1 Summary

Title:	A Phase I/IIa study to evaluate safety, biodistribution, dosimetry and preliminary diagnostic performance of ^{68}Ga-NeoBOMB1 in patients with advanced TKI-treated GIST using positron-emission tomography/computer tomography (PET/CT).
Short title:	MITIGATE-NeoBOMB1
Radiolabelled imaging product:	^{68}Ga-NeoBOMB1
Phase of trial:	I/IIa
Indication	Gastrointestinal stromal tumours previously or currently under TKI-treatment including at least 50% TKI-resistant patients
Objectives:	**Primary Objectives** **Phase I part:** ● Safety, tolerability ● Human pharmacokinetics and dosimetry data to determine the organ doses and to identify potentially dose-limiting critical organs through PBPK modelling **Phase I/IIa part**: ● Safety, tolerability ● Preliminary targeting properties of ^{68}Ga-NeoBOMB1 in advanced, GRP positive GIST tumours. **Secondary objectives** ● Targeting properties in comparison with standard imaging modalities such as FDG-PET or MRI ● Qualitative comparison of targeting properties of ^{68}Ga-NeoBOMB1 in resistant vs non-resistant tumour lesions in patients undergoing TKI treatment ● Identification of target tissue and improved target volume definition for potential locoregional treatment (RFA or external beam) ● To extrapolate absorbed tumour doses for potential application of ^{177}Lu NeoBOMB1 (in the first 6 patients) **Exploratory objectives**

	• Analysis of ^{68}Ga-NeoBOMB1 metabolites in urine • Mutational status of TKR • Correlation between GRPR and TKR expression
Endpoints:	**Primary Endpoints** **Safety & Tolerability** • Tolerability and safety of the administration of ^{68}Ga-NeoBOMB1 in a diagnostic dose • Last follow-up visit (visit 3) for previous participant in first 3 participants **Human Pharmacokinetics** • Generation of decay corrected time activity curves from ^{68}Ga-NeoBOMB1 PET/CT images in normal organs, tumour lesions. • Quantification of urinary excretion of ^{68}Ga-NeoBOMB1 • Calculation of half-life of ^{68}Ga-NeoBOMB1 in blood **Dosimetry** • Generation of non-decay-corrected time activity curves and residence times from ^{68}Ga-NeoBOMB1 PET/CT images in normal organs, tumour lesions • Calculation of absorbed doses and effective whole body dose of ^{68}Ga-NeoBOMB1, also by PBPK modelling of ^{68}Ga-NeoBOMB1 **Preliminary targeting properties** • Description of ^{68}Ga-NeoBOMB1 accumulation in tumour lesion (number of lesions, SUV value per lesion) and comparison with known tumour lesions. • Comparison of tumour targeting with immunhistopathology (at least in Phase I/IIa patients) **Secondary Endpoints** • Number of tumour lesion detected by ^{68}Ga-NeoBOMB1 in comparison with standard imaging modalities such as FDG-PET or MRI and comparison of resistant vs non-resistant patients • Target identification and volume definition based on ^{68}Ga-NeoBOMB1 images for potential locoregional treatment (RFA or external beam) • Absorbed tumour doses of ^{177}Lu NeoBOMB1 extrapolated from ^{68}Ga-dosimetric data and definition of dose limiting organ for radionuclide therapy **Exploratory Endpoints**

	• HPLC radiochromatography of patient urine after administration of ^{68}Ga-NeoBOMB1 • Description and comparison of mutational status through PCR analysis • TKI-GRPR co-expression analysis through immunohistochemistry or PCR
Type of trial:	Single centre Phase I/IIa study of ^{68}Ga-NeoBOMB1 carrying a fixed dose (activity) of a positron-emitting tracer (^{68}Ga) in patients with advanced TKI-treated GIST.
Trial design and methods:	Diagnostic PET-CT study with a novel tracer including safety assessment, dosimetry, pharmacokinetics and preliminary pharmacodynamics. Patients will receive a single injection of ^{68}Ga-NeoBOMB1 at 3 MBq / kg body weight (with a minimum of 150 and a maximum of 250 MBq)
Trial duration per participant:	7 – 34 days (up to 28 days prior to and EOS visit 6 days after to application of NeoBOMB1)
Estimated total trial duration:	August 2016 – October 2017
Planned trial sites:	Single Site, Medical University Innsbruck.
Total number of participants planned:	A minimum of 6 patients for phase I and up to 6 additional patients for phase IIa of the study
Main inclusion/ exclusion criteria:	**Inclusion Criteria** • Understanding and provision of signed and dated written informed consent by the patient or legally acceptable representative prior to any study-specific procedures • Patients with histologically confirmed advanced GIST • Previous or current TKI treatment • A minimum of 50% of patients showing either 1st-, 2nd- or 3rd-line TKI-resistance documented either through RECIST 1.1 criteria, Choi-criteria or FDG-CT/PET and showing presence of at least one surgically untreatable primary or metastasis confirmed with either 18F-FDG PET/CT or structural imaging (CT, MRI) and a minimum of 25% non-resistant patients. • Karnofsky performance status > 70% • Age > 21 years. • Participating men must use a single barrier method for contraception for 1 month after completion of the trial starting at the day of application of ^{68}Ga-NeoBOMB1. • Women of childbearing age must use two highly effective methods of contraception

during the trial and 6 months after its completion if not in menopause (defined as onset of menopause without menstruation for over 1 year) or after hysterectomy.

The following contraceptive methods with a Pearl Index lower than 1% are regarded as highly-effective:

- Oral hormonal contraception ('pill') (as far as its efficacy is not expected to be impaired during the trial, e.g. with IMPs that cause vomiting and diarrhoea, adequate safety cannot be assumed)
- Dermal hormonal contraception
- Vaginal hormonal contraception (NuvaRing®)
- Contraceptive plaster
- Long-acting injectable contraceptives
- Implants that release progesterone (Implanon®)
- Tubal ligation (female sterilisation)
- Intrauterine devices that release hormones (hormone spiral)
- Double barrier methods
- This means that the following are not regarded as safe: condom plus spermicide, simple barrier methods (vaginal pessaries, condom, female condoms), copper spirals, the rhythm method, basal temperature method, and the withdrawal method (coitus interruptus).
- The regulations for contraception are derived from Guideline ICH E8 Chapter 3.2.2.1 Selection of subjects together with ICH M3 Note 4

- Confirmed GRPR expression (phase II only)

Exclusion Criteria

- Renal insufficiency with an eGFR < 45 ml/min/1.72m^2 or intolerance to any constituents of intravenous CT-contrast agents, preventing their administration (in cases without an available recent and sufficient contrast-enhanced CT examination)
- Higher than grade 2 hematotoxicity (CTC > 2)
- Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and without evidence of recurrence for 5 years
- Participation in any other investigational trial within 30 days of study entry with potential interactions regarding the study drugs or the underlying disease
- Pregnancy, breast-feeding
- Patients with concurrent illnesses that might preclude study completion or interfere with study results
- Patients with bladder outflow obstruction or unmanageable urinary incontinence
- Known or expected hypersensitivity to ^{68}Gallium, Bombesin or to any of the excipients of NeoBOMB1.

	• Any condition that precludes raised arms position for prolonged imaging purposes. • Prior administration of a radiopharmaceutical within a period corresponding to 8 half-lives of the radionuclide used on such radiopharmaceutical. • History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study. • Clinically significant illness or clinically relevant trauma within 2 weeks before the administration of the investigational product. • Subjects with any kind of dependency on the investigator or is employed by the sponsor or investigator • Subjects held in an institution by legal or official order
Statistical methodology and analysis:	Primary outcome variables will be analysed descriptively, as follows: (1) mean, standard deviation, median and range for continuous variables; (2) median, range and frequency distribution for discrete (ordinal) variables, (3) frequency distribution for nominal variables. No interim/subgroup analysis is required. The safety analyses will be conducted on the ITT set. Analyses of other variables will be performed on the ITT and PP set. Deviation of results by using the PP Set will be discussed. All data will be listed and summary tables will be provided. The analysis will be performed after database lock, after the end of the study. Statistical analyses will be done with SPSS package (version 19.0 or later) by an experienced biostatistician.