the body caused by slower hepatic and/or renal clearance of the radiopharmaceutical itself or their radioactive metabolites should be taken into account. Thus, it is already stated in the SmPC that careful consideration of the benefit/risk ratio in these patients is required since an increased radiation exposure is possible.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the maximal approved effective dose is 8.2 mSv in prostate cancer (when the maximal recommended activity of 370 MBq is administered) and the dose proposed in glioma is only the half, these adverse reactions are expected to occur with a low probability. The important potential risk of contact with radiation (carcinogenic and hereditary risk) is already included in the RMP since the initial approval.

Fluciclovine (18F) has no or negligible influence on the ability to drive and use machines.

In the event of administration of a radiation overdose with fluciclovine (18F) the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis, frequent micturition and defecation. It might be helpful to estimate the effective dose that was applied.

In conclusion, comparable to the application in prostate cancer, safety issues are not a major concern in this application. All clinically relevant issues regarding the product safety risk (including from the radiation) are already adequate and sufficiently included in the product information.

Additional expert consultations:

Not recommended at present.

Assessment of paediatric data on clinical safety

N/A

2.4.2. Conclusions on clinical safety

In general, 18F-fluciclovine's safety profile is characterised by the absence of clinical relevant adverse events beside, which could not be handled in clinical practise without any problem.

This is explained by the fact that beside the specific risks from radiation, the diagnostic product is administered in very low concentrations were pharmacodynamics effects are not expected.

No new safety signals were detected from a comparison of the safety in glioma and prostate cancer trial patients investigated with 18F-fluciclovine. Hypersensitivity to the active substance or to any of the excipients is the most important risk and thus, contraindicated. More clarification about hypersensitivity events is again requested.

No treatment related serious adverse reactions have been observed during the conduct of the clinical studies. (Two SAE events including death were caused by worsening of the disease; progression of glioma). However, at present it needs to be clarified whether safety evaluation provided in glioma patients included in several very small trials is reliably (large variability in event rates reported between the trials). (OC)

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose of fluciclovine (18F) in the newly applied indication glioma is 4mSv and thereby only half of the approved 8.2 mSv in prostate cancer, the probability for any effects resulting from ionising radiation when the maximal recommended activity of 185 MBq (PCa: 370 MBq) is administered remains low.

3. Risk management plan

The MAH submitted an updated RMP version with this application.

This Type II variation provides evidence of the diagnostic efficacy, and safety of fluciclovine (18F) PET in adults for the proposed indication, detection and continuing assessment of glioma. The main proposed RMP changes were the following:

Summary of significant changes in this RMP

Section	Introduced change
Part I - Product overview	Added proposed additional indication of glioma and information about dosage.
Part II	
Module SI – Epidemiology of the Indication(s) and Target Population(s)	Added information about epidemiology of glioma.
Module SII - Non-Clinical Part of the Safety Specification	Added information, that only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus. It is unknown whether fluciclovine (18F) is excreted in breast milk. A risk to the suckling child associated with ionising radiation cannot be excluded.
Module SIII – Clinical Trial exposure	Updated with the exposure data from completed clinical studies to support the glioma indication: NMP-201, NMP-202, NMP-301 and NMP-302, BED-006 and BED -008.
Module SIV - Populations not studied in Clinical Trials	Updated of Exclusion Criteria in Pivotal Clinical Studies within the Development Programme by adding patients who were pregnant or lactating, or who could be pregnant and Patients aged under 18 years. Added children as not evaluated exposure of special populations.
Module SVI - Additional EU Requirements for the Safety Specification	Added information about dosage for glioma.
Module SVII - Identified and Potential Risks	Section " Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP " subsection "important identified risk" - the risk "Injection site reaction" was filled with the information about one case of injection site reaction reported in the glioma clinical studies. Subsection "Important potential risk" – the risk "PET imaging interpretation errors" was filled with the recieved false positive and false negative results in BED – 006 clinical trial. The statement that fluciclovine uptake in brain is not specific for glioma was added. The important potential risk due to contact with radiation (carcinogenic and hereditary risk) has been revised to "risk due to contact with radiation, including risk to the unborn or suckling child (carcinogenic and hereditary risk)". The pediatric patients with glioma have been added as missing information.

Module SVIII - Summary of the Safety Concerns	The important potential risk due to contact with radiation (carcinogenic and hereditary risk) has been revised to "risk due to contact with radiation, *including risk to the unborn or suckling child* (carcinogenic and hereditary risk)". The pediatric patients with glioma have been added as missing information.
Part V - Risk Minimisation Measures	Safety concern "PET imaging interpretation errors" was updated by adding special warning at SmPC section 4.4. Safety concern "Risk due to contact with radiation, including risk to the unborn or suckling child (carcinogenic and hereditary risk)" was updated by adding specific clinical measures at SmPC section 4.6 and PL. New safety concern "Pediatric patients with glioma" have been added with the accordingly proposed warnings at SmPC section 4.2 and PL.
Part VI - Summary of Activities in the Risk Management Plan by Product	Summary of the Risk Management Plan updated in line with new safety concerns described above.

Safety Specification

Epidemiology of the indications and target population

The MAH added proposed additional indication of glioma and information about dosage.

PRAC Rapporteur's comment:

The update is acceptable.

Non-clinical part of the safety specification

The MAH added statement as radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus, only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus. It is unknown whether fluciclovine (18F) is excreted in breast milk. A risk to the breastfed infant associated with ionising radiation cannot be excluded.

PRAC Rapporteur's comment:

The update of Part II Module SII is acceptable.

Clinical trial exposure

The module was updated with the exposure data from completed clinical studies to support the glioma indication: NMP-201, NMP-202, NMP-301 and NMP-302, BED-006 and BED -008.

PRAC Rapporteur's comment:

The update Part II Module SIII is acceptable.

Populations not studied in clinical trials

The MAH added patients who were pregnant or lactating, or who could be pregnant and patients aged under 18 years as Exclusion Criteria in Pivotal Clinical Studies.

PRAC Rapporteur's comment:

The update by adding pregnant and breastfeeding woman is acceptable, however as the fluciclovine (18F) PET is proposed for adults only, including patients aged under 18 years is not acceptable.

Additional EU requirements for the safety specification

The MAH added the dosage information related to glioma indication.

PRAC Rapporteur's comment:

The update is acceptable.

Identified and potential risks

New information

Section "Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP" subsection "important identified risk" - the risk "Injection site reaction" was filled with the information about one case of injection site reaction reported in the glioma clinical studies.

Subsection "Important potential risk" – the risk "PET imaging interpretation errors" was filled with the received false positive and false negative results in BED – 006 clinical trial.

The statement that fluciclovine uptake in brain is not specific for glioma was added.

The important potential risk due to contact with radiation (carcinogenic and hereditary risk) has been revised to "risk due to contact with radiation, including risk to the unborn or suckling child (carcinogenic and hereditary risk)".
The pediatric patients with glioma have been added as missing information.

Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Injection site reactions
Important potential risks	PET imaging interpretation errors Off-label use Risk due to contact with radiation, including risk to the unborn or

	suckling child (carcinogenic and hereditary risk)
Missing information	Patients with impaired renal function Patients with impaired hepatic function Paediatric patients with glioma

PRAC Rapporteur's comment:

The RMP has been updated according to GVP Module V Rev. 2 with the procedure EMEA/H/C/4197/II/10. However, the summary of safety concerns has not been critically reviewed and adopted as it stands. This was not considered appropriate taking into account that the criteria for inclusion of safety concerns in the RMP have changed in Rev. 2 of GVP Module V. Considering this, the safety specification was reviewed with this procedure.

Important identified risks

Taking into account, that the clinical impact of important identified risk "injection site reaction" is considered minimal in relation to the severity of the indication treated, this risk, therefore should not be classified as important. Based on the above-mentioned provisions it is assumed that the routine pharmacovigilance activities or routine risk minimisation activities are sufficient for the risk "injection site reactions", therefore the MAH should reconsider whether this safety concern should be kept in the RMP as important identified risk.

Important potential risks

Seeing that since the marketing authorisation of Axumin 31 post-marketing cases of false negative results have been reported (PSUR of Axumin 28 May 2018- 27 Nov 2018) and considering possible significant impact of interpretation errors, especially of the false negative results on the individual patient and the need for additional risk minimisation activities, important potential risk „PET imaging interpretation errors" should be reclassified as important identified risk.

The update of important potential risk due to exposure to radiation, including carcinogenic and teratogenic risks, "risk due to contact with radiation, including risk to the unborn or suckling child (carcinogenic and hereditary risk)" generally is acceptable, however, the wording proposed by the MAH should be revised as follows: "Risk due to contact with radiation, including risk to the ~~unborn~~ fetus or ~~suckling child~~ breastfed newborns and infants (carcinogenic and ~~hereditary~~ teratogenic risk).

Taking into account, that there were only two post-marketing reports out of 20,368 subjects exposed to fluciclovine (18F) where Axumin was use for indications that can be confirmed as off-label and considering that the use of Axumin is focused around the specific indications, administered in a nuclear medicine department in a hospital setting, the MAH should reconsider whether the definition of "important potential risk " still applies to off label use of medicinal product.

Missing information

The update of missing information by adding "pediatric patients with glioma" is not acceptable. Regarding the GVP Module V revision 2, missing information refers to gaps in knowledge about the safety of a

medicinal product for certain anticipated utilisation or for use in particular patient populations within the approved indication. Moreover, according to GVP Module V Rev. 2 important identified risks to be included in the RMP would usually warrant:

-further evaluation as part of the pharmacovigilance plan;
-product information advising on specific clinical actions to be taken to minimise the risk or additional risk minimisation activities.
Seeing that fluciclovine is indicated in adults only and additional risk minimisation activities are not foreseen for pediatric population, the proposal to update summary of safety concerns bringing the "pediatric patients with glioma" as missing information is not supported.

According to GVP-V revision 2, the absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP, therefore, the safety concerns: "patients with impaired hepatic function" and "patients with impaired renal function" should be removed from the summary of safety concerns and in all relevant sections of the RMP.

The RMP should be updated accordingly in all relevant sections of the RMP.

Conclusions on the safety specification

The PRAC Rapporteur, having considered the data submitted, was of the opinion that safety specification does not follow GVP Module V Rev. 2 recommendations and needs some revision.

Taking into account, that the clinical impact of important identified risk "injection site reactions" is considered minimal in relation to the severity of the indication treated, this risk, therefore should not be classified as important. The MAH should remove "injection site reactions" from the list of important identified risks. Important potential risk „PET imaging interpretation errors" should be reclassified as important identified risk. The missing information "pediatric patients with glioma" should be removed from the list of missing information. The wording proposed by the MAH for important potential risk due to contact with radiation "*risk due to contact with radiation, including risk to the unborn or suckling child (carcinogenic and hereditary risk)*" should be revised as follows: "Risk due to contact with radiation, including risk to the ~~unborn~~ **fetus** or ~~suckling child~~ **breastfed newborns and infants** (carcinogenic and ~~hereditary~~ **teratogenic** risk).

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Injection site reactions	**Routine risk minimisation measures:** • Listed as an ADR in Section 4.8 of the SmPC. • Section 4.2 of the SmPC provides information on the correct method of administration. • Section 4 of the PL warns of the side effects of pain and rash at the injection site and provides recommendations for reporting side effects. **Additional risk minimisation measures:** None.	Routine pharmacovigilance measures.
Important Potential Risks		
PET imaging interpretation errors	**Routine risk minimisation measures:** • Instructions and warning included in SmPC Section 4.4. • Section 4.2 of the SmPC provides information on the correct method of image acquisition. **Additional risk minimisation measures:** Provision of a self-training programme for prostate cancer containing the following information: • Physiological distribution of fluciclovine. • Image interpretation guidelines. • Examples of incidental findings on PET-CT with fluciclovine. • Examples of positive and negative findings on PET-CT with fluciclovine • Demonstration cases with image interpretation provided by an expert.	Routine pharmacovigilance measures.
Off-label use	**Routine risk minimisation measures:** • The indication for diagnostic use of the medicinal product is clearly stated in SmPC Section 4.1 and PL Section 1. **Additional risk minimisation measures:** None.	Routine pharmacovigilance measures.
Risk due to contact with radiation, including risk to the unborn or suckling child (carcinogenic and hereditary risk)	**Routine risk minimisation measures:** • Included as a warning in SmPC Section 4.8. • SmPC Section 4.4: advises that patients should be encouraged to drink sufficient amounts and void as often as possible during the first hours after the scan in order to reduce radiation exposure of the bladder. • SmPC Section 4.6 provides guidance for use in women of childbearing potential, warns that only essential investigations should be carried during pregnancy, and includes guidance on interruption of breast feeding. • Section 2 of the PL warns patients to inform their doctor if there is a possibility they might be pregnant have missed a period, or are breast feeding.	Routine pharmacovigilance measures.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Section 4 of the PL warns that the radiopharmaceutical will deliver low amounts of ionising radiation associated with the least risk of cancer and hereditary abnormalities. **Additional risk minimisation measures:** None.	
Missing Information		
Patients with impaired renal function	**Routine risk minimisation measures:** • SmPC Sections 4.2 and 4.4: warning of possible increased radiation exposure. • Warning in Section 2 of the PL for patients to report kidney problems to a doctor before receiving fluciclovine. **Additional risk minimisation measures:** None.	Routine pharmacovigilance measures.
Patients with impaired hepatic function	**Routine risk minimisation measures:** • SmPC Section 4.2: warning of possible increased radiation exposure. **Additional risk minimisation measures:** None.	Routine pharmacovigilance measures.
Paediatric patients with glioma	**Routine risk minimisation measures:** • SmPC Section 4.2: warning that safety and efficacy has not been established in children • Section 2 of the PL warns patients to talk to their doctor if they are under 18 years old. **Additional risk minimisation measures:** None.	Routine pharmacovigilance measures.

PRAC Rapporteur's comment:

The Risk minimization measures should be adjusted in accordance with annotations for safety concerns. Please, see the comments above in the section Summary of the safety concerns.

Conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications. However, the risk minimization measures should be adjusted in accordance with annotations for safety concerns.

Part VI "Summary of activities in the risk management plan by medicinal product"

Summary of the Risk Management Plan updated in line with new safety concerns described above

PRAC Rapporteur's comment:

The proposed updates could be acceptable provided the RMP is updated accordingly.

MS comment:

We propose to further discuss/specify the risks associated with off-label use and the need to keep this topic as an important potential risk. Furthermore, pending the CHMP safety assessment, the need for aRMM to avoid PET imaging interpretation errors in glioma indication should be discussed.

PRAC Rapporteur's comment:

Generally, the comment is supported. Taking into account, that there were only two post-marketing reports out of 20,368 subjects exposed to fluciclovine (18F) where Axumin was use for indications that can be confirmed as off-label and considering that the use of Axumin is focused around the specific indications, administered in a nuclear medicine department in a hospital setting, the MAH should reconsider whether the definition of "important potential risk" still applies to off label use of medicinal product.

Considering, that it is noted in the SmPC of the Axumin, that Fluciclovine (18F) images should be interpreted by personnel trained in the interpretation of PET images with fluciclovine (18F) and the SmPC of medicinal product contains instruction on interpretation of PET images with Fluciclovine (18F) in combination with MRI in patients with glioma, the impact of imaging interpretation errors on the benefit / risk balance of the product is likely to be minimal. However, following the positive CHMP safety assessment, if the need for aRMM would be considered necessary, it could be proposed to use the same aRMM, as proposed for prostate cancer indication.

MS comment:

In general we support the PRAC Rapporrteur's assessment and had some additional comments.

1. In our view, the summary of safety concerns proposed by the MAH should be revised in the following way:

Important Identified Risks	~~• Injection site reactions~~
Important Potential Risks	• PET imaging interpretation errors* ~~• Off-label use~~ • Risk due to contact with radiation**, <u>including risk to the unborn or suckling child (carcinogenic and hereditary risk)</u>#**
Missing Information	~~• Patients with impaired renal function~~ ~~• Patients with impaired hepatic function~~ • ~~**Paediatric patients with glioma**~~

*: may be upgraded to an important identified risk as suggested by the PRAC Rapporteur

#: may be renamed as suggested by the PRAC Rapporteur or may be removed altogether

2. The self-training material for Axumin, which is currently specific for prostate cancer, should be amended in order to provide HCPs also with information on interpreting Axumin images acquired for diagnosis and assessment of glioma in adults.

3. Annex II D should be amended in order to add that the educational programme should also contain information about the new indication regarding glioma.

4. Any additional safety concern brought forward as part of the clinical assessment in the CHMP Rapporteur's AR should be considered for inclusion in the RMP by the MAH. A rationale should be provided for including a safety concern or for not doing so, respectively.

5. The whole content of the RMP should be updated according to these recommendations. To support the assessment of the updated RMP, the MAH is requested to provide a clean as well as a track-change version of the updated RMP.

PRAC Rapporteur's comment:

Generally, the comment is supported. According to GVP-V revision 2, the absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP. As concluded by German collegues, regarding the information, provided in section 2.7.3 of the RMP:

Patients with impaired renal function

"No formal studies were performed investigating the use of Axumin in patients with renal impairment. However, the clinical trial population to support the prostate cancer indication included elderly males with reduced renal function by virtue of age; comorbidities, including diabetes and hypertension; and obstructive uropathy due to prostate disease. The product was well tolerated in this population. Careful consideration of the benefit/risk ratio in patients with renal impairment is required since increased radiation exposure is possible."

Patients with impaired hepatic function

"No formal studies were performed investigating the use of Axumin in patients with hepatic impairment. It is noted that Axumin is not metabolised by the liver and the main route of excretion from the body is via the urine. Careful consideration of the benefit/risk ratio in patients with hepatic impairment is required since increased radiation exposure is possible", this safety concern should be removed from the RMP.

Therefore, it is supported to remove the safety concerns: *"patients with impaired hepatic function" and "patients with impaired renal function".*

The proposal of German colleagues to amend the self-training material for Axumin, which is currently specific for prostate cancer also with information on interpreting Axumin images acquired for diagnosis and assessment of glioma in adults is supported. Therefore, Annex II D should be amended accordingly.

While pending the CHMP safety assessment, we support the possibility update any safety concern to be in line with the AR of CHMP rapporteur's team.

PRAC Rapporteur's initial conclusions

The RMP could be acceptable provided an updated RMP and satisfactory responses to the list of outstanding issues at the end of this assessment report are submitted.

Unresolved Issues

- The MAH considers that the definition of "important" still applies to "Off-label use", however the supporting arguments have not been provided. Considering that the criteria for inclusion of safety concerns in the RMP have changed in Rev. 2 of GVP Module V, it is considered that important potential risk „Off-Label use" is already well known to health professionals and do not require additional pharmacovigilance activities or additional risk minimisation measures. Therefore, the important potential risk „Off-Label use" should be removed.

- Glioma is a condition that can affect paediatric patients. However, the indication applied for refers to adults. Regarding the GVP Module V revision 2, missing information refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation or for use in particular patient populations within the approved indication. Potential off label use in children is not considered to be related to indication applied for. In addition, according to the MAH there is currently an approved PIP deferral in place for fluciclovine (18F). Therefore, the proposal to keep "pediatric patients with glioma" as missing information is not supported. The missing information "pediatric patients with glioma" should be removed.

3.1. Overall conclusion on the RMP

☒ The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in section 5 are submitted.

4. Changes to the Product Information

As a consequence of the applied new indication, sections SmPC 4.1, 4.2, 4.4, 4.6 and 5.1, 5.2 and 11 have been updated.

The Package Leaflet has been updated accordingly in sections 1, 2 and 3.

For detailed comments regarding the applicant's proposal for the changes in the product information please refer to Annex 3.

Assessor's comment:

Since this application is currently not approvable no specific comments regarding the proposed changes in the product information are provided.

4.1. User consultation

The MAH confirms that the addition of the information in regard to the proposed use in the diagnosis of Glioma will not cause significant changes to the Patient Leaflet format and overall readability.

The specified areas that have changed in PIL are shown below:

Section 1 :

That Axumin may be used in Glioma (a type of brain cancer)

Section 2:

Before administration of Axumin, an explanation of the necessary patient preparation. This has been aligned with the existing wording and style that of the approved indication, prostate cancer.

Pregnancy and Breast-feeding

Suitable warning and precautions for patients who are of child bearing age, pregnant, breast-feeding. Wording used has been aligned to core SmPC and PILs that are available for fluorinated radiolabelled diagnostic agents.

Axumin contains Sodium

The excipient warning for sodium content is updated as per the excipient guideline for labels and patient leaflets 9 October 2017 EMA/CHMP/302620/2017.

Section 3:

The recommended activity of Axumin to be administered in a case of a scan for suspected or assessment of glioma. This is aligned to wording used in the current approved indication.

Duration of the procedure:

The length of time required for the scan for a suspected glioma. This wording is aligned to wording used in the current approved indication for Axumin.

Assessor's comment:

A full user test was conducted during the initial approval and results were accepted from CHMP. As can be seen above the changes proposed for adding the new glioma indication are minor and otherwise the wording remains unchanged in line with the wording approved for Prostate Cancer. Therefore, the Assessor agree that an additional consultation in target patient groups is not required. In particular, as this application is currently not approvable.

4.1.1. Quick Response (QR) code

N/A

5. Updated Benefit-Risk Balance

5.1. Therapeutic Context

Fluciclovine (18F) is a diagnostic radiopharmaceutical for positron emission tomography (PET) imaging to visualize increased amino acid transport that occurs in malignant tumors. It was approved in Europe via the centralised procedure in May 2017, under the tradename Axumin®, and is indicated for PET in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.

It is a synthetic amino acid which is actively transported into mammalian cells by amino acid transporters, most notably by the LAT1 and ASCT2 transporters, which are known to be upregulated in cancer cells. Fluciclovine (18F) is not metabolized, nor is it incorporated into newly synthesized proteins.

PET imaging studies indicate that fluciclovine (18F) is not only preferentially taken up into prostate cancer where visualization of the image is not obscured by bladder uptake, but also in glioma compared with surrounding normal tissue.

Thus, this Type II variation applies for extension of indication and submitted data in order to provide evidence of the diagnostic efficacy, and safety of fluciclovine (18F) PET also in adults for the detection and continuing assessment of glioma.

Moreover, due to its limited radioactive half-life (approximately 110 minutes),18F-fluciclovine is manufactured and supplied to the imaging site on the day of the planned PET scan. It has the advantage that an on-site cyclotron to produce the tracer is not needed, in contrast to many other PET tracers. Furthermore, 18F-fluciclovine can be produced for commercial use with high standard conditions.

A relatively low administered activity is required for brain imaging because the uptake of 18F-fluciclovine into glioma tissue is high; thus, the radiation risk to staff and patients is low. The proposed recommendation is for a 10-minute PET scan to commence 10 minutes after 18F-fluciclovine administration; thus, there is no prolonged waiting for the patient or a prolonged, uncomfortable scan duration. Either PET-CT or PET-MRI equipment may be used, depending upon availability at the scan site.

Given the relatively short half-life of 18F and the relatively low radiation dose, the potential radiation risk to others from the patient after the scan is short-lived (10 radiation half-lives being less than 24 hours).

5.1.1. Disease or condition

Worldwide, the brain and central nervous system (CNS) is the 17th most common site of cancer (1.8% of new cases). The highest incidences of brain and CNS cancer are typically seen in developed regions, including Europe, where the annual age-standardised rate ranges from 5.8 to 7.0 cases per 100,000 men and from 4.4 to 5.1 per 100,000 women (Ferlay et al, 2015 [GLOBOCAN data]). Two of the most common CNS cancers, high-grade glioma and brain metastasis, occur more frequently during adulthood and especially among the elderly. In Europe, the peak of incidence (2008) was 18.5 per 100,000 in people aged 65 years or older (Crocetti et al, 2012).

Despite their relatively low incidence, these tumours are the 12th most common cause of death from cancer in adults (Ferlay et al, 2015 [GLOBOCAN data]). This is indicating a high degree of lethality, particularly in young people. Glioma, a heterogeneous disease with multiple histological subtypes of tumours arising from non-neuronal glial cells, is the most commonly occurring type of primary brain tumour accounting for 26.5% of all brain tumours and 80.7% of malignant tumours (Ostrom et al, 2017). Review of the data collected by 67 European registries between 1995 and 2002 revealed glioblastoma, the most aggressive form of glioma (WHO Grade IV), accounts for 30% or more CNS tumours in most countries (Sant et al, 2012). Glioblastoma is more common in older adults, with the incidence increasing with increasing age. The highest rates of glioblastoma are reported in patients aged 75 to 84 years, with cases 1.58 times more common in males than in females (Ostrom et al, 2017). Gliomas are associated with significant morbidity and mortality. Although survival rates vary considerably according to histological subtype and whether or not the tumour is malignant, relative survival estimates for glioblastoma are low, with 5.5% of patients surviving 5 years post-diagnosis (Ostrom et al, 2017). Symptoms vary depending on tumour size, type and location, with headache, nausea and vomiting, changes in behaviour, speech, vision or hearing, balance and walking problems, and seizures the most commonly presenting symptoms.

5.1.2. Available therapies and unmet medical need

Treatment options for glioma vary according to tumour histology and anatomic site of the tumour, but complete or near complete surgical removal is generally recommended. Surgery generally provides the best outcome for patients when as much of the tumour as possible is removed (maximal safe resection).

Other treatment options include radiation therapy, with combined temozolomide/radiotherapy being the standard of care for patients with glioblastoma (Stupp et al, 2014).

Accurate evaluation of tumour location and extent before or during surgery is essential to perform thorough resection (Wakabayashi et al, 2017) and relies heavily on the accuracy of radiographic assessment (Huang et al, 2015). Magnetic resonance imaging, with or without contrast, is the diagnostic method of choice for determining target treatment area in cases of suspected glioma due to its high soft-tissue contrast (Karlberg et al, 2017). Although morphologic assessment by MRI is precise, it lacks specificity and does not allow easy determination of tumour activity and metabolism (Dunet et al, 2012). Currently, the gold standard for tumour delineation is contrast-enhanced (CE)-MRI, with many sites also using FLAIR sequences to indicate the extent of peri-tumoural oedema. Furthermore, CT may be used in patients unable to undergo MRI. There are, however, limitations with these methods, in that FLAIR lacks specificity in differentiating between tumour tissue and the presence of oedema, necrosis and gliosis (Karlberg et al, 2017) and the contrast predominately visualises areas with a disrupted blood-brain-barrier (BBB) (Wakabayashi et al, 2017). On CE-MRI, glioblastoma cells can extend beyond the contrast enhanced area and more widely with increasing tumour size on CE-MRI (Miwa et al, 2014). Furthermore, the degree of BBB disruption varies between tumour type and grade, with many low-grade gliomas not reliably visualised using CE-MRI (Wakabayashi et al, 2017). Post-treatment assessments for response and tumour progression also rely on MRI and are fraught with diagnostic challenges. These include variability in image acquisition parameters, inter-reader variability, difficulty measuring irregularly shaped tumours, consistent interpretation of treatment-related radiographic changes, pseudoprogression secondary to radiation and chemotherapy (Huang et al, 2015).

Improved diagnostic imaging can be obtained using PET with various tracers to visualise biological processes, such as cell proliferation, membrane biosynthesis, glucose consumption and uptake of AA analogues (Albert et al, 2016). The addition of PET to MRI may improve the diagnostic accuracy of cerebral gliomas (Karlberg et al, 2017). However, it needs to be mentioned that in clinical practise currently 5-aminolevulinic acid (5-ALA) is used intraoperatively to define in-vivo delineation of malignant glioma during resection in adult patients. Several clinical studies have shown a higher percentage of complete tumour resections under 5-ALA, which has proved to result in more favourable outcome.

Recently published guidelines from the RANO working group/EANO emphasise the clinical utility of PET imaging in gliomas (Albert et al, 2016). Specifically, the superiority of AA PET tracers (e.g., 11C-MET, 18F-FET and 18F-FDOPA) over glucose PET tracers (such as 18F-FDG) is highlighted in this publication. The RANO working group/EANO recommend that implementing the use of AA PET into treatment planning is advantageous, as particularly 18F-FET PET allows a better delineation of tumour extent compared with standard MRI and additionally identifies intra-tumoural heterogeneity, including malignant foci in non-contrast-enhancing gliomas (Albert et al, 2016).

Limitations in terms of short half-lives, laborious synthesis and use of an on-site cyclotron for manufacture are known for the currently available PET AA tracers. Thus, the applicant has developed 18F-fluciclovine as a diagnostic radiopharmaceutical for PET imaging to visualise the increased AA transport that occurs in malignant tumours. Similar to 11C-MET and 18F-FET, 18F-fluciclovine is an AA analogue, actively transported into mammalian cells and thus accumulates in a manner that reflects AA metabolism in tissues. It has a short synthesis time and a long enough half-life for delivery (approximately 110 minutes), which eliminates the need for an on-site cyclotron, rendering the technique more readily available than 11C-MET (Schiavina et al, 2014).

The Marketing Authorisation Holder of 18F-fluciclovine is now applying for extension of the current indication to include the use in positron emission tomography (PET) imaging in adults for the detection and continuing assessment of glioma

5.1.3. Main clinical studies

The applicant has submitted trials NMP-P201, NMP-P202, NMP-P301/P302, BED-006 and BED-008 to provide data on the technical (reproducibility of image reads across readers and when re-read by the same reader a second time) and/or diagnostic performance (sensitivity and specificity) of 18F-fluciclovine PET imaging in combination with MRI, as well as the impact on diagnostic thinking (positive and negative predictive values) to justify approval of 18F-Fluciclovine in the intended indication "for the detection and continuing assessment of glioma".

Studies NMP-P201, NMP-P202 and P301/302 were small prospective trials, each including between 5 and 35 patients, all with primary glioma. They were all performed in the Japanese population by another sponsor (Nihon Medi-Physics Co., Ltd.).

In addition, the applicant has added **retrospective data** from further 18 patients (Finally analysed set) evaluated in **trial BED-008**. This analysis was planned to be conducted in 100 Caucasian patients, 82 were enrolled, but only 18 could be evaluated. Data is derived from three centers in the US and Norway. All but one of these patients suffered from recurrent glioma.

Studies NMP-P201 and **NMP-P202** were Phase 1/2, single administration, open-label studies designed to evaluate the safety and efficacy of 18F-fluciclovine administered as a single i.v. injection to patients with a suspected diagnosis of malignant glioma based on either clinical symptoms and/or brain MRI. In both studies, patients (n=5 [Study NMP-P201] and n=40 [Study NMP-P202]) received 18F-fluciclovine. Cranial dynamic PET scans were performed at 0 to 60 minutes after administration (scanned at 10, 30, 50 minutes after administration using 5, 10 and 15 minutes of PET list mode data to create image datasets simulating 87 MBq, 185 MBq and 270 MBq administered activity, respectively) in Study NMP-P201, and 10 to 20 minutes and 40 to 50 minutes after administration in Study NMP-P202.

Trial NMP-P301 and **NMP-P302** were declared as Phase 3, single administration studies designed to evaluate the safety and efficacy of 18F-fluciclovine administered as a single i.v. injection to patients with suspected malignant primary glioma, based on their clinical symptoms, clinical course and MRI examinations, who were scheduled for resection via craniotomy.

The methodology for image evaluation was essentially the same for the two studies, thus imaging data from the two studies were also combined and analysed in the Study NMP-P301/P302 CSR. In both studies, patients (n=20 [Study NMP-P301] and n=25 [Study NMP-P302]) received 18F-fluciclovine, with 10-minute cranial PET scans started 10 to 50 minutes after administration. Studies NMP-P301 and NMP-P302 included additionally an attempt to assess how patient management was impacted by the results of the 18F-fluciclovine PET imaging (i.e., whether the extent of resection planned using the navigational MRI images changed [increased, decreased or was unchanged] after incorporation of data from 18F-fluciclovine PET).

Moreover, trial NMP-P302 was primarily designed to show the presumed impact of 18F-Fluciclovine on the clinical outcome in terms of PFS at 9 months after resection in patients with primary glioma, but failed to show any favourable impact of the PET diagnostic included. (However, it seems to be the only trial in the program which might allow a sort of comparison of the impact of MRI alone.) In consequence, both studies are mainly seen as supportive for this application. Taking all prospective trials together, the analysed population included 85 patients with primary glioma.

Study BED-008 was a **retrospective data extraction study** investigating the effectiveness of 18F-fluciclovine PET scans to detect the presence or recurrence of malignant disease in patients with glioma, based on data analysed from three sites (Memorial Sloan Kettering Cancer Center [MSKCC], NY, US; Emory University, GA, US; Oslo University Hospital [OUH], Oslo, Norway) where 18F-fluciclovine had

been administered to patients as part of investigator-initiated trials (IIT) for the two former, or a compassionate use programme for the latter, prior to July 2017. At one of these sites (Emory), 18F-fluciclovine PET scanning had been performed for research purposes only; imaging was not clinically interpreted at the time it was performed, results were not used to guide biopsy sampling and were thus not eligible for inclusion in the full efficacy analysis. All the other studies above included only patients with suspected primary glioma, whereas Study BED-008 included a majority of patients with recurrent glioma (50/82 [61%]). However, at the end only 18 patients (17 with recurrent and 1 with primary glioma) could be included in the final analysis set.

In addition, the applicant has also submitted results from a Phase 3, **Blinded Image Evaluation (BIE) study (BED-006)** using 18F-fluciclovine PET images derived from Study NMP-P202. The study aimed to assess the inter- and intra-reader reproducibility of image reads when interpreted by naïve readers. In the applicant's view this trial was additionally intended to evaluate the efficacy of 18F-fluciclovine PET combined with MRI imaging, compared to MRI alone, in adults with glioma in order to assess diagnostic specifity and sensitivity correcting deficits regarding assessment in the complicated designed Japanese trials. Study BED-006 is claimed to provide data to support the technical and diagnostic performance, as well as impact on diagnostic thinking, of 18F-fluciclovine PET imaging in combination with MRI, compared to MRI alone. It is also claimed to illustrate the potential additive clinical value of 18F-fluciclovine PET in terms of increased tumour volume identified compared to MRI alone.

The relevant guideline [EMA GUIDELINE ON CLINICAL EVALUATION OF DIAGNOSTIC AGENTS (CPMP/EWP/1119/98/Rev. 1)] recommends explicitly for a pivotal trial the inclusion of a sufficient number of patients representative for the full population in which the diagnostic agent is intended to be used. This means with respect to the applied indication inclusion of patients:

- for screening in asymptomatic patients or those with other intracranial diseases, in patients with suspected but not confirmed disease,
- in patients with a confirmed disease for evaluation of its extent (initial staging), severity or prognosis
- in patients undergoing treatment to monitor its efficacy
- in previously treated patients to search for recurrence and
- in patients with a confirmed recurrence for evaluation of its extent (restaging), severity or re-evaluate the prognosis.

These requirements for a clinical development program intended to seek approval for the applied broad indication are considered not fulfilled by any of the trials performed.

5.2. Favourable effects

Although 18F-Fluciclovine has a limited radioactive half-life (approximately 110 minutes), it can be manufactured and supplied to the imaging site on the day of the planned PET scan. This means that, in contrast to many other PET tracers, an on-site cyclotron to produce the tracer is not needed. Thus, the tracer can be produced for commercial use with high standard conditions.

The applicant claims that the PPV and NPV of 18F-fluciclovine PET has been established in combination with MRI using definitive histological diagnosis as SoT. Across three small prospective Studies NMP-P202, NMP-P301/P302 in total 80 patients, the PPV for 18F-fluciclovine PET in both CE-T1W MRI positive and negative areas was reported ranging from 87.5% to 100.0% and 78.6% to 100.0%, respectively.

In the BIE Study BED-006, which conducted a blinded re-reading of 18F-fluciclovine PET images generated in Study NMP-P202, PPV for PET plus CE-T1W MRI ranged from 93.1% to 96.4% across three readers. In this study, the PPV for CE-T1W MRI alone was reported to be similar with 94.1% and slightly lower with 84.6% for FLAIR (or T2W) MRI alone.

The NPV was reported from the post-hoc BIE re-reading trial BED-006, but was not adequately assessed in the prospective clinical trials NMP-P202, P301 and P302. The NPV for PET plus CE-T1W MRI was described to range from 38.1% to 43.8% for the three readers across both timepoints, which is similar to the NPV of 37.5 % reported for FLAIR (or T2W) MRI alone. The NPV for CE-T1W MRI alone was lower at 26.7%.

Sensitivity and specificity (diagnostic performance) of 18F-fluciclovine PET was based on the re-reading assessment in the BIE trial BED-006 and was calculated to range from 64.9% to 75.7% and 77.8% to 88.9%, respectively, across three readers and both timepoints. Lower sensitivity and specificity were reported from the prospective trials. In the integrated NMP-P301/P302 study report the sensitivity of 18F-fluciclovine PET was only 58.0% (95% confidence interval: 44.2% to 70.6%) and the specificity of 18F-fluciclovine PET was only 61.5% (95% confidence interval: 35.5% to 82.3%).

In the prospective trials NMP-P202, P301 and P302, only patients with suspected primary glioma according to previous MRI diagnosis were included. The only source for recurrent glioma in this application is the retrospective analysis BED-008. From trial BED-008 the PPV (n, 95% CIs) for 18F-fluciclovine PET scanning to detect histologically confirmed recurrent brain tumor was 88.2% (n=17, 63.6%, 98.5%). The NPV and specificity could not be calculated as there were no patients with a negative 18F-fluciclovine PET scan.

Based in trial BED-006 a higher sensitivity of 18F-fluciclovine PET plus CE-T1W MRI compared to CE-T1W MRI alone, as well as the higher specificity of 18F-fluciclovine PET plus CE-T1W MRI compared to FLAIR (or T2W) MRI alone is claimed. This statement is derived from an re-analysis of 30 biopsies from areas which were CE-T1W MRI negative and PET positive. The applicant emphasises that this assessment was performed blinded to and independent of the result of the initial analysis. In this re-analysis 10 to 13 of these biopsies (depending on reader and timepoint), were true positives identified by PET plus CE-T1W MRI when they were negative on CE-T1W MRI alone. Thus, it is claimed that PET in combination with CE-T1W MRI was able to detect positive lesions that CE-T1W MRI alone did not.

Similarily 39 biopsies that were within a region positive on FLAIR (or T2W), four or five (again depending on reader and timepoint) were true negatives identified by PET plus CE-T1W MRI when they were false positive on FLAIR (or T2W) MRI. Thus, it is concluded by the applicant that PET in combination with CE-T1W MRI may provide additional discriminatory information compared to FLAIR (or T2W) MRI alone.

Additionally it is claimed as a favourable effect that analyses of the extent and intersection of VOIs (i.e., tumour volumes) between imaging modalities in BED-006 demonstrate an significant added VOI using PET plus CE-T1W MRI vs. CE-T1W MRI alone.

Results from BIE Trial BED-006 indicate good agreement of image interpretation across readers and timepoints, demonstrating reproducibility across readers and when images were re-read by the same reader for a second time. Analyses of inter-reader agreement of PET plus CE-T1W MRI reads based on the binary interpretation of the data (i.e., whether the biopsy location was within the PET positive region or not) indicated that concordance was high for all three readers overall and for pairwise inter-reader comparisons (Reader 1 vs. Reader 2, Reader 1 vs. Reader 3 and Reader 2 vs. Reader 3). Specifically, overall, 89.4% and 87.0% of scans were in agreement by all three readers at Timepoint 1 and Timepoint 2, respectively (Fleiss' Kappa, 0.86 and 0.82, respectively). At both timepoints, concordance was ~90% or higher for each pairwise inter-reader comparison (Cohen's Kappa, 0.78 to 0.91) (binary interpretation).

Safety data obtained in the small population of patients with glioma in the clinical trial programme indicate that 18F-fluciclovine in glioma is similarly well tolerated in this indication as it is in prostate cancer; it seems to pose no clinically significant safety issues beside radiation.

5.3. Uncertainties and limitations about favourable effects

The proposed fixed-dose posology was established in Japanese patients only. In the retrospective analysis BED-008 higher doses were administered in Caucasian patients outside Japan. Therefore, it is currently not clear whether the proposed fixed dose posology can be extrapolated to the EU population; in particular, as no bridging data is available which would allow comparing the imaging quality and outcome. Therefore, the proposed posology is not sufficiently justified for the proposed use in the EU population. (MO)

No adequately sized and designed pivotal phase 3 trial was submitted for this application. Instead, pivotal evidence is claimed from the results of 4 small prospective open clinical trials conducted in Japan including 5 to 35 patients (FAS in total ~ 80 patients) with primary glioma. In order to provide evidence for patients with recurrent glioma a retrospective analysis (BED-008) in a evaluable population of 18 patients was added. In the Rapporteur's view, this very restricted data base is not sufficient to support the broad indication applied for.

The applicant suggests taking the data collectively as pivotal. However, the assessment of the efficacy remains incomplete and confusing since outcome of different trials are partially and arbitrarily combined in order to bridge missing results in the various small trials. Moreover, some reported outcomes were derived from post-hoc re-analysis of available data. This approach is not adequate for confirmatory claims. Usually, such analyses would only be acceptable as explorative aiming to generate a hypothesis.

The 4 prospective trials had slightly different objectives and endpoints. Although the mode of endpoint evaluation was similar, the assessable outcome was likely biased by the biopsies taken in the different regions and Appraisal Regions defined. Since the planned approach was more exploratory than confirmatory, pooling of data was only provided for the analysis of PPV from trials NMP-P301/302. Additionally, inclusion of different glioma grades and the use of two doses (high and low dose of 18F-Fluciclovine) complicate the assessment and resulted partially very small subgroups (e.g. 1-3 patients) in which no conclusive and reliable assessment could be performed .

With respect to the claimed indication it is critical from a methodological point of view that the data presented do not allow any valid assessment of outcome from 18F-Fluciclovine PET in glioma diagnosis independent from MRI diagnostic, which has per se a high diagnostic accuracy. All patients included had PET and MRI. According to the study reports, selection of biopsy location, essential for the endpoint outcome, was based on findings of both methods in open trials. This means that the overwhelming majority of biopsies were taken in regions identified already with T1 or T2 FLAIR MRI alone. Thus, contribution of T1 or T2 FLAIR MRI alone is not sufficiently evaluable, since no independent blinded assessment was performed in order to define prospectively biopsy locations based on results of MRI alone or MRI together with PET. The applicant informs that the concept of these trials was to use an intra-patient control in order to collect data in a small number of patients. However, since neurosurgical investigators were reluctant to take more brain biopsies than justifiable to confirm diagnosis and resection volume in this indication, i.e. biopsies in apparently tumour-negative biopsies, which are essential to define diagnostic accuracy adequately, are not sufficiently available. This challenge significantly the reliability of the trial results submitted and essentially contributes to the irresolvable major concerns in this application.

Across Studies NMP-P202, NMP-P301/P302, the PPV and NPV for 18F-fluciclovine PET in both CE-T1W MRI positive and negative areas are described to be high (ranging from 87.5% to 100.0% and 78.6% to 100.0%, respectively). The PPV outcome is claimed as statistical highly significant (p-values between

<0.001 and 0.003). However, a comprehensible justification for the null hypothesis (PPV≤ 70.0) this calculation is based on, remains missing.

Even higher PPVs were reported from the retrospective Blinded-Image Evaluation (BIE) Study BED-006 in which 18F-fluciclovine PET images from Study NMP-P202 were re-assessed by three blinded trained reader. The PPV for PET plus CE-T1W MRI was reported even higher (ranging from 93.1% to 96.4% across three readers and for two 10-minute PET scans per patient starting between 10 and 20 minutes post-injection and between 40 and 50 minutes post-injection). However, in the same study, the PPV for CE-T1W MRI alone was similar 94.1% and the PPV for FLAIR (or T2W) MRI alone was slightly lower at 84.6% (one reader only for MRI scans). The comparison between PET and FLAIR (or T2W) MRI alone was added as an additional analysis and was not part of the Study NMP-P202 analysis. Apart of the artificial post-hoc character of this trial aiming to correct the deficits in the design of the NMP-trials, the robustness of the data is challenged since demonstration of diagnostic superiority claims depends from the outcome in 2-3 patients only. The overlapping CIs for the results for the three diagnostic methods compared and particularly the similar PPV for PET plus CE-T1W MRI and CE-T1W MRI alone does not allow confirming any diagnostic benefit for the addition of PET. At the end, a BIE study should primarily allow an assessment of inter-reader performance, but is clearly not seen as an adequate approach to define pivotally diagnostic accuracy. Assessment of NPV was not adequately addressed and assessable from the prospective trials, particularly not from trial NMP-P202. Thus, results regarding the NPV are mainly referring to the analysis provided from the BIE re-reading trial BED-006, which is viewed methodologically critical.

It needs to be considered that the NPV was not adequately addressed in the design of the prospective clinical trials NMP-P202, P301 and P302 due to the overall low number of negative biopsy expected in a trial primary aiming to collect glioma tissue for histopathological analysis. Since location of biopsy was mainly determinated by the intention to prove the tumour histology, the number of biopsies available in potential negative regions was not representative, particularly in trial NMP-P301 and 302. This is ethically fully correct, however, it illustrates also that the general trial design of the Japanese trials was very complicated and highly sophisticated, which is acknowledged in the applicant's response. In particular, the design resulted in fundamental limitations due to the intention to use each patient as its own control in order to reduce number of patients in the trials.

At the end, the resulting limitation, e.g absence of NPV assessment in the largest trial (NMP-P202), were so pronounced that the data generated become not interpretable.

18F-fluciclovine uptake is not specific for glioma and the applicant confirms in the response that it occurs also in processes in and around the brain, e.g. in other inflammatory conditions, such as active multiple sclerosis and brain abscesses. Since this important issue was not sufficiently investigated, the characterisation of NPV remains incomplete and not adequate for confirmatory claims.

The lack of reliable data regarding the PPV and particularly NPV in principle lowers also the reliability of calculations provided for specificity and sensitivity. A higher sensitivity of 18F-fluciclovine PET plus CE-T1W MRI compared to CE-T1W MRI alone, as well as the higher specificity of 18F-fluciclovine PET plus CE-T1W MRI compared to FLAIR (or T2W) MRI alone is claimed from re-reading BIE Trial BED-006. This claim is substantiated by the applicant with a re-analysis of 30 biopsies from areas, which were CE-T1W MRI negative, and PET positive. In this re-analysis, 10 to 13 of these biopsies (depending on reader and timepoint), were true positives identified by PET plus CE-T1W MRI when they were negative on CE-T1W MRI alone. However, the applicant stated that only one patient had a biopsy in a region which was FLAIR (T2W) MRI negative (Reader 3, Timepoint 2) in a region which was PET positive and CE-T1W MRI negative. All the other biopsies (12) in this region were FLAIR (T2W) MRI positive. It is thus concluded that PET in combination with CE-T1W MRI was able to detect positive lesions that CE-T1W MRI alone did not. However, 12/13 were positive in T2-FLAIR MRI also. Similarily 39 biopsies that were within a region

positive on FLAIR (or T2W), four or five (again depending on reader and timepoint) were true negatives identified by PET plus CE-T1W MRI when they were false positive on FLAIR (or T2W) MRI. Thus, it is concluded by the applicant that PET in combination with CE-T1W MRI may provide additional discriminatory information compared to FLAIR (or T2W) MRI alone. However, again it is not reported whether these lesions were also negative in CE-T1W MRI alone. Even considering that PET plus CE-T1W MRI may allow assessing a larger tumour than CE-T1W MRI alone and a smaller tumour volume than detected with FLAIR MRI, the issue remains that in contrast to the centralised approved intraoperatively administered diagnostic agent Gliolan® no positive clinical relevant benefit in terms of increased PFS or prolonged OS was shown in trial P-302.

In trial NMP-P202, which is the PET database for all conclusion in the BIE trial BED-006 sensitivity and specificity were only included as evaluation of "Semi-quantitative Indices to Enable Appropriate Visualization of Tumor Extents" derived from "simulations" in this trial. The applicant clarified that this approach was not further followed in BED-006. The mode of assessment was sufficiently explained with the applicant's response. However, in the Rapporteur's view the provided post-hoc calculations for sensitivity and specificity derived from a BIE trial are not sufficient for pivotal claims.

Similarly, calculation of sensitivity and specificity of 18F-Fluciclovine in NMP-P301/302 was confounded by the collected tissues. In this sample, negative biopsies were not adequately represented, which again lowers the reliability due to selection bias. Therefore, the calculations provided for diagnostic accuracy are deemed not sufficiently confirmative. The pivotal claims based on these parameters are also seen as not justified.

Considering that trial NMP-P302 showed an inferior outcome for the primary endpoint "9 months PFS" in patients pre-operatively assessed by PET/MRI in comparison to those assessed with MRI alone [PET+MRI: 33.3%(9.9 to 65.1%) versus MRI alone: 46.7% (21.3 to 73.4%)], no beneficial impact of adding 18F-Fluciclovine PET on patients management or outcome can be concluded compared to standard MRI diagnostics.

This seems to be in line with the results form trial BED-008 in 18 patients with recurrent glioma. In this trial the PPV (n, 95% CIs) for 18F-fluciclovine PET scanning to detect histologically confirmed recurrent brain tumor was 88.2% (n=17, 63.6%, 98.5%). The NPV and specificity could not be calculated as there were no patients with a negative 18F-fluciclovine PET scan. The PPV (n, 95% CIs) for MRI to detect histologically confirmed recurrent brain tumor was identical with 88.2% (17, 63.6%, 98.5%). Apart from the methodological concerns due to the non-confirmative trial design, the small number of patients in the FAS and the provided calculations in general, it is again noted that also in this trial no additional benefit from adding 18F-Fluciclovine PET to MRI was demonstrated even in the probably more complicated population with recurrent disease.

Results from BIE Trial BED-006 seemed to indicate that image interpretation across readers and timepoints may be in agreement, demonstrating reproducibility across readers and when images were re-read by the same reader for a second time. However, the clinical relevance of this analysis remains inconclusive considering that in the data base selected from l trial NMP-P202 the number of negative biopsies was significantly smaller compared to the positive biopsies. During the applicant's response it was confirmed that calculation of the confidence intervals for the kappa statistics performed in BED-006 is methodologically not reliable.

Moreover, intraoperative administration of 5-aminolevulinic acid (5-ALA) (Gliolan®) is available to define in-vivo delineation of malignant glioma during resection and data was used to define the sample size in the clinical trials. Since approval in 2007 in the EU this method is now seen as clinical standard for best tumour delineation during the surgical procedure, since administration of Gliolan has been shown to improve outcome and prognosis also in glioma patients after resection. There is no comparative data showing that outcome of 18F-Fluciclovine PET diagnostic has any additional benefit in comparison to MRI

and Gliolan for the patients. The outcome of trial NMP-P302 even seems to indicate an inferior outcome in the 18F-Fluciclovine arm in comparison to patients assessed with MRI alone regarding the 9-months PFS (primary endpoint of the trial).

Around one-third of WHO Grade II gliomas and a majority of Grade I gliomas do not show increased uptake of AA PET tracers. However, no data for WHO grade I glioma patients and only few data on grade II glioma patients is available from the submitted clinical trials. Although no grading of glioma is possible or claimed for 18F-fluciclovine, the impact of PET outcome on glioma grading remains not sufficiently assessable. In their response, the applicant clarified that this is still possible only by histopathology.

Despite these shortcomings, the applicant applies to extrapolate the results also to all other clinical settings in which the utility of AA PET has been described in the published literature. This claim for a broad indication is based on considerations published in the RANO/EANO group publication (Albert et al, 2016) which discussed clinical settings in which addition of AA PET might add potential clinical benefits in glioma patients. Use of AA PET prior to surgery to plan biopsy or surgical field or radiotherapy as well as the assessment of response and planning of subsequent treatment after surgery are mentioned in this recommendation. Additionally, the potential impact on differentiation between pseudoprogression and true progression as well as prognostication in general is also addressed referring to the published evidence for other AA PET agents.

Currently, 18F-FET PET is well-established for glioma diagnosis in Europe and a national MAA for 18F-FET PET exist at least in France. A lot of publications and even the RANO guideline recommends this diagnostic agent as standard for glioma diagnosis in clinical practise. Apart of the issue that the diagnostic performance of 18F-Fluciclovine in glioma is not sufficiently characterised and no convincing additional benefit from addition of 18F-Fluciclovine PET on top of MRI was demonstrated, the lack of any bridging data, which would allow any comparison between 18F-FET PET and 18F-Fluciclovine imaging results in glioma, precludes any claims regarding extrapolation. In addition, the current wording of the indication does not reflect the concomitant use of MRI in conjunction with 18F-Fluciclovine PET, which is considered not sufficiently justified.

There is a clear risk for misinterpretation of 18F-fluciclovine scans. An accurate evaluation of tumour extent before or during surgery is essential to perform a thorough resection of the glioma for best patient outcome. However, this is still mainly based on the accuracy of MRI radiographic assessment or the intraoperative use of 5-ALA (Gliolan).

In the limited number of patients included in 18F-fluciclovine clinical programme, a number of cases of false negative and false positive results compared to the histological SoT were reported. Thus, image interpretation errors can occur; this means even a negative image does not rule out the presence of glioma and a positive image does not confirm the presence of glioma. Due to the limited number of biopsies available in a small number of patients included in different trials this risk cannot be defined.

5.4. Unfavourable effects

All radiation exposures carry a theoretical risk for the development of secondary cancer. However, the administration of 185 MBq of 18F-fluciclovine for diagnostic purposes in the proposed patient population is considered acceptable in the view of the life-threatening nature of glioma.

The treatment related adverse reactions for fluciclovine (18F) administration include dysgeusia, injection site reactions (pain, redness at injection site) and parosmia. Overall, these events are rare and usually mild, occurring in ≤0.2% of patients exposed to fluciclovine (18F). This is in line with the experience from

other F-18 based radiopharmaceuticals for which no serious adverse reactions have been observed to date.

There is the potential for misinterpretation of the PET images, which may result in inappropriate treatment. Therefore, this issue is supposed by the applicant as an important potential risk in the RMP.

If approved, there is the potential for the product to be used off-label for other diagnostic situations beyond the precise indication applied for which is also considered to be an important potential risk in the RMP.

The effective dose of fluciclovine (18F) is ~4 mSv when the maximal recommended activity of 185 MBq is administered, adverse reactions due to radiation are expected to occur with a very low probability.

5.5. Uncertainties and limitations about unfavourable effects

The safety information in patients that have received repeated injections is limited (up to 5); however, no worsening of adverse reactions or new adverse reactions were expected or observed.

Small changes in lab parameters and vital signs have been observed. However, these are considered of no clinical relevance and are probably chance findings not related to the imaging agent.

Fluciclovine (18F) is expected to be used in special populations such as elderly and patients with renal or hepatic impairment. The applicant has provided limited safety information of fluciclovine (18F) in the elderly population. No specific safety data in patients with impaired renal function or impaired hepatic function have been provided. This has been included as missing information in the RMP.

5.6. Effects Table

Table: Fluciclovine (18F) for positron emission tomography (PET) imaging together with CE T1-and T2W FLAIR MRI diagnostic of adult patients with glioma

Effect	Short Description	On site read	*Blinded read*	Control	Uncertainties/ Strength of evidence	References
Favourable Effects (as claimed by the applicant only)						
In primary glioma patients (FAS n=80						
PPV	Positive predictive value to detect histologically confirmed glioma	87.5 to 100%	93.1 to 96.4%	T1-MRI 94.1%	High degree of uncertainties/ Calculation not reliable	Trial NMP-P202,P301 ,P302 BIE-trial BED-006
NPV	Negative predictive value to exclude histologically confirmed	?	38.1 to43.8%	T2-FLAIR MRI 37.5%	High degree of uncertainties/ Calculation not reliable	Trial NMP-P301,P302, BIE-trial BED-006

Effect	Short Description	On site read	*Blinded read*	Control	Uncertainties/ Strength of evidence	References
	glioma					
Sensitivity		58.0%	64.9% to 75.7		High degree of uncertainties/ Calculation not reliable	BIE-trial BED-006
Specificity		61.5%	77.8 to 88.9%		High degree of uncertainties/ Calculation not reliable	BIE-trial BED-006
9 months PFS after surgery and tumour delination with PET/MRI		33.3% (9.9 to 65.1%)		46.7% (21.3 to 73.4%)	High degree of uncertainties/ Calculation not reliable	Trial P302
In recurrent glioma patients (FAS n=17)						
PPV	Positive predictive value to detect histologically confirmed recurrent Glioma	88.2% (63.6 – 98.5)	93.1 to 96.4%	T1-MRI 94.1%	High degree of uncertainties/ Calculation not reliable	Based on retrospective analysis presented as trial BED008
NPV	Negative predictive value to exclude histologically confirmed recurrent glioma	Not calcu-lated	N/A		High degree of uncertainties/ Calculation not reliable	
Sensitivity		N/R	N/A		Missing	
Specificity		Not calcu-lated	N/A		Missing	

Effect	Short Description	On site read	*Blinded read*	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Injection site reaction	%	0.6%				
Dysgeusia	%	0.4%				
Parosmia	%	0.2%				
Abbreviations: PPV Positive predictive value, NPV negative predictive value Notes: none						

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

A correct diagnosis and visualisation of tumour extent is clearly a benefit for a patient with glioma; an incorrect diagnosis (e.g. false negative or false positive results of the diagnostic tests) may be detrimental for a patient and can have important consequences in patient management.

Clinical benefit of a diagnostic agent needs to be demonstrated by appropriate characterisation of its technical performance, diagnostic performance and demonstration of an impact on diagnostic thinking. These aspects may have an impact on patient management and clinical outcome.

Accurate evaluation of tumour location and extent before or during surgery is essential to perform thorough resection. In glioma patients it relies significantly on the accuracy of radiographic assessment. Magnetic resonance imaging (MRI), with or without contrast, is the diagnostic method of choice for determining target treatment area in cases of suspected glioma due to its high soft-tissue contrast. Thus, CE-T1W MRI together with T2W FLAIR MRI is currently seen as gold standard for this indication. However, although morphologic assessment by MRI is precise, it lacks specificity. Published data indicates that AA-PET may improve diagnostic imaging by visualising biological processes, such as cell proliferation, membrane biosynthesis, glucose consumption and uptake of AA analogues. This may add an additional important benefit to MRI diagnostic alone, resulting in a more correct characterisation of the target treatment area for resection or for a more reliable monitoring of radiation or chemotherapy treatment effects.

Up to now, none of the AA-analogues PET imaging agent has been approved via the centralised procedure for the glioma indication. This is due to the very short half-life and the need of on-site cyclotron production of these tracers.

Significant differences regarding the imaging performance of AA-analogues in the glioma setting are described in the literature. Therefore, a sufficient and reliable characterisation of the technical and diagnostic performance as well as the impact of diagnostic thinking in the intended target population is essential for the applied extension of indication for 18F-Fluciclovine. However, literature and recommendations referring to 18F-FET are regarded as supportive only because bridging data which would allow a comparison of the diagnostic performance of the well-established 18F-FET and 18F-fluciclovine remain lacking. During response the applicant has submitted a comparison (concordance

and discordance) between 18F-fluciclovine and another amino acid PET tracer, [11C-methyl]-methionine (11C-MET) from trial BED-008. It is reported that 18 patients had imaging with both methods. 17 patients (94.4%) were positive on both 11C-MET and 18F-fluciclovine PET imaging. One patient was considered negative on 11C-MET PET but positive on 18F-fluciclovine PET. Considering the 60-day period between both PET imagings, the retrospective nature of this data and the missing of SoT it remains difficult to interpret this explorative supportive data in the context of this application. A prospective head-to head comparison is more informative. Nevertheless, it is agreed that data further confirming a proof-of principle and it seems possible (but not proven) that differences at least to 11C-MET are not very pronounced. Thus, more prospective pivotal data generated with 18F-fluciclovine is needed to justify the broad indication applied for.

Moreover, since the applicant's claim for a broad indication ("for PET imaging in adults for the detection and continuing assessment of glioma") is mainly based on published literature only, it is important to have at least some valid bridging data in addition. This should allow a valid comparison between the performance and outcome in different clinical glioma settings with well-established and guideline recommended PET-agents (e.g. 18F-FET-PET).

With respect to the clinical development in the new indication, the applicant has not submitted an adequately sized and designed pivotal phase 3 trial as needed according the relevant guideline document. Instead, pivotal evidence is claimed from the results of 4 small prospective open clinical trials conducted in Japan including 5 to 35 patients (FAS in total ~ 80 patients) with primary glioma. In order to provide evidence for patients with recurrent glioma a retrospective analysis (BED-008) of 18 patients was added. In the Rapporteur's view, this very restricted database is not sufficient to support the broad indication applied for.

The applicant suggests taking the data collectively as pivotal. However, the assessment of the efficacy remains incomplete and confusing since outcome of different trials are partially and arbitrarily combined in order to bridge missing results in the various small trials. Moreover, some reported outcomes were derived from post-hoc re-analysis of available data. In addition, according to the information provided in the study reports, the study protocols of all trials were significantly changed several times during the conduct and - probably more important - even after the results has been generated. This further questions the reliability of the data.

The 4 prospective trials had slightly different objectives and endpoints. Although the mode of endpoint evaluation was similar, the assessable outcome was likely biased by the biopsies taken in the different regions and Appraisal Regions defined. Since the planned approach was more exploratory than confirmatory, pooling of data was only provided for the analysis of PPV from trials NMP-P301/302. Additionally, inclusion of different glioma grades and the use of two doses (high and low dose of 18F-Fluciclovine) complicate the assessment and resulted partially in very small subgroups (e.g. 1-3 patients) in which no conclusive and reliable assessment could be performed.

Furthermore, it is critical from a methodological point of view that the data presented do not allow any valid assessment of outcome from 18F-Fluciclovine PET in glioma diagnosis independent from MRI diagnostic, which has per se a high diagnostic accuracy. All patients included had PET and MRI. However, it remains essential that the benefit of adding PET diagnostic to MRI can be clearly assessed. It needs to be assessed whether the higher diagnostic accuracy leads to a clinically relevant benefit, e.g. as it was demonstrated for Gliolan in the target population.

According to the study reports, selection of biopsy location, essential for the endpoint outcome, was based on findings of both methods in open trials. This means that the overwhelming majority of biopsies were taken in regions identified already with T1 or T2 FLAIR MRI alone. Thus, the contribution of T1 or T2 FLAIR MRI alone is not sufficiently evaluable, since no independent blinded assessment in order to define prospectively biopsy locations based on results of MRI alone or MRI together with PET was performed as

it required for a confirmatory trial. This is an important uncertainty, since it precludes a valid assessment of efficacy in the small number of patients investigated.

Referring to the provided PPV and NPV of 18F-fluciclovine PET in combination with MRI using definitive histological diagnosis as SoT the applicant claims that impact on diagnostic thinking was sufficiently demonstrated. Across three small prospective Studies NMP-P202, NMP-P301/P302 including between 20 and 35 patients each, the PPV for 18F-fluciclovine PET in both CE-T1W MRI positive and negative areas is reported to range from 87.5% to 100.0% and 78.6% to 100.0%, respectively. From the BIE Study BED-006, which conducted a blinded re-reading of 18F-fluciclovine PET images generated in Study NMP-P202, PPV for PET plus CE-T1W MRI ranged from 93.1% to 96.4% across three readers. However, the PPV for CE-T1W MRI alone was reported to be similar with 94.1% and slightly lower with 84.6% for FLAIR (or T2W) MRI alone.

Moreover, the NPV was reported from the post-hoc BIE re-reading trial BED-006, but was not adequately assessed in the prospective clinical trials NMP-P202, P301 and P302. The NPV for PET plus CE-T1W MRI was described to range from 38.1% to 43.8% for the three readers across both timepoints, which is similar to the NPV of 37.5 % reported for FLAIR (or T2W) MRI alone.

Due to the similar outcome in the small populations investigated and the overlapping ranges of the reported PPV and NPV between the three methods assessed, an additional benefit with respect to the impact on diagnostic thinking for the addition of 18F-Fluciclovine PET was not sufficiently demonstrated compared to the baseline MRI alone. Moreover, the methodological deficits in the insufficient clinical development program points criticised above indicate further important remaining uncertainties with regarding the claimed favourable effect.

With respect to the demonstration of diagnostic performance the applicant claims a higher sensitivity of 18F-fluciclovine PET plus CE-T1W MRI compared to CE-T1W MRI alone, as well as the higher specificity of 18F-fluciclovine PET plus CE-T1W MRI compared to FLAIR (or T2W) MRI alone. This claim is mainly based on the results of re-reading of data from trial NMP-P202 in the trial BED-006. From this source sensitivity and specificity are reported to range from 64.9% to 75.7% and 77.8% to 88.9%, respectively. However, in the prospective trials NMP-P301/P302 the sensitivity and the specificity of 18F-fluciclovine PET plus MRI were significantly lower i.e. 58.0% (95% confidence interval: 44.2% to 70.6%) and 61.5% (95% confidence interval: 35.5% to 82.3%), respectively. Since calculation in BED-006 was based on a "re-analysis" of 30 biopsies from areas which were CE-T1W MRI negative and PET positive performed and lower values were noted in the prospective analysis, the reliability of the results is challenged. The approach of reanalysing biopsies seems methodologically inacceptable for confirmatory claims. At the end the reliability of demonstration of an improvement in diagnostic performance by adding 18F-Fluciclovine PET to MRI is considered low.

Similarly, the claim for favourable effect regarding a higher accuracy of determining tumour extension derived from a significant added VOI using PET plus CE-T1W MRI vs. CE-T1W MRI alone from analyses of the extent and intersection of VOIs (i.e., tumour volumes) between imaging modalities from the BIE trial BED-006 is not convincing since the VOIs in FLAIR (or T2W) MRI alone are not adequately assessable compared to PET plus CE-T1W MRI. Moreover, trial P302 aiming to demonstrate a clinical relevant benefit from a presumed better tumour size characterisation with 18F-fluciclovine failed to show the expected outcome. Therefore, it seems difficult to prove sufficiently a relevant clinical benefit for the patients.

With respect to the technical performance, there is no sufficient data to confirm that the applied fixed-dose posology, which was established in Japanese patients only, results in the same technical performance and image quality to be appropriate for the EU population also.

In conclusion, from the results of the submitted small, mainly explorative clinical trials neither the diagnostic performance of 18F-Fluciclovine in terms of sensitivity and specificity nor it impact on

diagnostic thinking in terms of positive and negative predictive value was sufficiently and reliably characterised. Moreover, a reliable demonstration that the technical performance in the EU population is appropriate and the fixed dose posology results in a comparable image quality in the EU population as observed during the clinical development in Japan, is missing. Adequate bridging data is not available to compare the efficacy of the applied product with that of AA analogues well characterised and established in clinical practise in the intended target population (e.g 18F-FET) to justify the claimed broad indication applied for.

In conclusion, efficacy of 18F-Fluciclovine in the indication applied for has not been reliably demonstrated.

The adverse reactions seemed to be similarly well tolerated as in the approved prostate cancer indication and no serious safety risks have been described with this radiopharmaceutical. The remaining uncertainties regarding unfavourable effects are deemed not important. However, it needs to be considered that in each patient, any additional radiation exposure must be justified by a likely benefit. A benefit is currently not convincingly demonstrated and thus, missing.

5.7.2. Balance of benefits and risks

The data submitted do not allow a conclusion that 18F-Fluciclovine is beneficial in the diagnosis and continuing assessment of glioma. The fixed-dose posology applied for was established in Japanese patients only and it is remains not clear whether this posology can be extrapolated to the EU population as BMI and distribution of BW is different between Japanese and EU patients. In addition, evidence is based on results of four prospective trials (NMP-P201, NMP-P202 and P301/302) with numerous major methodological flaws, a retrospective analysis (BED-008) and a re-analysis (BED-006) of data that was already assessed in study NMP-P202. In addition, assessments in order to define prospectively biopsy locations based on results of MRI alone or MRI together with PET was performed in an unblinded manner and the additional benefit on diagnostic performance by adding 18F-Fluciclovine PET to the baseline MRI alone remains unclear. Probably due to the concept to use an intra-patient control approach in the Japanese trial program in order to collect data in a small number of patients, the reliability of the reported diagnostic key parameters (PPV,NPV, specificity and sensitivity) claimed to demonstrate diagnostic accuracy remains low, which seems to indicate irresolvable major concerns in this application.

An adequately powered and designed pivotal phase 3 trial performed in a sufficient number of patients is considered essential to justify the broad indication.

In the absence of a convincing and reliable demonstration of an efficacy benefit from the addition of 18F-Fluciclovine to CE-T1 and T2W-FLAIR MRI the small risks derived from the radiation exposures and other adverse effects are not outweighed.

5.7.3. Additional considerations on the benefit-risk balance

The applicant’s claim, that 18F-Fluciclovine PET brings a significant clinical benefit over existing therapies based on improved efficacy, improved safety and/or a major contribution to patient care is currently not sufficiently justified. 18F-Fluciclovine in addition to MRI has not demonstrated a significant clinical benefit in comparison to existing diagnostic tools.

5.8. Conclusions

The overall B/R of Axumin in the new indication for *PET imaging in adults for the detection and continuing assessment of glioma* is negative.