Clinical Trials Summary for out of hours Important Reference

Lancashire Teaching Hospitals NHS Foundation Trust

Acronym study title	**MK_5684_004 OMAHA STUDY_** A Phase 3, Randomized, Open-label Study of MK-5684 Versus Alternative Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) That Progressed On or After Prior Treatment with One Nextgeneration Hormonal Agent (NHA)
Study Details	MK-5684 (previously ODM-208) is a first-in-class, oral, non-steroidal, selective inhibitor of CYP11A1, the first and rate-limiting enzyme of steroid biosynthesis. MK-5684 suppresses the production of all steroid hormones and precursors that may activate the androgen receptor (AR) signaling pathway. This Phase 3 study builds on the accumulating data from Phase 1/2 3124001 CYPIDES on the management of AI and serves as preliminary evidence of the clinical benefit, safety and tolerability of MK-5684 in the treatment of the AR LBD mutation-positive and -negative participant population.
Principal Investigator PI **Sub PI's**	Dr Omi Parikh Dr Natalie Charnley (Sub-I)
Research Nurse Team	Catherine Walmsley (Oncology RN)
Drug therapy	MK-5684 + HRT MK-5684 will be administered at a dose of 5 mg (two 2.5 mg tablets) orally BID for a total daily dose of 10 mg. MK-5684 should be taken BID at the same time each day. Tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. MK-5684 should be taken with food. Dexamethasone and fludrocortisone must be taken with MK-5684. Dexamethasone will be administered at a starting dose of 1.5 mg (three 0.5 mg tablets) orally QD in the morning with food. Fludrocortisone will be administered at a starting dose of 0.1 mg (one 0.1 mg) orally QD in the morning with food. Fludrocortisone may be adjusted in 0.05 mg increments by splitting the 0.1 mg tablet. Dexamethasone and fludrocortisone dosage may be adjusted during the study for each participant per guidance in Section 6.6.2. If more than one dose is skipped, inform participants to contact their clinic site as soon as possible. If the participant forgets to take MK-5684, the dose should be taken as soon as possible up to 4 hours after the planned dosing time. After this, the missed dose should not be taken but instead the next scheduled dose should be taken at the planned time. If doses are missed, this must be indicated in the source documents and CRFs. If MK-5684 needs to be interrupted for any reason, administration of the treatment with glucocorticoid (dexamethasone) and mineralocorticoid (fludrocortisone) must be continued. Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to:

	Arm 1: MK-5684 + HRT Arm 2: Alternative NHA (abiraterone + prednisone, or enzalutamide) The alternative NHA must be confirmed, and the rationale documented by the investigator before randomization of each participant. Below is an overview of the treatment arms: • 28-day cycles of treatment • MK-5684 or Abiraterone or Enzalutamide are dispensed (and container returned) on day 1 (+/- 3 days) of each 28-day cycle ▪ MK5684 is taken twice daily at home. On Clinic Day, morning dose should be taken after blood collection ➢ MK5684 is taken with Dexamethasone and Fludrocortisone. Both Dexamethasone and Fludrocortisone are taken once daily ▪ Abiraterone is taken once daily at home ➢ Abiraterone is always taken with Prednisone/prednisolone. Prednisone/prednisolone is taken twice daily ▪ Enzalutamide is taken once daily at home. This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.
Side Effects of this drug:	**An emergency kit is also provided to each participant for emergency use in case of suspected adrenal crisis.**

6.6.1 Dose Modification and Toxicity Management Related to MK-5684

MK-5684 dose interruption for participants who experience therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 6. An interruption of MK-5684 for more than 14 days regardless of etiology will require Sponsor approval before treatment can be resumed.

Table 6 Dose Modification and Toxicity Management Guidelines for Adverse Events Associated With MK-5684

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/ Schedule for Restarting Treatment	Criteria for Discontinuation After Consultation With Sponsor
Hematological Toxicities:				
• Any Grade ≥3 hematological toxicity that persists for ≥7 days	Yes	Treatment may be restarted when AE resolves back to baseline or to ≤ Grade 1 within 14 days	Same dose level*	Permanent discontinuation should be considered for recurrent Grade ≥3 hematological toxicity that persists for ≥7 days, or for any severe or life-threatening event
Nonhematological Toxicities:				
• Persistent Grade ≥3 nausea, vomiting or diarrhea despite optimal medical intervention (not used as a prophylactic regimen)	Yes	Treatment may be restarted when AE resolves back to baseline or to ≤ Grade 1 within 14 days	Same dose level*	Permanent discontinuation should be considered for recurrent persistent Grade ≥3 nausea, vomiting or diarrhea, or for any severe or life-threatening event
• Any Grade 3 or 4 nonhematological toxicity of any duration (not including laboratory, unless clinically significant medical intervention is required to treat the participant, or the abnormality leads to hospitalization, or the abnormality persists for >1 week)	Yes	Treatment may be restarted when AE resolves back to baseline or to ≤ Grade 1 within 14 days	Same dose level*	Permanent discontinuation should be considered for recurrent Grade 3 or 4 nonhematological toxicity, or for any severe or life-threatening event

AE=adverse event.
*Restarting treatment of MK-5684 at the same dose level may be pursued if considered beneficial to the participant. This requires consultation between the investigator and the Sponsor and written documentation (via SCF) of the collaborative decision on participant management.

If toxicity does not resolve to baseline or to ≤ Grade 1 within 14 days after last dose of intervention, MK-5684 should be discontinued after consultation with the Sponsor.

Participants who have interrupted MK-5684 treatment due to toxicity not meeting the discontinuation criteria listed above and recovered from treatment-related toxicity may resume MK-5684 treatment at the same dose level after careful assessment of the nature and course of the toxicity, and extent of resolution by the investigator, and with mutual agreement of the investigator and the Sponsor.

Any toxicity that meets the above-mentioned dose interruption criteria but is assessed by the investigator to be related to sub-optimal level of replacement treatment therapy, and that recovers within 7 days after adjusting the dose of replacement treatment therapy will not lead to treatment interruption of MK-5684, after careful assessment of the case.

In the event that a patient calls this hotline for advice:	Normal working hours: **For <u>clinical queries</u> please contact: Dr Omi Parikh** **Email: omi.parikh@lthtr.nhs.uk** **Tel: Tel: 01772 52 4574 / 3191 (Sec)** **Research Nurse: Catherine Walmsley** **Tel/email** Tel:01772 52 8475 In case of serious illness, trauma, vomiting or diarrhoea, Hydrocortisone sodium succinate, 100mg iv/im and iv saline infusion must be administered **without delay to avoid life threatening adrenal crisis.** Emergencies will be treated according to the decision of the physician in charge or the investigator, when available. At the event of an acute adrenal crisis or if patient deteriorates while using increased doses of glucocorticoid therapy, the patient must be admitted to a hospital and parenteral corticosteroid treatment and rehydration should be started. The initial work-up should consist of imaging and blood tests including common tests for infections, blood glucose, complete blood cell count, Creactive protein (CRP), creatinine, creatine kinase (CK), sodium, potassium, cortisol, ACTH, TSH, free T4, phosphate, and calcium and, other tests considered necessary. This diagnostic work-up should not overly delay the start of the treatment for acute adrenal insufficiency. Acute adrenal crisis is managed according to the institutional hospital emergency room. The guidelines recommend that the management starts with a rapid 1000 ml intravenous (i.v.) isotonic saline rehydration and a bolus of hydrocortisone 100 mg i.v. This is followed by hydrocortisone given either 200 mg as a 24h i.v. infusion or alternatively, 50 mg q.i.d. Further intravenous rehydration should be administered as required and usually the patients need 4-6 litres of rehydration during the initial 24h. Tapering of the i.v. hydrocortisone dosing may start the following day by reducing the dose of hydrocortisone to 50 mg b.i.d. When hydrocortisone is given at the dose of 50 mg/day or greater, fludrocortisone administration may be on hold. ODM-208 should be on hold until the patient's condition has been stabilised and the i.v. hydrocortisone dose is less than 50 mg/day