SYNOPSIS

Name of Sponsor/Company: Repos PharmaAB **Name of investigational product:** Repos Mebendazole (Repos MBZ) **Name of active ingredient:** mebendazole		(For regulatory authority use only)
Title of study A phase 2a TDM*-guided clinical study on the safety and efficacy of mebendazole in patients with advanced gastrointestinal cancer or cancer of unknown origin *TDM, therapeutic drug monitoring, i.e. individualized dosing based on measurement of drug serum concentrations		
Principal Investigator Peter Nygren, Dept. of Oncology, University Hospital, Uppsala, Sweden		
Study centre Clinical Research and Development Unit (KFUE), Department of Oncology, Uppsala University Hospital , Uppsala, Sweden		
Study period *First patient in (signed ICF):* 25 May 2018 *First dose:* 28 May 2018 *Last dose:* 22 October 2018 *Last patient out:* 14 November 2018 *Decision of permanent stop*: 16 January 2019		**Phase of development** Phase 2a

Objectives

Primary:

- Safety profile of Repos MBZ.
- Anti-tumour efficacy: tumour response rate and prolongation of time to tumour progression (TTP) according to RECIST 1.1.

Secondary:

- The single dose pharmacokinetic (PK) profile of Repos MBZ.
- The steady state PK profile of Repos MBZ.
- Repos MBZ induced changes in blood cytokines and immune cells.
- Overall survival.
- Change in tumour load and TTP according to irRECIST

Explorative objectives

- Association between Repos MBZ efficacy and properties of the diagnostic tumour tissue, e.g. genetic changes and infiltration of immune cells (optional)
- Changes, compared with the diagnostic tissue, in fresh tumour biopsy properties, after 4 weeks of treatment at the target S-mebendazole concentration (optional)
- Association between S-mebendazole and efficacy and safety.

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Explorative objectives cont.

- Association between Repos MBZ efficacy and properties of the diagnostic tumour tissue, e.g. genetic changes and infiltration of immune cells (optional)
- Changes, compared with the diagnostic tissue, in fresh tumour biopsy properties, after 4 weeks of treatment at the target S-mebendazole concentration (optional)
- Association between S-mebendazole and efficacy and safety.

Methodology
A prospective, single armed, open label, single centre, phase 2a study.

Number of patients (planned) and patient disposition
30 patients evaluable for tumour response, i.e. being on treatment with Repos MBZ on at least 6 out of the first 8 weeks of the study protocol, reached a S-mebendazole concentration of ≥ 250 ng/mL, and performed the tumour response assessment at week 8. It was expected that a total of 50 patients needed to be included in the study to reach the target number of patients as above.

No of enrolled patients:	11
No. of treated patients (continuous treatment):	10
No. of patients completing treatment:	0
Efficacy population:	7
Safety population:	11

Diagnosis
Patients with measurable tumours of advanced gastrointestinal cancer or cancer of unknown origin, in good performance status and with preserved major organ function, not amenable to standard anticancer therapy but in which a pharmacological cancer treatment attempt is considered reasonable.

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Inclusion criteria

1. At least 18 years of age
2. Histologically confirmed diagnosis of squamous cell cancer or adenocarcinoma, including primary cancer of the liver, of the gastrointestinal tract or cancer of unknown origin.
3. Measurable disease according to RECIST 1.1.
4. Defined time to tumour progression on the standard/experimental treatment preceding the trial treatment.
5. Locally advanced or metastatic disease not amenable to standard treatment, i.e. progress on standard therapy or observed/expected intolerance to standard therapy.
6. Primary or metastatic involvement of the liver.
7. Inclusion criterion no.6 was removed from protocol version 1.2 during the course of the study, for details refer to Section 9.7.1.
8. Pharmacological treatment attempt considered reasonable.
9. Females of childbearing potential should use adequate contraception throughout the study:
10. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
11. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
12. Intrauterine device (IUD)
13. Intrauterine hormone-releasing system (IUS)
14. Bilateral tubal occlusion
15. Vasectomized partner
16. Sexual abstinence
17. Signed informed consent.

Exclusion criteria

1. Anti-tumour therapy within 3 weeks prior to study drug administration day 1.
2. Ongoing infection or other major recent or ongoing disease that, according to the Investigator's assessment, poses an unacceptable risk to the patient.
3. WHO performance status ≥ 2.
4. Child-Pugh B or C liver function status if hepatocellular carcinoma.
5. Inadequate laboratory parameters reflecting major organ function i.e.:
6. neutrophils ≤ 1.3 x 10^9/l
7. platelets ≤ 100 x 10^9/l
8. bilirubin > 1.5 x ULN
9. ALAT > 5 x ULN
10. GFR <50 mL/min (calculated from P-creatinine)
11. prothrombin complex/INR outside normal range
12. Current active participation in any other interventional clinical study.
13. Contraindications to the investigational product, e.g. known or suspected hypersensitivity or inability to oral drug administration.
14. Pregnancy or lactation.
15. Lack of suitability for participation in the study, e.g. expected difficulties to follow the protocol procedures, as judged by the Investigator.

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Investigational product, dosage and mode of administration
Repos MBZ, capsule 50, 100 and 200 mg p.o.

Active control, dosage and mode of administration

No active control was used.

Duration of treatment (planned)

16 weeks

Summary of study procedures:

Single dose pharmacokinetic (PK) phase week -1: Following baseline assessments, i.e. tumour imaging by CT/MRI of abdomen and chest within 3 weeks of 1st dose, blood chemistry/haematology and baseline samples for translational research within 1 week of 1st dose, the patient took 1 capsule Repos MBZ 100 mg, preferably within 1 h after breakfast, together with 40 mL Calogen Extra Shot (Nutricia) fat containing nutritional soft-drink, at approximately 8 AM Monday. At pre-dose, 0.5h, 1h, 2h, 3h, 4h, 6h and 8h after dose, blood samples were taken for analysis of S-mebendazole. If C_{max} after intake of 100 mg Repos MBZ exceeded a concentration of 400 ng/mL, the patient went off study since a too high drug exposure would be expected even from the lowest dose of Repos MBZ available.

Treatment phase: Started on Friday morning week -1 (study day 5) with a Repos MBZ dose aimed to reach a S-mebendazole C_{max} close to 300 ng/mL (1 μM; accepted range 250 – 350 ng/mL). The starting dose of Repos MBZ was dependent on the C_{max} observed during the PK study phase.

Drug intake was supposed to be as close as possible to 8 AM and 8 PM continuously. The drug was advised to be taken with or within 1 h after intake of food and together with 40 mL Calogen Extra Shot (Nutricia) nutritional drink to provide fat for optimal drug uptake.

S-mebendazole was measured again Monday week 1 (study day 8). Sampling for serum mebendazole concentration during the therapeutic study phase was adjusted and reduced based on the T_{max} observed in the pharmacokinetic study phase and the experience that T_{max} is shorter during repeated compared with single mebendazole dosing. The time-points for plasma concentration sampling for assessment of C_{max} for dose adjustment were subsequently individualized based on the repeat-dose observations. Based on the PK result the dose was adjusted with start the following Friday at approximately 8 AM. This procedure was repeated weekly until the target S-mebendazole concentration had been reached. The S-mebendazole level was then to be checked on Monday treatment week 4, 8, 12 and 16 as applicable, and if necessary adjusted as described above. The daily dose of Repos MBZ was not allowed to exceed 4 g.

Blood sampling for cytokines and immune cells was done at baseline and then weekly until the target S-mebendazole concentration has been reached, and then at week 4, 8, 12 and 16.

Blood samples for the safety assessments were collected weekly during treatment.

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All patients were asked (optional) for access to archived paraffin embedded tissue from their primary tumour or metastasis for analysis of mutational status, gene- and protein expression and/or tumour infiltrating cells, as applicable.

Furthermore, for translational research and mechanistic characterization, patients with liver metastasis suitably located for safe biopsing were asked (optional) to provide a fresh tumour biopsy at baseline and after 4 weeks of treatment on the target S-mebendazole concentrations (250 – 350 ng/mL).

Duration of the treatment phase:

Each patient was planned to receive 16 weeks of continuous Repos MBZ treatment twice daily. Tumour status was assessed after 8 and 16 weeks on treatment unless there is unequivocal signs of tumour progression with clinical deterioration before the latter time-point.

Treatment was temporarily stopped for up to 3 weeks for adverse events to recover (max 2 temporary stops were allowed). Treatment was permanently stopped upon unacceptable adverse event, unequivocal clinical deterioration, unequivocal tumour progression according to irRECIST criteria or patient withdrawal of consent. All changes in tumour volume at 1st tumour CT/MRI assessment 8 weeks from start of Repos MBZ (1st dose in treatment phase) were to be confirmed at the assessment 16 weeks from start of therapy if signs of progressive disease at 8 weeks were equivocal according to irRECIST. Thus, a patient with equivocal progressive disease according to irRECIST at 1st tumour evaluation would continue therapy to the 2nd evaluation unless there were signs of deterioration due to progressive disease as judged by the physician in charge of the patient. Patients who were withdrawn from treatment, but still retained their consents, were scheduled for a so-called Pre-termination visit as soon as possible (i.e. a Final follow-up visit for patients prematurely withdrawn from study drug) and a tumour evaluation at the discretion of the Investigator.

After completing 16 weeks of study treatment the patient went off protocol but had the option to get access to continued treatment with Repos MBZ, at the same dose as that at the end of week 16, if this was considered to benefit the patient according to the physician in charge of the patient. If objective tumour progression had not been observed in these patients during treatment within the protocol, CT/MRI scans for evaluation of tumour status were planned to be done every 8th week until progressive disease was confirmed. All patients were followed for survival until end of study.

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Criteria for evaluation:

All patients that had received at least 1 dose of Repos MBZ, were included in the PK and safety analyses, respectively.

Patients that had received at least 6 out of the first 8 weeks of study medication with C_{max} ≥250 ng/mL at any time and had tumour CT/MRI assessment 8 weeks from start of Repos MBZ treatment were included in the tumour response and TTP analyses according to the RECIST 1.1 criteria.

Primary endpoints:

Safety

- Number of AEs probably or possibly related to the study drug, graded according to CTCAE 4.03
- Changes in lab parameters and vital sign over time vs baseline

Efficacy

- Best overall radiological response according to RECIST 1.1.
- Time to tumour progression on Repos MBZ compared with time to progression on the treatment just preceding participation in this protocol.

Secondary endpoints:

- C_{max}, T_{max} and $T_{1/2}$ after single dose Repos MBZ.
- Number of patients that reach the steady state S-mebendazole target concentration of 300ng/mL (accepted range 250 – 350 ng/mL), time to reach this concentration and S-mebendazoleconcentration variation over time.
- Immunological changes induced by mebendazole from baseline, as reflected in cytokines and immune cells in blood
- Overall survival from start of treatment phase to death from any cause.
- Best overall radiological response according to irRECIST 1.1.

Explorative endpoints:

- Association between mebendazole efficacy (response rate and TTP) and tumour properties from archival tumour tissue including grade, molecular subtype (Ras/Braf mutation and MSI status as applicable), gene- and protein expression and tumour infiltration and subtypes of macrophages and lymphocytes.
- Change in the properties analyzed in archival tumour tissue at baseline to 4 weeks of treatment at the target S-mebendazole concentration in fresh tumour biopsies (optional).
- Mean S-mebendazole concentration during treatment phase in relation to

  safety and efficacy in terms of CTCAE 4.03 grade 3 and 4 toxicity, tumour response and TTP, respectively.

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Statistical methods

In this Phase 2a study no formal hypothesis testing was performed and all endpoints were evaluated by descriptive methods. Qualitative variables are summarized in frequency tables by dose. The quantitative variables are summarized by number of observations, means, standard deviations, medians, minimum and maximum values by dose. Where relevant the results are presented by day and treatment period. All variables are also presented in per-patient data listings.

Determination of sample size:

The patients included in the study were in most cases heavily pre-treated difficult to treat cancer types. An objective radiological response rate of $\geq$ 10%, i.e. at least 3 responses among the 30 patients evaluable for tumour response, would have been regarded as promising for Repos MBZ as an anticancer drug.

In the same way, if ≥30% of the patients evaluable for TTP, had a TTP that was ≥ 1.3 times longer on treatment with Repos MBZ than on the treatment just preceding this study, this would have been regarded as promising for Repos MBZ as an anticancer drug.

Patient demography

Five (5) females and 6 males were enrolled in the study. The mean age of the patients was 55.8 years ranging from 22 to 73 years. The mean weight was 71.7 kg (range 47-99 kg) and the mean BMI was 23.8 kg/m^2 (range 17-33 kg/m^2).

Four (4) patients were diagnosed with rectal adenocarcinoma, 3 patients with adenocarcinoma of the colon, 1 patient with anal squamous cell carcinoma, 1 patient with hepatocellular carcinoma, 1 patient with pancreatic carcinoma and 1 patient with oesophageal squamous cell carcinoma, The liver function of the single patient with hepatocellular carcinoma, was assessed by the Child-Pugh scale and the patient had well compensated liver function at Screening (score A).

Seven (7) of 11 patients had had oncological surgery performed in the past, most often with a curative intention (e.g. hepatectomy, colectomy, prostatectomy, proctectomy, cholecystectomy, colostomy, kidney ablation, pulmonary resection and hip arthroplasty due to metastasis.

All patients had received prior chemotherapy, (e.g. irinotecan, oxaliplatin, capecitabine, folinic acid and fluorouracil) before enrollment in the study, in most cases with palliative intention. The patients had received between 2 and 9 different lines of prior chemotherapy treatments.

At screening, 4 patients had ECOG status ‘fully active’ (grade 0) and 7 patients had status ‘restricted in physically strenuous activity’ (grade 1). At the Pre-termination visit, no patient had status ‘fully active’ (grade 0) and only 1 patient was ‘restricted in physically strenuous activity’ (grade 1). Six (6) patients had ECOG status ‘capable of all self-care but unable to carry out any work’ (grade 2) whereas 2 patients were ‘capable of limited self-care and confined to bed or chair more than 50% of waking hours’ (grade 3). One patient died before the Pre-termination visit was performed (grade 5). In conclusion, there was a gradual decline in the patients’ daily living abilities during the study and all patients deteriorated between Screening and the Pre-termination visit.

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Efficacy results

Eleven (11) patients were enrolled in the study, but only 10 started continuous treatment and were included in this efficacy conlusion.

- Seven (7) of 10 patients were evaluated for tumour response at week 8 using the RECIST 1.1 criteria. All 7 patients had progressive disease (PD), accompanied by an increase in the CEA tumour marker for 5 patients.
- None of the 10 patients completed the 16 week continuous Repos MBZ treatment. Nine (9) patients were prematurely withdrawn from the study due to progressive disease and 1 patient was prematurely withdrawn due to a non related AE (death due to pneumonia/heart failure).
- Nine (9) of 10 patients in the treatment phase were deceased at database closure and the survival time from first dose of Repos MBZ to death ranged between 36 and 207 days. One patient was still alive at database closure (patient 107) and had survived for 231 days after the first test dose of Repos MBZ was administered.
- Biomarkers involved in tumour progression and inflammatory response showed no obvious pattern that could be related to drug exposure or treatment outcome. Notably, the patient still alive at database closure (patient 107) showed changes in cytokines compatible with expected pharmacodynamic effects of mebendazole.

Safety results

- Repos MBZ was safe and well tolerated following continuous treatment at doses up to 4000 mg per day.
- Nine (9) SAEs, of which 3 were fatal, were reported by 5 patients. No SAEs were related to study treatment. No dose limiting toxicities were observed.
- All 11 patients reported AEs and the majority were of moderate intensity (27 of 63 AEs; 42.9%).
- The vast majority of all AEs (59 of 63 AEs; 93.7%) were unlikely related to study treatment.
- The most commonly reported AEs were *abdominal pain* (4 patients; 4 events), *decreased appetite* (4 patients; 4 events), *nausea* (3 patients; 3 events) and *vomiting* (3 patients, 3 events).
- Two patients discontinued study treatment due to AEs (*hemiparesis* and *cerebrovascular event*), both events assessed as unlikely related to study treatment.
- There were no significant changes over time in vital signs, physical examinations, ECG that were related to study treatment.
- There were no significant changes in any lab values over time (haematology/biochemistry) that could be related to study treatment.
- With respect to the administered dose of Repos MBZ, there were no clear differences in the safety profile between patients who received the maximum allowed dose (4000 mg per day) and patients who received a lower dose of Repos MBZ.
- Overall, no major safety issues were raised for Repos MBZ.

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Overall conclusions

In conclusion, the safety results indicated that continuous treatment with Repos MBZ is safe and tolerable at doses up to 4000 mg per day in patients with heavily pre-treate GI cancer. There were no life-threatening or fatal SAEs with a causal relationship to treatment with Repos MBZ. Furthermore, there were no significant changes over time in vital signs, physical examinations, ECG or laboratory assessments related to Repos MBZ. Thus, the decision to prematurely stop the study was based on the lack of anti-tumoural effect whereas safety was not an issue.

Mebendazole remains an interesting drug candidate and it might be worthwhile to evaluate its potential anti-tumoural properties in patients with less advanced disease or in other cancer diagnoses, perhaps in another dosage form with better bioavailability or in combination with other cancer drugs.

Date of report:

16 October 2019