SUPPLEMENTARY APPENDIX

Targeted Inhibition of CYP11A1 in Castration-Resistant Prostate Cancer

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SUPPLEMENTARY METHODS

1. Glucocorticoid and Mineralocorticoid Replacement

Glucocorticoid and mineralocorticoid replacement therapy was required in this study. Dexamethasone was initially selected as glucocorticoid replacement therapy in phase 1 at a starting dose of 1 mg/day (equivalent to prednisone and hydrocortisone doses of ~7 mg and ~27 mg, respectively). Further assessment of the type and the dose of corticosteroid replacement therapy was conducted during the first 4 weeks of ODM-208 treatment to determine whether they better prevented adrenal insufficiency -like events (Table S2). The safety profile of the tested glucocorticoid replacement therapies with ODM-208 appeared to be similar. Mineralocorticoid substitution comprised a single oral morning dose of fludrocortisone, starting at 0.05 mg, with adjustment as clinically indicated. Experience from patients in phase 1 informed the glucocorticoid replacement agents and the recommended starting doses used for patients in phase 2: oral, once-daily dexamethasone 1 mg and fludrocortisone 0.1 mg. Replacement therapy continued and was gradually withdrawn after the end of treatment, as clinically required to avoid secondary adrenal insufficiency (Figure S1). For patients still on replacement therapy at the end of study (EOS), adrenal recovery was followed at patient visits that took place at week 4 and (if needed) week 8 after EOS to check general health (e.g., physical examination, blood pressure, pulse rate), and serum levels of cortisol, aldosterone, electrolytes, renin, pregnenolone, and dehydroepiandrosterone sulfate. If replacement therapy was still required beyond these two post-EOS visits, patients were followed up by phone call at weeks 16 and 24 after EOS to check their status and record the

doses and types of glucocorticoid/mineralocorticoid being taken. ODM-208–related adverse events were recorded throughout the adrenal recovery period.

2. Diagnosis and Management of Adrenal Insufficiency-Like Syndrome

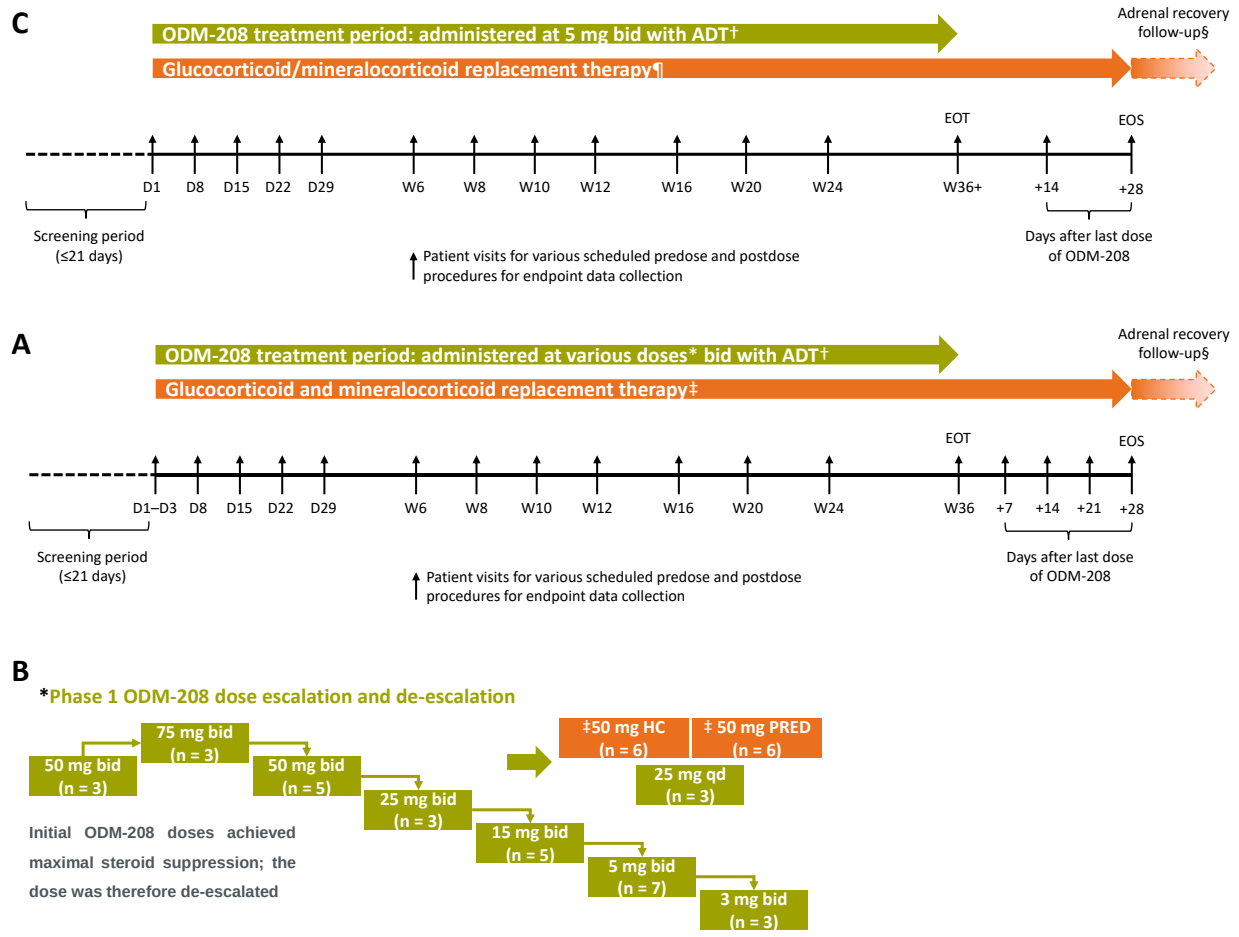
Monitoring of replacement glucocorticoid and mineralocorticoid dose was based mainly on clinical assessments of a patient's symptoms and their clinical status including weight, blood pressure, and electrolytes. Adrenal insufficiency-like events were determined based on clinical signs and symptoms observed during these events of asthenia/fatigue, nausea, vomiting, abdominal pain, lowered serum sodium, elevated serum potassium, fever, elevated serum C-reactive protein, anorexia, weight loss, and orthostatic hypotension. Additional replacement (double or triple the dose of glucocorticoid and/or increased fludrocortisone dose and/or increased consumption of electrolyte-containing fluids) was considered whenever the patient reported persistent, new, or worsened symptoms or signs; in the event of unexplained electrolyte disturbance; or if they had concurrent illness or injury. An emergency kit was also provided to each patient for use in case of suspected adrenal crisis. In the event of an adrenal crisis or deterioration, the patient was admitted to hospital and provided with parenteral corticosteroid and rehydration according to published consensus guidelines.[1] In addition to study visits, patients were contacted via telephone on days 5, 12, 19, 26 (phase 1 and 2), 36, and 50 (phase 2 only) to determine the patient's general status and adverse events.

SUPPLEMENTARY FIGURES

Figure S1. CYPIDES Study Design.

Panel A shows phase 1. Panel B shows the dose-escalation and de-escalation schedule for phase 1.

Panel C shows phase 2.

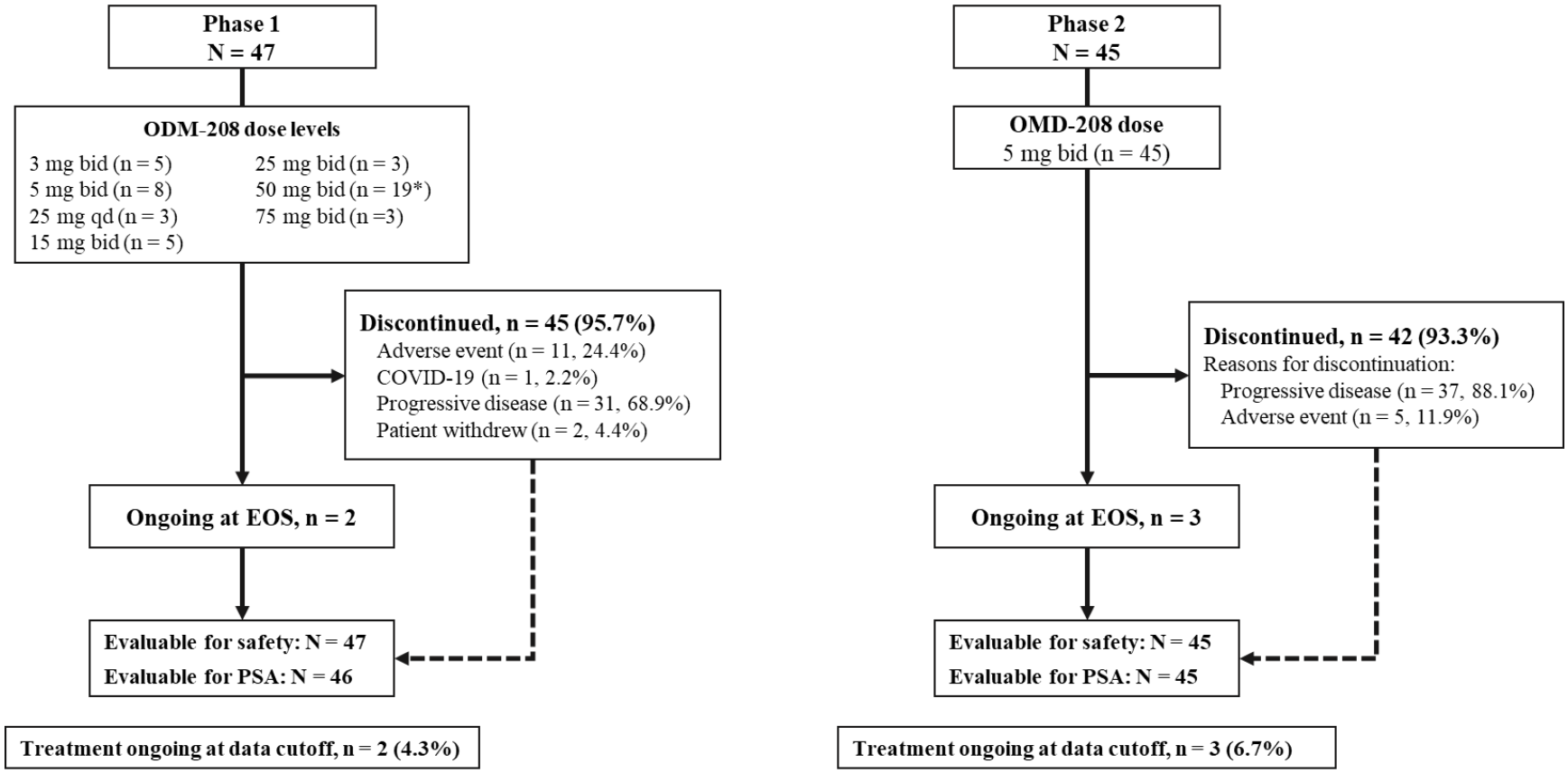


* Doses tested (administered via a 3+3 study design) were: 3, 5, 15, 25, 50, and 75 mg bid, and 25 mg QD.
† All patients continued ADT with a gonadotropin-releasing hormone analog (agonist or antagonist) or had undergone bilateral orchiectomy prior to the start of this study.
‡ Glucocorticoid replacement comprised dexamethasone, hydrocortisone, or prednisone; fludrocortisone was used for mineralocorticoid substitution.
§ Glucocorticoid and mineralocorticoid replacement therapy continued after the end of the study and was gradually withdrawn as clinically required to avoid secondary adrenal insufficiency.
¶ Dexamethasone 1.0 mg and fludrocortisone 0.1 mg administered once daily in the morning.

ADT denotes androgen-deprivation therapy, bid twice daily, D*n* day *n*, EOS end of study, EOT end of treatment, HC hydrocortisone, PRED prednisone, QD once daily, W*n* week *n*.

Figure S2. Study Disposition.

The data cutoff date for the analyses was January 23, 2023.

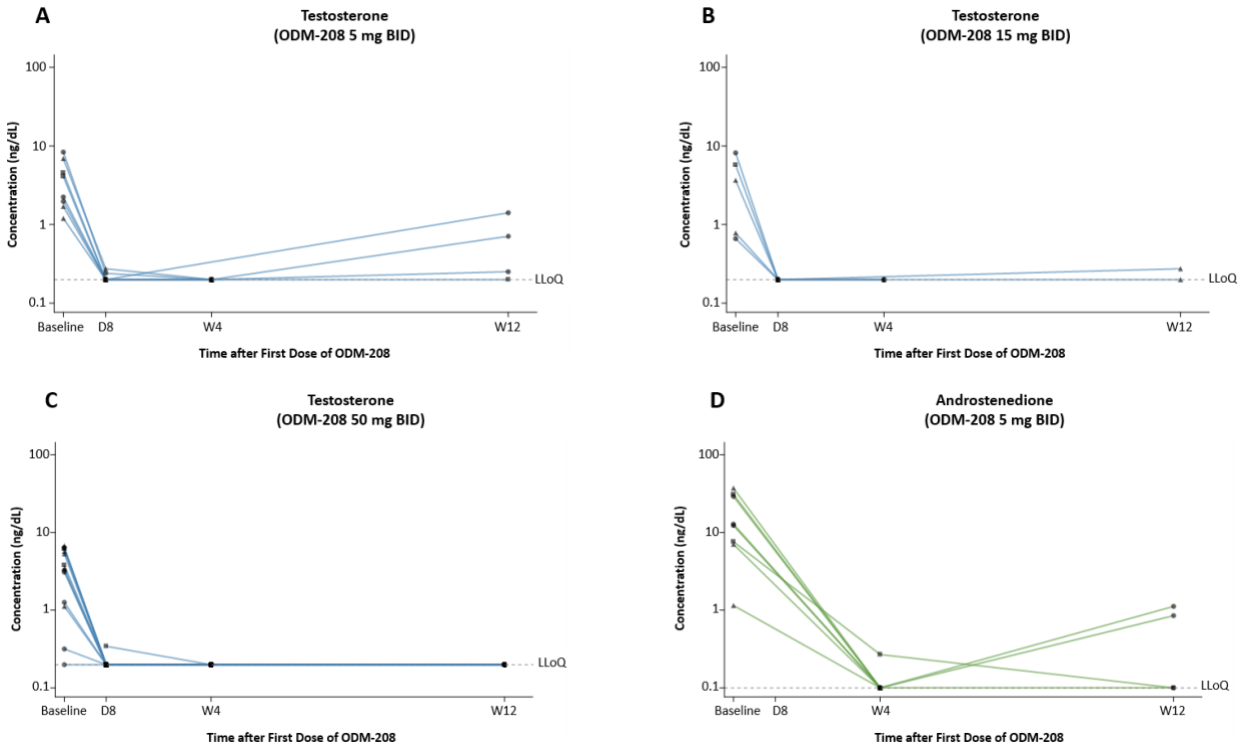


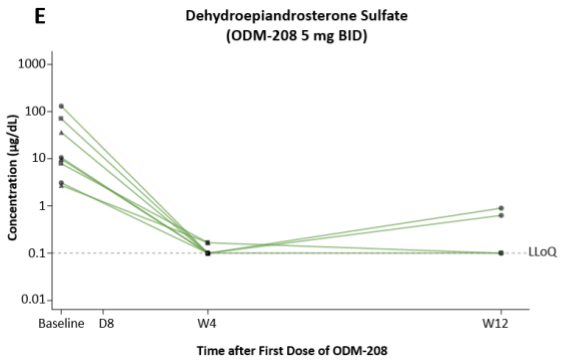
* Alternative steroid regimens to ODM-208 were studied at the 50 mg bid dose level.

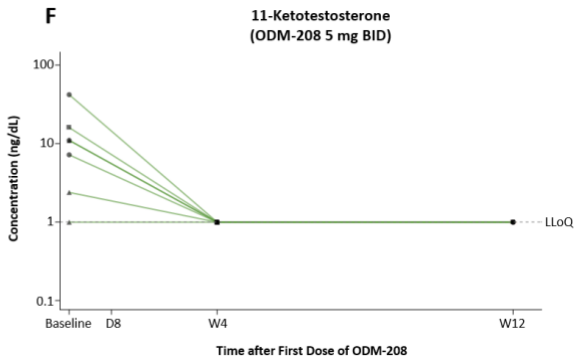
bid denotes twice daily, EOS end of study, PSA prostate-specific antigen.

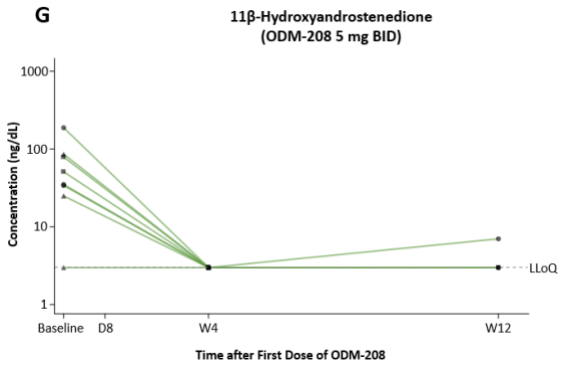
Figure S3. Serum Levels of Steroid Hormones in the Phase 1 Dose Cohort.

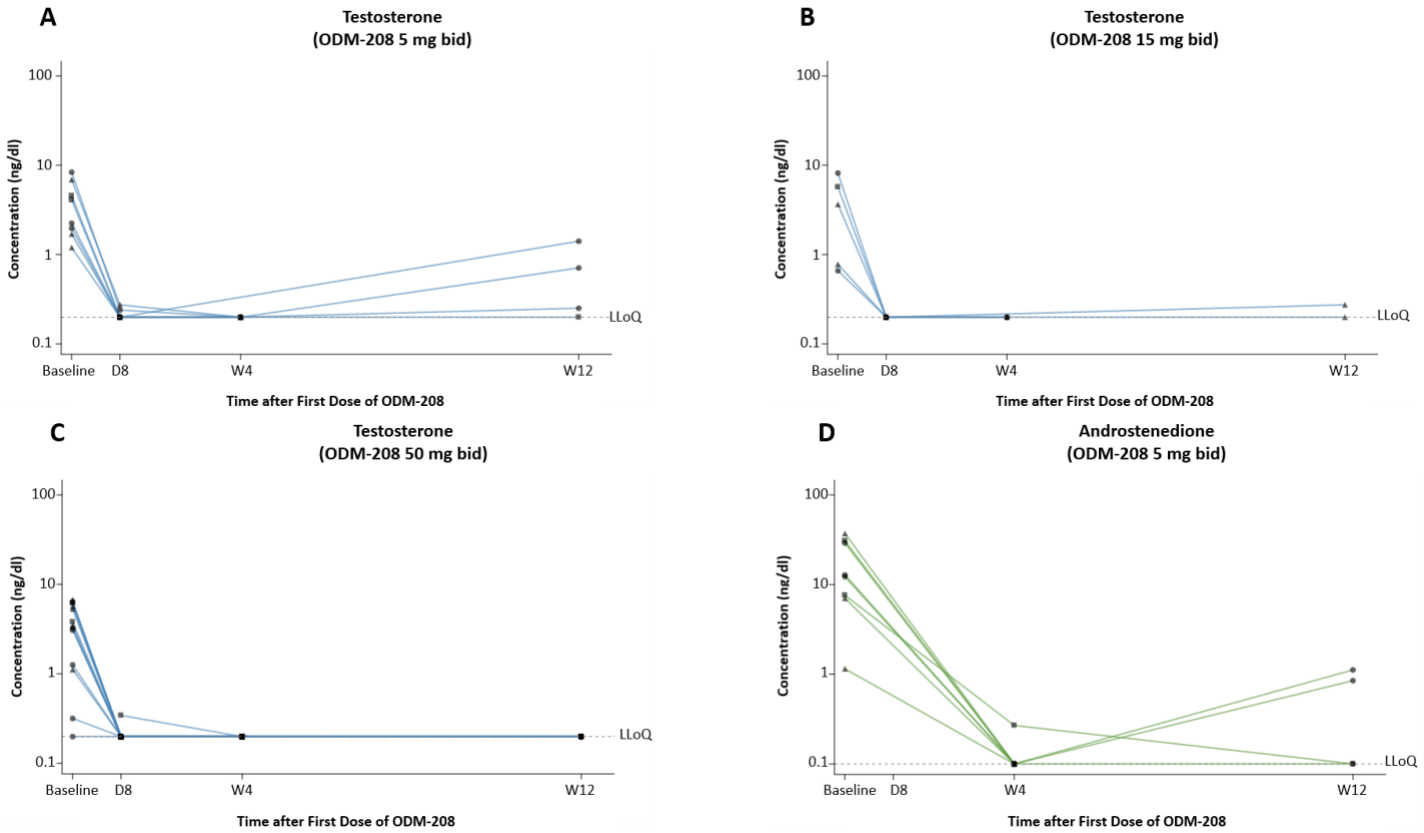
Testosterone at ODM-208 dose levels: Panel A shows 5 mg bid, Panel B shows 15 mg bid, and Panel C shows 50 mg bid. Panel D shows androstenedione, Panel E shows dehydroepiandrosterone sulfate, Panel F shows 11-ketotestosterone, and Panel G shows 11β-hydroxyandrostenedione, at an ODM-208 dose of 5 mg bid (the RP2D).

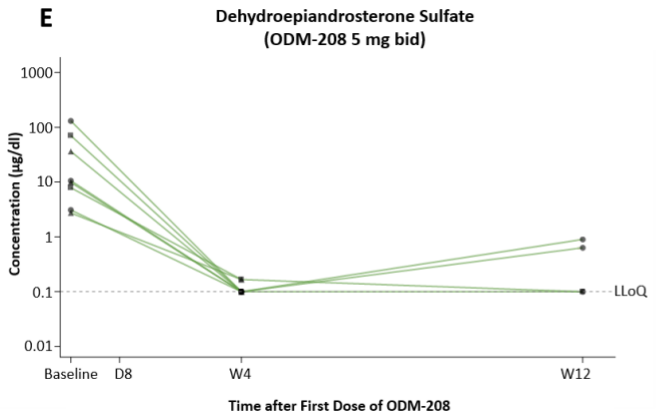


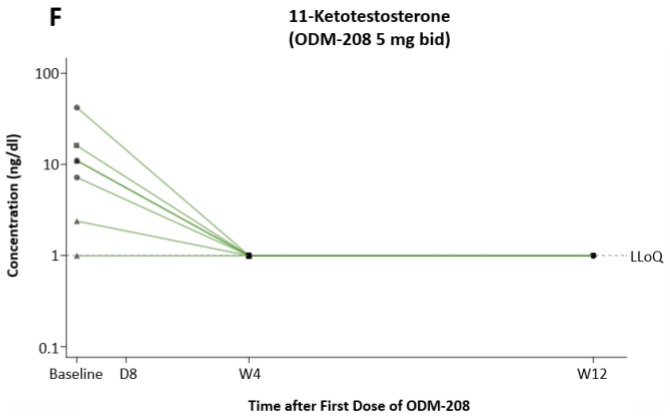

E
Dehydroepiandrosterone Sulfate
(ODM-208 5 mg BID)
Concentration (µg/dL)
1000
100
10
1
0.1
0.01
LLoQ
Baseline
D8
W4
W12
Time after First Dose of ODM-208

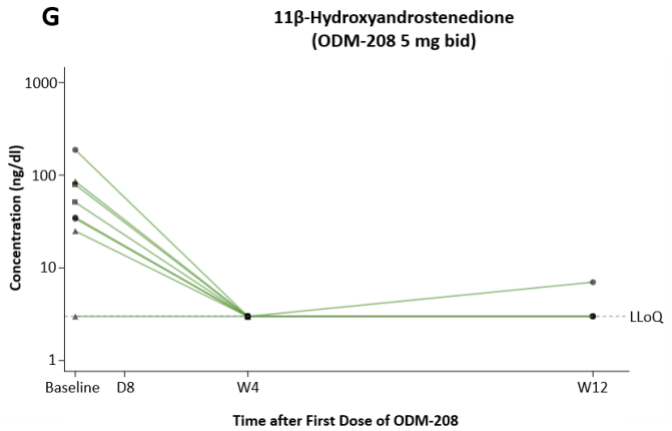

F
11-Ketotestosterone
(ODM-208 5 mg BID)
Concentration (ng/dL)
100
10
1
0.1
LLoQ
Baseline
D8
W4
W12
Time after First Dose of ODM-208


G
11β-Hydroxyandrostenedione
(ODM-208 5 mg BID)
Concentration (ng/dL)
1000
100
10
1
LLoQ
Baseline
D8
W4
W12
Time after First Dose of ODM-208


A
Testosterone
(ODM-208 5 mg bid)
B
Testosterone
(ODM-208 15 mg bid)
C
Testosterone
(ODM-208 50 mg bid)
D
Androstenedione
(ODM-208 5 mg bid)
Concentration (ng/dl)
100
10
1
0.1
LLoQ
Baseline
D8
W4
W12
Time after First Dose of ODM-208







bid denotes twice daily, D*n* day *n*, LLoQ lower limit of quantification, RP2D recommended phase 2 dose, W*n* week *n*.

SUPPLEMENTARY TABLES

Table S1. Representativeness of study participants

Category	Description
Disease	Metastatic castration-resistant prostate cancer (mCRPC).
Demographics	All participants were male with median age approximately 70 years which is comparable to the median age of the global prostate cancer patient population.
Geography	The participants were enrolled in Finland, France and the United Kingdom (no participants were enrolled at sites in the United States) at major cancer centers. Although race was not recorded, the population was likely predominantly Caucasian.
Prior treatment	Participants in the trial had received extensive prior treatment with 1-2 prior novel hormonal agents (abiraterone, enzalutamide) and 1-2 lines of taxane chemotherapy, commonly in addition to other systemic anti-cancer therapies.
Overall representativeness of the trial	The trial enrolled patients with advanced castration-resistant prostate cancer in Europe who had progressed despite several prior systemic therapies, and who lacked further proven treatment options. It is reasonable to assume that these patients were reflective of the general population with this condition in Europe, although no comment can be made concerning racial diversity. Treatment availability and clinical practice varies around the world and comparable patients in different regions might have received different prior treatments. The anticipated distribution of race and ethnicity in this trial may not reflect the worldwide population.

Table S2. ODM-208 and Glucocorticoid/Mineralocorticoid Replacement Therapy Dosing Tested in Phase 1.

		ODM-208 Dose†						
Glucocorticoid Replacement Therapy*		3 mg bid	5 mg bid	25 mg QD	15 mg bid	25 mg bid	50 mg bid	75 mg bid
Dexamethasone	1–1.5 mg qd — no.	6	6	3	4	3	8	3
Hydrocortisone	40 or 80 mg qd — no.‡						6	
Prednisone	5–20 mg QD — no.						5	

* All patients used fludrocortisone 0.05–0.1 mg QD. bid denotes twice daily, DLT dose-limiting toxicity, QD once daily.

† The starting dose of ODM-208 was 50 mg bid. The dose was escalated to 75 mg bid, but de-escalated back to 50 mg bid due to a DLT (adrenal insufficiency). Doses were thereafter studied in the following order: 25 mg bid, 25 mg QD, 15 mg bid, 5 mg bid, and 3 mg bid (see Fig. S1).

‡ A higher dose was used from day 2 for the first 4 weeks, and gradually tapered down thereafter to 40 mg hydrocortisone or the equivalent dose.

Table S3. Steroid Hormones Monitored During Phase 1 and Phase 2 of the CYPIDES Study, with the Lower Limits of Quantification and Blood Sampling Schedules.

		Blood Sampling Schedule	
Steroid Hormone	**LLoQ***	**Phase 1**	**Phase 2**
Testosterone	0.2 ng/dl	<u>Before protocol amendment 3</u> D1 and D8 (predose, then 1, 2, 4, 6, 9, and 12h postdose) and then predoses on D29, W12, and W24, and every 12 weeks thereafter <u>After protocol amendment 3</u> D1 (predose and 1, 2, 6, 12, 24, and 36 h postdose), D8 (predose and then 12 h postdose), and then predoses on D29, W12, and W24, and every 12 weeks thereafter	Predose on D1, D8, D29, W12, W24, and every 12 weeks thereafter
Cortisol	1 µg/dl (phase 2)	Predose on D1, D8, D29, W12, W24, and every 12 weeks thereafter, post-treatment visits, and at EOS and follow-up† (local testing). Added in protocol amendment 3	Predose on D1, D8, D29, and W12, then on D14 and D28 (EOS) after last dose of ODM-208, and during follow-up† (central testing)
Aldosterone	0.2 ng/dl(phase 2)	Predose on D1, D8, D29, W12, W24, and every 12 weeks thereafter, post-treatment visits, and at EOS and follow-up† (local testing)	Predose on D1, D8, D29, and W12, then on D14 and D28 (EOS) after last dose of ODM-208, and during follow-up† (central testing)
Androstenedione	0.1 ng/dl	Predose on D1, D29, and W12	Predose on D1, D8, D29, and W12
11β-Hydroxyandrostenedione	3 ng/dl	Predose on D1, D29, and W12	NM
11-Ketotestosterone	1 ng/dl	Predose on D1, D29, and W12	NM

Dehydroepiandrosterone sulfate	0.1 µg/dl	Predose on D1, D29, and W12, and at EOS and follow-up†	Predose on D1, D8, D29, W12, and at EOS and follow-up†
Pregnenolone	10 ng/dl	Predose on D1, D29, and W12, and at EOS and follow-up†	Predose on D1, D8, D29, W12, and at EOS and follow-up†
Progesterone	10 ng/l	Predose on D1, D29, W12§	NM
Estradiol	1 pg/l	Predose on D1, D29, W12§	NM

* Steroid hormone concentrations were measured using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) at LabCorp Esoterix Endocrinology (Calabasas, CA) or LabCorp Central Laboratory (Geneva, Switzerland). Dexamethasone and fludrocortisone do not interfere with the assay method.[2] D*n* denotes day *n*, EOS, end of study, hr hour, LLoQ lower limit of quantification, NM not measured, W*n* week *n*.

† To monitor adrenal recovery. If patients still required glucocorticoid and/or mineralocorticoid therapy at the EOS visit, they continued to be followed for adrenal recovery with blood tests conducted at 4 and 8 weeks thereafter. If replacement therapy was needed beyond that time, patients were contacted by telephone at 16 and (if necessary) 24 weeks from the EOS.

§ Collected from a subset of phase 1 participants (until Protocol Amendment 3).

Table S4. Patient Demographics and Baseline Characteristics.

Characteristic	Phase 1 (All Doses Combined) N=47	Phase 2 (5 mg bid) N=45
Age, median (IQR) — yr	70.0 (61 - 73)	69.0 (61 - 75)
Body mass index, median (IQR) — kg/m^2	26.7 (24.8 – 28.6)	25.8 (23.5 – 27.7)
ECOG performance status — no. (%)		
0	17 (36.2)	10 (22.2)
1	30 (63.8)	35 (77.8)
PSA concentration, median (IQR) — µg/l	126.0 (30.7 – 385.9)	319.6 (137.9 – 768.5)
Gleason total score — no. (%)*		
5	1 (2.3)	0
6	1 (2.3)	0
7	14 (32.6)	16 (38.1)
8	13 (30.2)	6 (14.3)
9	14 (32.6)	17 (40.5)
10	0	3 (7.1)
NA	4 (9.3)	3 (7.1)
Testosterone, median (IQR) — ng/dl	3.8 (1.4 – 6.0)	3.2 (1.1 – 6.5)
Sites of metastases — no. (%)†		
Bone only	21 (44.7)	10 (23.3)
Bone and lymph node	14 (29.8)	10 (23.3)
Bone, lymph node, and visceral	7 (14.9)	5 (11.6)
Bone and visceral	3 (6.4)	3 (7.0)

Lymph node only	1 (2.1)	10 (23.3)
Lymph node and visceral	1 (2.1)	4 (9.3)
Visceral only	0	1 (2.3)
NA	0	2 (4.7)
AR mutation — no. (%)		
Yes	20 (42.6)	45 (100)
Number of mutations — no. (%)		
0	27 (57.4)	0
1	9 (19.1)	30 (66.7)
2	9 (19.1)	9 (20.0)
3	1 (2.1)	6 (13.3)
4	1 (2.1)	0
Type of *AR* mutation — no. (%)‡		
p.T878A	13 (38.2)	19 (28.8)
p.L702H	11 (32.4)	27 (40.9)
p.H875Y	6 (17.6)	14 (21.2)
p.T878S	2 (5.9)	2 (3.0)
p.V716M	1 (2.9)	2 (3.0)
p.F877L	1 (2.9)	1 (1.5)
p.W742C	0	1 (1.5)
AR amplification — no. (%)§		
Yes	13 (27.7)	16 (35.6)
Prior lines of systemic therapy — no. (%)		
1	1 (2.1)	0

2	2 (4.3)	7 (15.6)
≥3	44 (93.6)	38 (84.4)
Select prior systemic therapies — no. (%)		
Taxanes		
Docetaxel	44 (93.6)	44 (97.8)
Cabazitaxel	25 (53.2)	31 (68.9)
Taxane-naïve	3 (6.4)	0
Abiraterone	34 (72.3)	38 (84.4)
Enzalutamide	36 (76.6)	31 (68.9)
Abiraterone and enzalutamide	24 (51.1)	25 (55.6)

* % of patients with Gleason total score is calculated based on patients with available score (n=43 for phase 1 and n=42 for phase 2

† % of patients with metastases is calculated based on patients with available data (n=47 for phase 1 and n=43 for phase 2).

‡ Individual patients may have harbored more than one mutation, so patient numbers may not necessarily total 47 (phase 1) or 45 (phase 2).

ECOG denotes Eastern Cooperative Oncology Group, LHRH luteinizing hormone-releasing hormone, NA not available.
§ Copy number >2.

Table S5. Summary of Treatment-Emergent Adverse Events and List of Adverse Events (Regardless of Causality) Occurring in ≥10% of Patients in Either the Phase 1 or Phase 2 Cohorts by Preferred Term and Maximum NCI CTCAE (v4.03) Grade.

	Phase 1 (All Dose Cohorts Combined) N=47		Phase 2 (5 mg bid) N=45		All Phase 1+2 N=92	
Adverse Events by Preferred Term, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
All	47 (100.0)	33 (70.2)	45 (100)	36 (80.0)	92 (100)	69 (75.0)
Anemia	16 (34.0)	7 (14.9)	17 (37.8)	6 (13.3)	33 (35.9)	13 (14.1)
Fatigue	14 (29.8)	0	17 (37.8)	3 (6.7)	31 (33.7)	3 (3.3)
Asthenia	14 (29.8)	2 (4.3)	13 (28.9)	2 (4.4)	27 (29.3)	4 (4.3)
Hyponatremia	15 (31.9)	6 (12.8)	10 (22.2)	2 (4.4)	25 (27.2)	8 (8.7)
Adrenal insufficiency	17 (36.2)	15 (31.9)	6 (13.3)	3 (6.7)	23 (25.0)	18 (19.6)
Hyperkalemia	13 (27.7)	1 (2.1)	9 (20.0)	1 (2.2)	22 (23.9)	2 (2.2)
Muscle spasms	14 (29.8)	0	8 (17.8)	1 (2.2)	22 (23.9)	1 (1.1)
Edema peripheral	10 (21.3)	0	12 (26.7)	0	22 (23.9)	0
Tumor pain	10 (21.3)	4 (8.5)	11 (24.4)	3 (6.7)	21 (22.8)	7 (7.6)
Dyspnea	6 (12.8)	0	12 (26.7)	2 (4.4)	18 (19.6)	2 (2.2)
ALT increased	10 (21.3)	1 (2.1)	7 (15.6)	0	17 (18.5)	1 (1.1)
AST increased	8 (17.0)	1 (2.1)	9 (20.0)	0	17 (18.5)	1 (1.1)

Insomnia	8 (17.0)	0	9 (20.0)	0	17 (18.5)	0
Nausea	7 (14.9)	0	10 (22.2)	0	17 (18.5)	0
Bone pain	7 (14.9)	1 (2.1)	9 (20.0)	2 (4.4)	16 (17.4)	3 (3.3)
ALP increased	6 (12.8)	3 (6.4)	8 (17.8)	3 (6.7)	14 (15.2)	6 (6.5)
Amylase increased	9 (19.1)	4 (8.5)	4 (8.9)	1 (2.2)	13 (14.1)	5 (5.4)
Arthralgia	5 (10.6)	0	8 (17.8)	1 (2.2)	13 (14.1)	1 (1.1)
Back pain	7 (14.9)	0	6 (13.3)	2 (4.4)	13 (14.1)	2 (2.2)
Diarrhea	4 (8.5)	1 (2.1)	9 (20.0)	2 (4.4)	13 (14.1)	3 (3.3)
Hypertension	8 (17.0)	5 (10.6)	5 (11.1)	3 (6.7)	13 (14.1)	8 (8.7)
Myalgia	6 (12.8)	0	7 (15.6)	0	13 (14.1)	0
Pyrexia	7 (14.9)	0	6 (13.3)	0	13 (14.1)	0
Decreased appetite	4 (8.5)	0	8 (17.8)	1 (2.2)	12 (13.0)	1 (1.1)
Abdominal pain	4 (8.5)	1 (2.1)	7 (15.6)	0	11 (12.0)	1 (1.1)
Blood creatinine increased	6 (12.8)	0	5 (11.1)	0	11 (12.0)	0
Hypocalcemia	4 (8.5)	0	7 (15.6)	0	11 (12.0)	0
Urinary tract infection	5 (10.6)	0	6 (13.3)	1 (2.2)	11 (12.0)	1 (1.1)
Constipation	5 (10.6)	1 (2.1)	5 (11.1)	0	10 (10.9)	1 (1.1)
Hypokalemia	4 (8.5)	1 (2.1)	6 (13.3)	0	10 (10.9)	1 (1.1)
Hypotension	3 (6.4)	0	7 (15.6)	2 (4.4)	10 (10.9)	2 (2.2)

Weight increased	5 (10.6)	0	5 (11.1)	0	10 (10.9)	0
CPK increased	7 (14.9)	2 (4.3)	1 (2.2)	0	8 (8.7)	2 (2.2)
Headache	7 (14.9)	0	2 (4.4)	0	9 (9.2)	0
Pulmonary embolism	5 (10.6)	5 (10.6)	3 (6.7)	3 (6.7)	8 (8.7)	8 (8.7)
Lipase increased	5 (10.6)	3 (6.4)	1 (2.2)	1 (2.2)	6 (6.5)	4 (4.3)

ALP denotes alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, bid twice daily, CPK creatine phosphokinase, NCI CTCAE (v4.03) National Cancer Institute Common Terminology Criteria for Adverse Events version 4.30.

Table S6. Treatment-Emergent Adverse Events Occurring in ≥15% of Patients in Any Dose Group of Phase 1 (N=47) by Preferred Term and Dose Group.

	ODM-208 Dose							
Preferred Term — no. (%)	**3 mg bid (n=6)**	**5 mg bid (n=8)**	**25 mg QD (n=3)**	**15 mg bid (n=5)**	**25 mg bid (n=3)**	**50 mg bid (n=19)**	**75 mg bid (n=3)**	**Total (N=47)**
Adrenal insufficiency	2 (33.3)	2 (25.0)	1 (33.3)	3 (60.0)	2 (66.7)	6 (31.6)	1 (33.3)	17 (36.2)
Anemia	1 (16.7)	4 (50.0)	2 (66.7)	2 (40.0)	0	5 (26.3)	2 (66.7)	16 (34.0)
Hyponatremia	3 (50.0)	5 (62.5)	1 (33.3)	2 (40.0)	1 (33.3)	2 (10.5)	1 (33.3)	15 (31.9)
Asthenia	3 (50.0)	3 (37.5)	1 (33.3)	1 (20.0)	1 (33.3)	4 (21.1)	1 (33.3)	14 (29.8)
Fatigue	1 (16.7)	1 (12.5)	0	5 (100.0)	0	6 (31.6)	1 (33.3)	14 (29.8)
Muscle spasms	4 (66.7)	3 (37.5)	1 (33.3)	0	1 (33.3)	5 (26.3)	0	14 (29.8)
Hyperkalemia	4 (66.7)	3 (37.5)	1 (33.3)	2 (40.0)	2 (66.7)	1 (5.3)	0	13 (27.7)
ALT increased	1 (16.7)	2 (25.0)	0	2 (40.0)	0	5 (26.3)	0	10 (21.3)
Edema peripheral	2 (33.3)	2 (25.0)	0	1 (20.0)	0	5 (26.3)	0	10 (21.3)
Tumor pain	0	1 (12.5)	1 (33.3)	1 (20.0)	2 (66.7)	4 (21.1)	1 (33.3)	10 (21.3)
Amylase increased	0	3 (37.5)	0	1 (20.0)	0	4 (21.1)	1 (33.3)	9 (19.1)
AST increased	1 (16.7)	2 (25.0)	1 (33.3)	1 (20.0)	0	3 (15.8)	0	8 (17.0)
Hypertension	1 (16.7)	0	1 (33.3)	0	0	5 (26.3)	1 (33.3)	8 (17.0)
Insomnia	2 (33.3)	2 (25.0)	1 (33.3)	1 (20.0)	0	2 (10.5)	0	8 (17.0)

ALT denotes alanine aminotransferase, AST aspartate aminotransferase, bid twice daily, QD once daily.

Table S7. Patients with elevated serum thyroid stimulating hormone or bilirubin concentration during ODM-208 treatment

Patient	Adverse event	Maximum severity	Event duration	ODM-208 dose	Action taken	Event present at baseline
Patient 1	TSH increase	Grade 2	Ongoing	10 mg bid	Levothyroxine initiated	Yes
Patient 2	Bilirubin increase	Grade 1	11 days	10 mg bid	None	Yes
Patient 3	Bilirubin increase	Grade 1	35 days	10 mg bid	None	No

bid denotes twice daily, TSH thyroid stimulating hormone.

Table S8. Median Steroid Hormone values and number of patients with values below LLoQ during and after ODM-208 5mg bid treatment.

	Study visit								
		On-treatment						Post-treatment	
Steroid Hormone†	**Baseline**	**Day 8**		**Week 4**		**Week 12**		**~ 4 weeks**	
	Median* (IQR)	Median* (IQR)	<LLoQ N (%)‡	Median* (IQR)	<LLoQ N N (%)‡	Median* (IQR)	<LLoQ N (%)‡	Median* (IQR)	<LLoQ N (%)‡
Testosterone (ng/dl)	3.0 (1.3-6.2)	0.2 (0.2-0.2)	46 (87%)	0.2 (0.2-0.2)	42 (88%)	0.2 (0.2-0.3)	24 (69%)	ND	
Cortisol (µg/dl)	9.3 (6.1 – 14.0)	1.0 (1.0 1.0)	45 (87%)	1.0 (1.0 1.0)	44 (90%)	1.0 (1.0 1.0)	31 (89%)	5.3 (2.1 -10.0)	4 (15%)
Androstenedione (ng/dl)	20.3 (7.3 – 32.0)	0.2 (0.1-0.3)	11 (24%)	0.1 (0.1 - 0.1)	37 (77%)	0.1 (0.1 - 0.1)	23 (68%)	5.7 (2.4 – 21.3)	0 (0%)
11β-Hydroxyandrostenedione (ng/dl)	42.9 (29.5 -82.5)	ND		3.0 (3.0 – 3.0)	8 (100%)	3.0 (3.0 – 5.0)	3 (75%)	ND	
11-Ketotestosterone (ng/dl)	11.0 (2.4 – 16.0)	ND		1.0 (1.0 – 1.0)	8 (100%)	1.0 (1.0 – 1.0)	4 (100%)	ND	
Dehydroepiandrosterone sulfate (µg/dl)	14.5 (5.7-32.0)	0.3 (0.1-0.7)	16 (36%)	0.1 (0.1-0.1)	42 (86%)	0.1 (0.1-0.1)	30 (86%)	4.0 (2.4-7.6)	0 (0%)
Pregnenolone (ng/dl)	10.0 (10.0 – 14.0)	10.0 (10.0 – 10.0)	42 (98%)	10.0 (10.0 – 10.0)	49 (100%)	10.0 (10.0 – 10.0)	33 (94%)	10.0 (10.0 – 10.5)	16 (67%)

* The detection limit (LLoQ, see Table S3) value was used as a surrogate when calculating the median and the IQR when no hormone was detected in serum.
IQR denotes interquartile range; LLoQ, lower limit of quantification; ND not done.

† Serum aldosterone and progesterone were not measured in the cohort treated with 5 mg bid.

‡ The number of patients with available data varies between analyte and visit due to missing samples

Table S9. Best RECIST Overall Response, and Time-to-Event Endpoints.

	Phase 1 (*AR*^{mut} or *AR*^{wt})			Phase 2* (*AR*^{mut} only)
RECIST Overall Response (RECIST-Evaluable Population)	**All Patients N=18**			**All Patients N=30**
PR — no. (%)	3 (16.7)			8 (26.7)
SD — no. (%)	7 (38.9)			13 (43.3)
Non-CR/non-PD — no. (%)†	3 (16.7)			4 (13.3)
PD — no. (%)	5 (27.8)			5 (16.7)
Objective response rate (CR+PR) — %	16.7			26.7
Disease control rate (CR+PR+SD) — %	55.6			70.0
		Phase 1		**Phase 2***
Time-to-Event Endpoints (Kaplan–Meier Estimates, Safety Population), Median (IQR)	**All patients N=47**	***AR*^{mut} n=20**	***AR*^{wt} n=27**	**All *AR*^{mut} N=45**
Duration of RECIST overall response — months	NR (2 to NR)	NR (2 to NR)	NA	4 (2 to 6)
Time to any progression — months	4 (2 to 14)	5 (2 to 14)	4 (2 to 8)	5 (2 to 8)
Time to radiographic progression — months	5 (2 to 25)	5 (2 to 25)	5 (2 to 9)	5 (2 to 8)

Time to PSA progression — months	7 (4 to 15)	14 (5 to 25)	6 (4 to 9)	7 (4 to NR)
Duration of PSA response — months	4 (2 to 11)	4 (2 to 14)	3 (2 to 5)	2 (2 to 4)
Time to treatment discontinuation — months	4 (2 to 6)	5 (2 to 14)	3 (1 to 5)	4 (3 to 8)

* Patients in phase 2 harbored only *AR*^{mut} mutations (patients with *AR*^{wt} disease were excluded from study entry).

† Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits (per RECIST guidelines, non-CR/non-PD is preferred over SD for non-target lesions).[3]

AR^{mut} denotes androgen receptor ligand-binding domain gene mutation, *AR*^{wt} wild-type androgen receptor ligand-binding domain gene, CI confidence interval, CR complete response, NA not applicable, NR not reached, PD progressive disease, PR partial response, PSA prostate-specific antigen, RECIST Response Evaluation Criteria in Solid Tumors, SD stable disease.

SUPPLEMENTARY REFERENCES

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