Protocol Synopsis

Study Title:

An open-label, single-centre, phase I, multi-dose escalating study to investigate the safety and preliminary efficacy of an intravenous (i.v.) infusion of the anti-GRP78 monoclonal IgM antibody PAT-SM6 in patients with relapsed or refractory multiple myeloma.

Protocol Number: PATCT-SM6-02

Principal Investigator and Study Centre:

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Study Duration:

For each subject the study duration will be at least 2 months. The whole study duration is planned to be approximately 1½ year.

Study Phase: I

Objectives:

Primary

- To evaluate the safety and tolerability of escalating doses of an intravenous (i.v.) infusion of PAT-SM6 in subjects with relapsed or refractory multiple myeloma.

Secondary

- To evaluate the efficacy and pharmacodynamics by analysis of serum and urine M protein, serum free light chains (FLC) κFLC and λFLC, total immunoglobulins, β2-microglobulin, C-reactive protein (CRP), exploratory biomarkers and anti-PAT-SM6 antibodies.
- To evaluate the duration of response and the progression free survival.

Study endpoints:

Primary Endpoints

- Overall frequency of AEs (clinical symptoms, laboratory abnormalities, serious adverse events [SAEs] and treatment limiting adverse events)

Secondary Endpoints

- Serum concentrations of PAT-SM6
- Pharmacodynamics and efficacy will be evaluated by analysis of serum and urine M protein, immunfixation, serum κFLC and λFLC, total immunoglobulins, β2-microglobulin, CRP, in vitro exploratory biomarkers, immune monitoring including anti PAT-SM6 antibodies to assess immunogenicity

Methodology:

Open-label, single-centre, dose escalation phase I study designed to investigate the safety and tolerability of intravenous (i.v.) infusions of PAT-SM6 administered over 90 minutes.

A screening examination will be performed within 14 days prior to dosing. Eligible subjects will receive 4 doses of PAT-SM6 (cycle 1: Day 1 and Day 3, cycle 2: Day 8 and Day 10). Subjects will be hospitalised for at least 48 hours after each dose administration (i.e. from Day 1 to Day 5 in cycle 1 and from Day 8 to Day 12 in cycle 2). During hospitalisation subjects will be under constant surveillance. Subjects will return for ambulatory visits on Days 15, 22, 29 and 36 for safety, pharmacokinetic (PK) and pharmacodynamic (PD) assessments.

Serological staging will be performed at baseline, on Day 29 (+/- 2 days) and Day 36 (+/-2 days).

Response will be assigned by the International Myeloma Working Group (IMWG) uniform response criteria for multiple myeloma. Complete response (CR) will be confirmed by bone marrow aspiration; CT scans or other radiograph are only intended when clinical symptoms are suspicious for progressing disease or otherwise clinically indicated.

If a subject shows an at least partial response (PR) on Day 29 or Day 36 (4 doses) the sponsor discusses with the Data Safety Monitoring Board (DSMB) to give an additional 2 doses (therefore the maximal number of doses for each subject is 6 doses) and a further staging will be performed 14 and 21 days after the last dose administration.

A completion visit will be performed 4 days after the last serological staging (e.g. after cycle 2 on Day 40).

Four dose groups (cohorts) are planned: 0.3 mg/kg followed by doses of 1 mg/kg, 3 mg/kg and 6 mg/kg. Subjects will be enrolled in a strict sequential order.

Individual safety results obtained until Day 5 will be evaluated by the investigator and the sponsor before the next subject of the same dose group will be treated. After completion of all 3 subjects of a dose group, safety results of all subjects obtained until Day 15 will be reviewed by the DSMB and a decision for dose escalation will be made. Interim doses can be administered if the increase is thought to be too high.

Subjects who show definite signs of progressive disease including hypercalcemia, new osteolytic lesions or new soft tissue plasmocytoma will be withdrawn from the study at any time.

In case dose limited toxicity (DLT) was seen in a subject, further dosing of subjects in the same dose group will be discussed with the DSMB, in case of a second DLT in the same dose group dose escalation will be stopped and the study will be continued at the next lower intermediate dose level or the previous tested dose will be regarded as the maximum tolerated dose (MTD). The MTD is defined as the dose level below the dose inducing a DLT in 2 subjects within one dose level.

Number of Subjects (Planned):

Three subjects are planned to be included in each of the 4 dose groups, i.e. for the 4 planned dose groups: 12 evaluable subjects.

- Dose group 1: Dose 0.3 mg/kg n=3
- Dose group 2: Dose 1 mg/kg n=3
- Dose group 3: Dose 3 mg/kg n=3
- Dose group 4: Dose 6 mg/kg n=3

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

Subjects will be eligible for the study if they meet all the following criteria:

1. Male or female subjects ≥ 18 years of age
2. Relapsed or refractory multiple myeloma defined as: Failure of at least 2 previous therapies including an immunomodulatory agent (thalidomide or lenalidomide) and a proteasome inhibitor (unless the subjects were not eligible or refused to receive those treatments), and with progressive disease, defined by an increase of serological or urine myeloma parameters by 25% to the last value
3. Presence of serum M-protein ≥ 1 g per 100 mL (≥ 10 g/L) and/or urine M-protein ≥ 200 mg per 24-hour period and/or serum FLCs ≥ 10 mg per 100 mL (≥ 100 mg/L) combined with an abnormal ratio of lambda and kappa chains
4. Life expectancy of > 6 months
5. Karnofsky performance status ≥ 60%, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
6. Absolute neutrophil count (ANC) ≥ 1.0 (1,000/mm^3) and platelets ≥ 30 × 10^9/L without previous transfusion within the last 2 weeks before first study drug administration
7. Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault equation)
8. Total bilirubin ≤ 2 × upper normal limit (UNL)
9. Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × UNL

10. Haemoglobin ≥ 8 g/dL
11. If a female of childbearing potential, confirmation of a negative pregnancy test before enrolment and use of double-barrier contraception, oral contraceptive plus barrier contraceptive, or confirmation of having undergone clinically documented total hysterectomy and/or oophorectomy, tubal ligation
12. If a male, use of an effective barrier method of contraception during the study and for 3 months after the last dose if sexually active with a female of childbearing potential
13. Ability to comply with all study-related procedures, medication use, and evaluations
14. Ability to understand and give written informed consent, and comply with the protocol

Exclusion criteria:

Subjects are not eligible for the study if they meet one of the following criteria:

1. Primary refractory multiple myeloma
2. Previous treatment with cytotoxic chemotherapy or large-field radiotherapy or other myeloma-specific therapy within 28 days prior to the screening visit (radiation to a single site as concurrent therapy is allowed)
3. Treatment with a systemic investigational agent within 28 days prior to the screening visit
4. Hypercalcemia (> 2.7 mmol/L)
5. Extramedullary plasmocytoma not originating from bone or plasma cell leukaemia
6. Previous allogenic stem cell transplantation
7. Known or suspected hypersensitivity to the excipients contained in the study drug formulation
8. Significant uncontrolled cardiovascular disease or cardiac insufficiency (New York Heart Association [NYHA] classes III-IV)
9. Prior therapy with other monoclonal antibodies
10. Clinical or laboratory evidence of active hepatitis B (positive HBsAg with negative HBsAb) or hepatitis C (positive HCV antibody and detectable HCV RNA with ALT above the normal range)
11. Positive HIV test result (ELISA or Western blot)
12. History of ischemic colitis, stroke or myocardial infarction within the last 6 months
13. Presence of diarrhoea of grade 2 or higher
14. Any active uncontrolled systemic infection
15. Any antibiotic therapy due to infections 2 weeks prior to first study drug administration
16. Regular dose of corticosteroids during the 2 weeks prior to study entry or anticipated need of corticosteroids exceeding prednisone 20 mg/day or equivalent, or any other immunosuppressive therapy within 2 weeks prior to study entry.
17. Major surgery ≤ 4 weeks prior to first study drug administration or ongoing side effects of such surgery
18. Systemic diseases (cardiovascular, renal, hepatic, etc) that would prevent study treatment
19. Multiple myeloma with central nervous system involvement.
20. Second active malignant disease, currently requiring treatment (with the exception of basal cell carcinoma of the skin or curative surgery treated tumours).
21. Pregnancy or breastfeeding in women and women of childbearing potential not using an acceptable method of birth control
22. History of non-compliance to medical regimens or subjects who are considered potentially unreliable and/or not cooperative
23. Any concurrent disease or medical condition that is uncontrolled or is deemed to interfere with the conduct of the study as judged by the investigator.
24. Any clinical condition equal to the protocol definition of DLT.
25. Any condition which in the judgement of the investigator would place the subject at undue risk.
26. Employee of the investigator or trial site, as well as family members of the employees or the investigator.

Test Product, Dose and Mode of Administration:
PAT-SM6 (anti-GRP78 monoclonal IgM antibody)

PAT-SM6 will be administered i.v. undiluted via a volumetrically controlled infusion pump over 90 minutes. Subjects will remain under supervision until at least 48 hours after start of dosing.

The planned doses are: 0.3 mg/kg, then 1.0 mg/kg, 3 mg/kg and a maximum dose of 6 mg/kg.

Within 1 hour prior to dosing subjects will receive a pre-medication of antihistaminic drugs like 2 mg Clemastin i.v. and 50 mg Ranitic i.v.

In case of high tumour load the subjects should receive oral hydration of approximately 2 L/day and an i.v. hydration of approximately 2-4 L/day within the first day. The schedule of hydration should be determined by monitoring of the clinical condition (e.g. vital parameters), renal function (e.g. creatinine, urea, uric acid) and LDH. The subject should be weighed daily and diuretic drugs should be administered accordingly.

Duration of Treatment:
Each subject will receive at least 4 doses of PAT-SM6 with the option to give 2 more doses in case of response.

Reference Therapy, Dose and Mode of Administration:
Not applicable

Criteria for Evaluation:

Safety:

Safety parameters will be evaluated at screening and at regular intervals during the treatment and follow-up period and at the final follow-up visit.

Measurements include: Adverse events, local tolerability, physical examination, electrocardiogram (ECG), vital signs and safety laboratory parameters (haematology [including coagulation], clinical chemistry, urinalysis, cytokines and immunoglobulin), ECOG performance status, anti-PAT-SM6 antibody determination

Efficacy and pharmacodynamics:

Overall response rate (complete response [CR] + partial response [PR]+ minimal response [MR]), further tumour response rates (CR, PR,MR, very good partial response [VGPR]), and stable disease (SD) rate according to IMWG uniform criteria.

Duration of response, time to progression (TTP), and PFS

Absolute and percentage change from baseline in serum and urine M-protein levels

Absolute and percentage change from baseline in serum FLC levels and serum FLC ratio

Pharmacokinetics:

PAT SM6 concentration will be measured pre-dose and 0.5 hour after start of infusion, at the end of the infusion (1.5 hours) and 3, 6 and 24 hours after start of infusion on Days 1 and 10 and pre-dose on Days 3 and 8.

Pharmacokinetics parameters: C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf}, λ_z, t½, CL, V_z

Statistical Methods:

This study is not aimed to proof any hypothesis. All parameters will be evaluated by descriptive methods and no confirmatory testing will be done.