Clinical Trials Summary for out of hours Important Reference

Lancashire Teaching Hospitals NHS Foundation Trust

Acronym study title	CYPIDES_ Safety and pharmacokinetics of ODM-208 in patients with metastatic castration-resistant prostate cancer
Study Details	**Phase 2** of the study consists of a pre-screening period for centralized analysis of the AR LBD mutations in plasma circulating tumour DNA (ctDNA), and a screening period of maximum 21 days. The treatment period will continue until disease progression (after disease progression the treatment may be continued if the patient is considered to clinically benefit from the treatment as judged by the investigator), or until death, intolerable toxicity or any other discontinuation criterion is met. The study contains a post-treatment period (28 days), and if needed, adrenal recovery will be followed after the end-of-study visit (for a maximum of 24 weeks). The trial medication has a risk of causing adrenal insufficiency. Dexamethasone 1 mg and fludrocortisone 100 µg as single oral doses every morning will be used as replacement therapy. The replacement therapy will be closely monitored during the study and the doses can be adjusted, if clinically indicated as judged by the investigator.
Principal Investigator PI Sub PI's	Dr Omi Parikh
Research Nurse Team	Catherine Walmsley (Oncology RN) Karen Jones CRF
Drug therapy	ODM-208 is a novel nonsteroidal selective inhibitor of CYP11A1 (cytochrome P450 cholesterol side-chain cleavage enzyme, P450scc), blocking enzymatic activity of the first step of the steroidogenic pathway in which cholesterol is converted to pregnenolone. This inhibition leads to deficiency to produce androgens, lucocorticoids and mineralocorticoids.
Side Effects of this drug:	The most common treatment-related AEs were adrenal insufficiency in 13 patients (34.2%), fatigue in 8 patients (21.1%), hyponatremia in 6 patients (15.8%), amylase increased in 5 patients (13.2%), asthenia in 4 patients (10.5%), oedema peripheral in 4 patients, hyperkalaemia in 4 patients, muscle spasms in 3 patients (7.9%), decreased appetite in 3 patients, headache in 3 patients, hypertension in 3 patients and alanine aminotransferase increased and aspartate aminotransferase increased in 3 patients each. 20 patients (52.6%) experienced serious adverse events (SAEs). The most common SAE was adrenal insufficiency in 11 patients (28.9%). Glucocorticoid deficiency, which presumably reflects the same condition, occurred in one patient, and together with adrenal insufficiencies, these serious events occurred in a total of 12 patients (31.6%). The majority of the subjects experiencing adrenal insufficiency SAE were treated with high-

	dose i.v. hydrocortisone (1-2 days) and with temporary interruption of ODM-208 leading to a rapid improvement in the symptoms. The SAEs occurred typically 17 days after starting the study treatment (range 3 days – 56 days). The signs and symptoms of adrenal insufficiency included asthenia/fatigue, nausea, vomiting, abdominal pain, muscle cramps/pain, lowered serum sodium, elevated serum potassium, fever and elevated serum CRP.
Drug Therapy:	Dose of ODM 208 (trial medication) is 5mg twice daily with food. Dexamethasone 1mg and fludrocortisone 100 µg as single oral doses every morning. Doses can be adjusted if clinically indicated.
In the event that a patient calls this hotline for advice:	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

Omi Parikh (updated with discussion with Dr Yiannakis) 16/12/2021