29 January 2026
EMADOC-1700519818-2759690
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Akeega

International non-proprietary name: Niraparib / Abiraterone acetate

Procedure No. EMA/VR/0000282377

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AAP	abiraterone acetate plus prednisone
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukemia
AR	androgen receptor
ARPI	androgen receptor pathway inhibitors
BICR	Blinded Independent Central Review
BPI-SF	Brief Pain Inventory Short Form
BRCA	breast cancer gene
BRIP1	interacting protein C terminal helicase 1
CCO	clinical cutoff
CDK12	cyclin-dependent kinase 12
cfDNA	cell-free DNA
CH	clonal hematopoiesis
CHEK2	checkpoint kinase 2
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTD	Common Technical Document
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Oncology Cooperative Group
eDISH	evaluation of drug-induced serious hepatotoxicity
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FANCA	Fanconi anemia complementation group A
FAS	Full analysis set
FDC	fixed-dose combination
FOIA	Freedom of Information Act
GnRHa	gonadotropin-releasing hormone analogue
HR	hazard ratio
HRD	homologous recombination deficiency
HRQoL	health-related quality of life
HRR	homologous recombinant repair
IB	Investigator’s Brochure

ICF	informed consent form
ICH	International Conference of Harmonisation
IDMC	Independent Data Monitoring Committee
IF	Information fraction
IRB	Institutional Review Board
IEC	Independent Ethics Committee
IPCW	inverse probability censoring weighted
IVRS	interactive voice response system
IWRS	interactive web response system
mHSPC	metastatic hormone-sensitive prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
nira	niraparib
NE	not estimable
PALB2	partner and localizer of BRCA2
PARPi	poly (adenosine diphosphate-ribose) polymerase inhibitor
PBO	placebo
PCWG	Prostate Cancer Working Group
PFS2	time from randomization to the date of first progression (radiographic, clinical, or PSA progression) on the first subsequent therapy or death from any cause, whichever occurred first
PK	pharmacokinetic
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PRO CTCAE	Patient-reported Outcomes Common Terminology Criteria for Adverse Events
PSA	prostate-specific antigen
PT	preferred term
RAD51B	RAD51 paralog B
RAD54L	RAD54-like
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
RTSM	Randomization and Trial Supply Management
RR	relative risk
SAP	statistical analysis plan
SDR	source data review
SDV	source data verification
SOC	System Organ Class
TCC	time to initiation of cytotoxic chemotherapy

TEAE	treatment-emergent adverse event
TSP	time to symptomatic progression
TST	time to subsequent therapy
TTPP	time to pain progression

Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen Cilag International submitted to the European Medicines Agency on 30 June 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include AKEEGA with prednisone or prednisolone for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) and HRR-mutations (germline and/or somatic), based on interim results from study 67652000PCR3002 (AMPLITUDE); this is a phase 3 randomized, placebo-controlled, double-blind study of niraparib in combination with abiraterone acetate and prednisone versus abiraterone acetate and prednisone for the treatment of participants with deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-sensitive Prostate cancer (mCSPC); As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Additionally, sections 5.3 and 6.6 of the SmPC are also being updated as a result of ERA assessment. Version 3.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. In addition, the MAH is requesting an additional year of market protection for a new indication.

The requested variation(s) proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0244/2020 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. During the procedure the MAH withdrew the request.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Carolina Prieto Fernandez

Timetable	Actual dates
Submission date	30 June 2025
Start of procedure:	19 July 2025
CHMP Rapporteur's preliminary assessment report circulated on:	12 September 2025
PRAC Rapporteur's preliminary assessment report circulated on:	15 September 2025
Joint Rapporteur's updated assessment report circulated on:	09 October 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	16 October 2025
MAH's responses submitted to the CHMP on:	27 November 2025
CHMP and PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	01 January 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	23 January 2026
CHMP opinion:	29 January 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH initially applied for the following extension of indication:

"Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) and HRR gene alterations (germline and/or somatic)."

The final approved indication is:

"Akeega is indicated with prednisone or prednisolone in combination with androgen deprivation therapy (ADT) for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) and BRCA 1/2 mutations (germline and/or somatic)."

Epidemiology

Prostate cancer is the fourth most frequently diagnosed cancer and a leading cause of cancer death in men worldwide, with an estimated 1.5 million new cases (7.3% of all new cancers) in 2022 (Bray 2024). In Europe, prostate cancer is the most common cancer in men, with 473,144 new cases,

representing the 20% of all cancers in men; and 115,194 (10.5%) of cancer deaths in 2022 (IARC 2022).

Biologic features

Defects in DNA damage repair pathways, including those arising due to deleterious germline or somatic HRR gene alterations, are known to lead to genomic instability and aggressive disease in patients with metastatic prostate cancer (Custodio-Cabello 2024; Mateo 2017; Warner 2019).

Approximately 20% to 30% of metastatic prostate cancers harbour deleterious alterations in DNA damage repair (DDR) genes, including those in the HRR pathway. Among patients with mHSPC, the proportion of patients that harbour deleterious HRR gene alterations is as high as 28.6% of which 12.4% are BRCA and 16.2% are non-BRCA HRR gene alterations (Olmos 2025). BRCA1 and BRCA2 are the most well characterized HRR genes, and BRCA mutations are associated with aggressive and rapidly progressive disease, earlier emergence of resistance to standard-of-care treatments, and poor survival in metastatic prostate cancer patients (Castro 2019; Custodio-Cabello 2024; Mateo 2017; Olmos 2025; Saad 2023).

Clinical presentation, diagnosis and stage/prognosis

At the time of diagnosis, the majority of patients have localised disease. Patients diagnosed at an early stage are amenable to curative therapy, however advanced stages are life-threatening. Patients who present with metastatic disease at initial presentation typically have cancers with a more aggressive biology and have a shorter overall survival compared with patients who develop metastatic recurrence years after the initial diagnosis of primary prostate cancer. For patients diagnosed with metastatic disease, the 5-year survival rate is 30% (American Cancer Society 2021, Siegel 2021).

Metastases are a major cause of morbidity and mortality; and therefore, pose a substantial burden as they are associated with skeletal-related events, pain, and the need for further radiation therapy or surgery and need for additional therapies (Smith 2012). Although patients with metastatic castrate-sensitive disease will initially respond to androgen-receptor (AR)-directed therapies, they will ultimately develop castration-resistant disease, whereupon duration of response to treatment and survival times are short.

Management

In the EU (Parker C, et al. ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020) standard treatment for all patients with mHSPC irrespective of any HRR gene mutations includes doublet therapy with the addition of either docetaxel or an AR-pathway inhibitor (abiraterone, enzalutamide, apalutamide or darolutamide) to androgen deprivation therapy (Cornford 2024; Gillessen 2020; Lowrance 2023; Parker 2020) or triplet therapy with all three combined. Randomized, Phase 3 trials have shown that the addition of an AR pathway inhibitor to ADT has greater clinical benefit than the use of ADT alone (Armstrong 2022; Chi 2021; Davis 2019; Fizazi 2019;).

Radiotherapy to the primary tumour combined with the systemic treatment is recommended for patients with low-volume disease. ADT alone is recommended as first-line systemic treatment in men who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel.

Alterations in HRR-associated genes have been shown to lead to poor outcomes in prostate cancer patients with existing therapies. Survival in patients with biomarker-unselected mHSPC has

improved due to recent treatment advances, however, it remains a universally lethal disease. Overall survival at 4 years in a biomarker unselected population is approximately 60% (Chi 2021; Smith 2022) and is worse in patients with high-risk disease, with a median OS of approximately 4 years (Fizazi 2017). Similar to what has been observed in patients with mCRPC, outcomes with standard AR-based therapies are inferior in patients with mHSPC who have BRCA gene alterations (Castro 2019; Chanza 2022; Gebrael 2025; Lee 2022; Nombela 2019), including increased risk of radiographic progression for patients with HRR alterations and significantly shorter median OS than in patients with mHSPC and no HRR gene alterations (Olmos 2025).

There are currently no treatment options available that specifically target the HRR pathway in patients with mHSPC and HRR gene alterations. There is thus a clinical unmet need for new therapies that may help improve outcomes in this patient population and delay the progression to mCRPC, a uniformly fatal disease.

2.1.2. About the product

Akeega is a **fixed-dose combination (FDC)** of the individual drug substances niraparib and abiraterone acetate as film-coated tablets.

Niraparib is an orally available, highly selective PARPi, with activity against PARP-1 and PARP-2 DNA-repair polymerases. In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death.

Abiraterone acetate is a prodrug of abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal, and prostatic tumour tissues. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals.

The FDC is formulated in two strengths:

- 100 mg/500 mg film-coated tablets (‘regular-strength’). Each film-coated tablet contains 100 mg of niraparib (as tosylate monohydrate) and 500 mg of abiraterone acetate.
- 50 mg/500 mg film-coated tablets (‘low-strength’). Each film-coated tablet contains 50 mg of niraparib (as tosylate monohydrate) and 500 mg of abiraterone acetate.

Approved indication:

Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

Recommendations for use:

Akeega is for oral use. The tablets must be taken as a single dose, once daily on an empty stomach. Akeega must be taken at least two hours after eating and food must not be eaten for at least one hour after taking Akeega.

The recommended starting dose of Akeega is 200 mg/1000 mg (two 100 mg niraparib/500 mg abiraterone acetate tablets), as a single daily dose at approximately the same time every day. The 50 mg/500 mg tablet is available for dose reduction.

Medical castration with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in patients not surgically castrated.

Akeega should be used with prednisone or prednisolone at a dose of:

- 5 mg daily for treatment of mHSPC
- 10 mg daily for treatment of mCRPC

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The Applicant received Scientific Advice on the development of niraparib and abiraterone acetate for the treatment of men with metastatic castration-sensitive prostate cancer with DNA-repair gene defects or CDK12 mutation from the CHMP on 30 April 2020 (EMEA/H/SA/4392/2/2020/II). The Scientific Advice pertained to the following clinical aspects:

- The design of a proposed open-label, multinational, randomized Phase 3 study to evaluate the efficacy and safety of niraparib+AA-P.
- The overall suitability of the design to support an application for a marketing authorisation in the proposed indication
- The possible initiation of the study using separate drug products with introduction of a niraparib/AA FDC tablet in the ongoing study.

A pre-submission meeting with the Rapporteurs was held on 7th May 2025.

2.1.4. General comments on compliance with GCP

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH GCP guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application. An updated Environmental Risk Assessment has been provided in which the environmental data submitted as part of the initial MAA has been used (EMEA/H/C/005932) and no new ERA studies have been performed for this updated ERA.

2.2.1. Ecotoxicity/environmental risk assessment

Data of the single agents are presented below.

Table 1 ERA risk assessment

Substance (INN/Invented Name): Abiraterone Acetate/Zytiga

CAS-number (if available): 154229-19-3

PBT-assessment			
Parameter	**Result**		**Conclusion**
Bioaccumulation	log K_{OW}	5.12	
	BCF	903 (for low conc, 0.13 µg/L) 931 (for high conc, 1.3 µg/L)	Not B
Persistence	DT_{50} (at 12ºC)	$DT50_{water}$: 4.6 d $DT50_{soil}$: 38.2 d $DT50_{system}$: 7.0-10 d	Not P
Toxicity	NOEC (fish)	NOEC = 0.000013 mg L^{-1}	T
PBT Statement	Abiraterone acetate is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined	0.306	µg L^{-1}	>0.01 threshold: (Y)
Other concerns (e.g. chemical class)			Y. Potential EAS
Phase II Physical-chemical properties and fate			
Study type	**Test Protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Sludge: Koc = 7705 - 11806 L kg^{-1} Soil: Koc = 29184 - 363061 L kg^{-1}	• Batch equilibrium method with three soils and two sludges • Groundwater assessment *via* bank filtration and porewater triggered. • Soil assessment triggered.
Ready Biodegradability Test/CO_2 evolution/ 28 d	OECD 301B	12.56%	Not readily biodegradable.

Aerobic degradation in soil/One soil (sandy loam)/120 d	OECD 307	DT50 (12°C) = 34 d %CO2 = 55.1%	Evolution of $^{14}CO2$ (ultimate biodegradation) was 55.1% of the applied radioactivity accumulatively at Day 120. Metabolites identified were: [14C]abiraterone and dehydrogenated [14C]abiraterone. One soil (Sandy loam)
Aerobic Transformation in Aquatic Sediment systems/Taunton River and Weweantic River aerobic sediments/100 d	OECD 308	At 12°C: DT50water = 4.9 d DT50sediment = ND DT50whole system = 7.0-10.4 d % shifting to sediment = sediment-bound residue 28.2% and 22.1%	Evidence of primary biodegradation was observed for [14C] Abiraterone acetate in the aerobic water/sediment test samples

Phase IIa Effect studies

Study type	Test Protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Pseudokirchn eriella subcapitata*	OECD 201	EC50 (72h) NOEC (72 h)	>1000 1000	µg L^{-1}	NOEC value is the same for both measures of growth (biomass and growth rate)
Daphnia sp. Reproduction Test	OECD 211	NOEC (21d)	0.47	µg L^{-1}	
Fish, Early Life Stage Toxicity Test/Fathead minnow (*Pimephales promelas)*	OECD 210	NOEC (35d)	1.1	µg L^{-1}	
Activity Sludge, Respiration Inhibition Test	OECD 209	EC50 (3h)	> 10^6	µg L^{-1}	NOEC (3h) = 1000 mg/L
Soil Microorganisms : Nitrogen	OECD 216	%effect	>250	mg kg^{-1}	The nitrate production was inhibited by 3.9% on day 28.

Transformation Test					The empirical EC10, EC25 and EC50 values for nitrogen transformation were estimated to be > 250 mg kg^{-1} dry soil Sandy loam soil
Seedling Emergence and Seedling Growth Test/ Bean, Oat, Tomato	OECD 208	EC50 (14d) NOEC (14d)	>261 >261	mg kg^{-1}	Normalized to 3.4% organic matter
Acute Toxicity to Earthworms/ *Eisenia fetida*	OECD 207	LC50 (14d) NOEC (14d)	>340 340	mg kg^{-1}	Normalized to 3.4% organic matter
Chronic Toxicity/ *Collembola*	ISO 11267	EC50 (28 d) NOEC (28 d)	456 340	mg kg^{-1} diet	Normalized to 3.4% organic matter
Sediment dwelling organism/*Chiron omus riparius*	OECD 218	NOEC (28 d)	454.55	mg $kgDW^{-1}$	Normalized to 10% organic carbon
Phase IIb Effect studies					
Modified Partial Life-Cycle Exposure/Fathea d Minnow (*Pimephales promelas*)/ F0: 31 d, F1: 90 d post hatch	OECD 229	NOEC (#hatching per female, 31d)	0.013	µg L^{-1}	
Bioconcentratio n and Metabolism/Rai nbow Trout (*Oncorhynchus mykiss*) / flow through system/18 d accumulation and 22 d depuration	OECD 305	BCF	625 (for low conc, 0.13 µg/L) 576 (for high conc, 1.3 µg/L 903 (for low conc) 931 (for high conc)	L kg^{-1}	%lipids: Percent lipids at steady state (wet weight tissue basis) low 3.46% and high 3.76 % Percent lipids at steady state (dry weight tissue basis) low 19.65
					% and high 22.74 % With lipid normalisation of 5%
Substance (INN/Invented Name): Niraparib tosylate monohydrate/Zejula					

CAS-number (if available): 1038915-60-4			
PBT assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log KOW	-0.6-2.1	not B
	BCF		
Persistence	DT50 (at 12ºC)	DT50water: 2.3-14 d DT50sediment: 742-996 d >> 180 d DT50whole system: 329-478 d >> 180 d	vP
Toxicity	NOEC (fish)	0.032 mg L^{-1}	Not T
PBT Statement	Niraparib is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PECsurfacewater, default	1.0	µg L^{-1}	>0.01 threshold: Y
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test Protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	*Sludge:* KFoc = 1,597-3,483 L kg^{-1} *Soil:* KFoc = 34,073-173,972 L kg^{-1}	KOC for sludge is below the trigger for Tier B assessment (>10,000 L kg^{-1}).
Ready Biodegradability Test		Assumed to be not readily biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	At 12°C: *Schoonrewoerdsewiel*: DT50, water = 2.3 d DT50sediment = 742 d DT50, whole system = 478 d %shifting to sediment = 94-99% *Emperor Lake:* DT50, water = 14 d DT50, sediment = 996 d DT50, whole system = 329 d %shifting to sediment = 75-91%	>10% shifting to sediment		
Phase IIa Effect studies					
Study type	**Test Protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/Pseudokirchneriella subcapitata	OECD 201	NOEC	1000	µg L-1	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	44,000	µg L-1	
Fish, Early Life Stage Toxicity Test/Pimephales promelas	OECD 210	NOEC	32	µg L-1	Lowest NOEC in long-term studies, used for PNEC calculations
Daphnia sp. Reproduction Test	OECD 211	NOEC	320	µg L-1	
Sediment dwelling organism/Chironomus riparius	OECD 218	NOEC10% o.c	3373.9	mg kgDW-1	Normalized to 10% organic carbon

2.2.2. Discussion and conclusion on non-clinical aspects

No new non-clinical data have been submitted with this procedure which is acceptable.

According to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*), the ERA dossier should be updated for type II variations if there is an anticipated increase in the environmental exposure, e.g. a new indication which results in an increase in the extent of the use. The applicant has submitted an updated ERA, in which the environmental data submitted as part of the initial MAA has been used and no new environmental studies have been performed. However some data and ecotoxicological studies submitted by the Applicant in the initial MAA are not in line with the current version of the guideline and deficiencies have been identified for abiraterone acetate and niraparib tosilate monohydrate ERA.

Regarding abiraterone acetate, Tier A effect studies for soil compartment for abiraterone differ from those recommended in Table 11 of the guideline. Chronic Collembola toxicity test following ISO 11267 and acute toxicity to earthworm test following OECD 207 are no longer recommended. Instead, toxicity tests following OECD 232 and OECD 222/220 should be followed, respectively. The CHMP acknowledges the similarity between OECD 232 and ISO 11267. However, the Applicant should perform the chronic toxicity study in earthworms following OECD 222 or OECD 220 (**REC**).

Furthermore, the tailored assessment strategy for abiraterone as an endocrine active substance should include long-term adverse effect studies and not only a screening test. Therefore, the study following OECD 229 is considered insufficient and a fish sexual development test or a fish full lifecycle test should be performed, following OECD 234 or OECD 240 recommendations, respectively **(REC).**

Regarding Phase I, the MAH is asked to provide the source of the prevalence data used for the Fpen refinement, including the relevant literature for the member state concerned. Such data should be published by a reliable and independent source (**REC**).

Based on the ERA submitted in this application, the new/extended indication leads to a significant increase in environmental exposure further to the use of abiraterone. This information is reflected in section 5.3 of the SmPC.

Considering the above, abiraterone should be used according to the precautions stated in the SmPC section 6.6 in order to minimise any potential risks to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2. Clinical Development Program for Prostate Cancer in mHSPC

Objective of Study	Study (Status)	Study Design	Study Population/Treatment Regimens	Participants Randomized
Pivotal study supporting the current mHSPC submission				
Pivotal efficacy and safety study of niraparib plus AAP compared to AAP alone in patients with deleterious germline or somatic HRR gene-mutated mHSPC	67652000PCR3002 AMPLITUDE (ongoing)	Phase 3, randomized, placebo-controlled, double-blind, multinational study to evaluate the safety and efficacy of nira+AAP versus AAP alone in men over the age of 18 years with deleterious germline or somatic HRR gene-mutated mHSPC	Participants with mHSPC with HRR gene alterations who previously received ≤6 cycles of docetaxel, 45 days of AAP, or 6 months of ADT Niraparib 200 mg and AA 1,000 mg as FDC, plus prednisone 5 mg Placebo and AA 1,000 mg plus prednisone 5 mg	696 All HRR 387 BRCA
Prior prostate cancer studies in mCRPC				
Pivotal efficacy & safety of niraparib and AAP combination therapy in mCRPC; primary ADR data for mCRPC indication	64091742PCR3001 MAGNITUDE (ongoing in long-term extension; final analysis complete)	Phase 3, randomized, placebo-controlled, multicenter, double-blind study to assess the efficacy and safety of niraparib in combination with AAP in men with mCRPC who previously received no prior treatment for mCRPC except for ≤4 months of AAP Cohort 1 provides the pivotal efficacy and safety data for combination treatment with niraparib & AAP Cohort 2: (men with mCRPC without HRR gene alterations) was terminated after a preplanned futility analysis was met. Cohort 3 provides a description of the clinical experience with the FDC tablet	Cohort 1: participants with mCRPC and HRR gene alterations Niraparib 200 mg and AAP (1,000 mg/10 mg) as SAC	423 All HRR 225 BRCA
			Cohort 2: participants with mCRPC and no HRR gene alterations Niraparib 200 mg and AAP (1,000 mg/10 mg) as SAC	247[1]
			Cohort 3: participants with mCRPC and HRR gene alterations Niraparib/AA (200 mg/1,000 mg) as FDC tablet plus prednisone (10 mg)	95 All HRR 52 BRCA

AA=abiraterone acetate; AAP=abiraterone acetate plus prednisone; ADR=adverse drug reaction; AR=androgen receptor; BRCA=breast cancer gene; FDC=fixed-dose combination; HRR=homologous recombination repair; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; rPFS=radiographic progression-free survival; RS=regular strength; SAC=single-agent combination; TEAE=treatment-emergent adverse event

Note: HRR gene alterations included BRCA1, BRCA2 (breast cancer gene 1, 2), BR1P1 (BRCA1 interacting protein C-terminal Helicase 1 gene), CDK-12 (cyclin-dependent kinase 12), CHEK2 (checkpoint kinase 2 gene), FANCA (Fanconi anemia complementation Group A gene), PALB2 (partner and localizer of BRCA2 gene), RAD51B (RAD51 paralog B), and RAD54L (RAD54-like.

[1] In MAGNITUDE Cohort 2, enrollment was stopped after futility was declared from a prespecified analysis. In total, 247 participants were randomized, and 246 participants were treated.

2.3.2. Pharmacokinetics

The updated clinical pharmacology assessments for the current submission include the PK as well as PopPK and exposure-response (ER) analysis results of the pivotal study AMPLITUDE, in support of the application for patients with deleterious germline or somatic HRR gene-mutated mHSPC.

Analytical methods

Method validation

In study AMPLITUDE (67652000PCR3002), niraparib and its major metabolite, M1, were analysed using two analytical LC-MS/MS methods: PRA-NL-SML-2194 and SHBTM-2077. These bioanalytical methods were developed and validated at PRA Health Sciences (Amerikaweg 18, 9407 TK Assen, The Netherlands) and Frontage Shanghai (1227 Zhangheng Road, Shanghai, Pilot Free Trade Zone, China), respectively. Cross-validation of the Frontage Shanghai method with the PRA/ICON method was performed.

The mentioned analytical methods can be found in the initial regulatory procedure (EMEA/H/C/005932).

Sample analysis (Study AMPLITUDE)

ICON Bioanalytical Laboratories

A total of 2266 human plasma samples for niraparib and M1 were analysed at ICON (former PRA Health Sciences, Assen, the Netherlands) according to method validation PRA-NL-SML-2194. Study samples were stored in a freezer at a nominal temperature between -55ºC and -90°C.

Sample analysis was carried out in 27 runs. One calibration curve and 4 QC levels were included in every run. Three runs (9, 10 and 13) were rejected for niraparib: QC acceptance criteria were not

met for these runs. All runs were accepted for Metabolite M1. Accuracy and precision of the accepted runs were within ±15% of the nominal value (±20% at the LLOQ).

Overall, 10 niraparib and 4 M1 samples were re-assayed due to the following reasons: No internal standard response was obtained, inadequate internal standard response, and poor chromatography.

Incurred sample reanalysis was performed in 4 runs with 168 samples per analyte and the percent difference in more than 67% of the samples were within ±20%.

Frontage Laboratories

A total of 365 samples were analysed in accordance with method validation SHBTM-2077. All samples were received frozen and were stored at -70°C.

The total duration of sample storage (from first sample collection to the last sample analysed) was 671 days (validated long-term stability is 765 days at -70ºC).

Frontage sample analysis was carried out in 3 runs. All runs were accepted. One calibration curve and 4 QC levels (4 replicates of each level, 2 for run 5) were included in every run. Accuracy and precision of the accepted runs were within ±15% of the nominal value (±20% at the LLOQ).

No re-assayed samples occurred.

Incurred sample reanalysis was performed in 2 runs with 30 samples per analyte and the percent difference in more than 67% of the samples were within ±20%.

Target population

AMPLITUDE study

Study 67652000PCR3002 (AMPLITUDE) is an ongoing, randomized, double-blind, placebo-controlled, multinational Phase 3 interventional study to evaluate the safety and efficacy of nira+AAP compared with PBO+AAP in men over the age of 18 years with deleterious germline or somatic HRR gene-mutated mHSPC receiving ADT (ie, GnRHa [agonist or antagonist], or surgical castration).

A total of 696 men with mHSPC were enrolled in the study with 348 participants randomly assigned to each treatment arm (nira+AAP or PBO+AAP). Treatment was administered once daily and was continuous; a treatment cycle was defined as 28 days.

Study treatment administered

AMPLITUDE used the approved dose of niraparib and abiraterone acetate (AKEEGA SmPC, USPI 2024). The dose of prednisone in the study was consistent with the approved dosing for AAP in mCSPC (ZYTIGA SmPC 2024, ZYTIGA USPI 2024).

Low-strength FDC (niraparib 50 mg/AA 500 mg per tablet) and single-agent niraparib (or placebo) were provided when applicable to allow for dose reduction as for management of TEAEs.

PK sampling

Plasma samples for analysis of niraparib concentrations were collected at predose and at 1 to 3 hours postdose on Day 1 of Cycles 2 and 3, and at predose or ≥3 hours postdose on Day 1 of Cycles 4 to 7.

Results

Table 3. Summary of Plasma Niraparib Concentrations (ng/mL) for Cycles 2 Through 7 by Treatment; AMPLITUDE PK Analysis Set

	Nira + AAP
Analysis set: PK	335
C2D1, PREDOSE	
N	297
Mean (SD)	427.2 (259.55)
Median	376.0
CV (%)	61
IQ range	(266.0; 539.0)
Range	(9; 1910)
C2D1, 1 TO 3H POSTDOSE	
N	292
Mean (SD)	591.3 (291.06)
Median	563.0
CV (%)	49
IQ range	(394.0; 741.5)
Range	(10; 1860)
C3D1, PREDOSE	
N	290
Mean (SD)	392.1 (220.69)
Median	350.0
CV (%)	56
IQ range	(255.0; 485.0)
Range	(5; 1720)
C3D1, 1 TO 3H POSTDOSE	
N	298
Mean (SD)	559.6 (264.36)
Median	543.0
CV (%)	47
IQ range	(373.0; 717.0)
Range	(8; 1650)
C4D1, PREDOSE	
N	258
Mean (SD)	375.6 (246.53)
Median	337.5
CV (%)	66
IQ range	(229.0; 504.0)
Range	(5; 1990)
C4D1, >=3H POSTDOSE	
N	45
Mean (SD)	568.6 (271.09)
Median	495.0
CV (%)	48
IQ range	(446.0; 730.0)
Range	(6; 1410)
C5D1, PREDOSE	
N	232
Mean (SD)	324.8 (186.10)
Median	304.0
CV (%)	57
IQ range	(211.0; 410.5)
Range	(5; 1360)
C5D1, >=3H POSTDOSE	
N	54
Mean (SD)	497.6 (226.32)
Median	492.0
CV (%)	45
IQ range	(363.0; 618.0)
Range	(11; 1050)
C6D1, PREDOSE	
N	238
Mean (SD)	328.6 (157.01)
Median	322.0
CV (%)	48
IQ range	(215.0; 414.0)
Range	(5; 905)
C6D1, >=3H POSTDOSE	
N	52
Mean (SD)	539.6 (248.29)
Median	508.5

Population PK modeling

The objective of the PopPK analysis was to characterize the PK of niraparib in participants in the AMPLITUDE study.

The data used in the PopPK analyses were obtained from the AMPLITUDE study.

The PK of niraparib was evaluated in the AMPLITUDE study, while the PK of abiraterone was not evaluated.

Analysis dataset

The analysis datafile included a total of 2,551 niraparib PK samples from 340 adult participants with mHSPC from the AMPLITUDE study (Table *4*). Of those 340 participants, 6 (1.8%) participants contributed only with dosing records but no observation records.

Table 4. Summary of Doses and Observations Excluded From the PopPK Analysis by Reason for Exclusion

Record Type	Reasons	Records Affected	Records Remaining	Participants Affected	Participants Remaining
Dose	All Doses	NA	5,987	NA	347
	Dose_Date/Time_Incomplete	8	5,979	7	340
Observation [a]	All Samples	NA	2,551	NA	340
	Not_Done (missing)	160	2,391	73	334
	Sample_Date/Time_Incomplete	1	2,390	1	334
	BQL	49	2,341	39	334
	Outlying_observation[b]	10	2,331	8	334

BQL=below quantification limit; NA=not applicable; PK=pharmacokinetic(s); PopPK=population PK.
[a] Niraparib concentration.
[b] See Section 5.1.1.

A summary of the covariates (identified in the previous PopPK model) in the current PopPK analysis dataset is provided in 5 and Table6*5*.

Table 5. Summary of Baseline Covariates Included in the PopPK Analysis (Study AMPLITUDE)

Variable	Labels	Value
N		340
Categorical		
HRR gene mutation group, n(%)	BRCA1 or BRCA2	187 (55)
	Other	153 (45)
	N missing (%)	0 (0)
Race, n(%)	White, not Hispanic or Latino	199 (58.5)
	White, Hispanic or Latino	30 (8.8)
	Asian	74 (21.8)
	Other	37 (10.9)
	N missing (%)	0 (0)
CRCL category, n(%)	CRCL ≥ 90 (mL/min)	158 (46.5)
	60 ≤ CRCL <90 (mL/min)	128 (37.6)
	30 ≤ CRCL <60 (mL/min)	52 (15.3)
	15 ≤ CRCL <30 (mL/min)	2 (0.6)
	CRCL <15 (mL/min)	0 (0)
	N missing (%)	0 (0)
Continuous		
CRCL (mL/min)	Mean (SD)	90.6 (30.8)
	Median	86.6
	Range	(19.6; 198)

BRCA=breast cancer gene; CRCL=creatinine clearance; HRR=homologous recombination repair; N=number of participants; n=number of participants in the specified category; PK=pharmacokinetic(s); PopPK=population PK; SD=standard deviation.

Table 6. Summary of Time-varying Covariate Formulation in the PopPK Analysis Dataset

Niraparib Formulation	Observations n(%)	Participants[a] n(%)
Capsule	25 (1.1)	7 (2.1)
FDC tablet regular strength (500 AA/100 niraparib)	2,084 (89.4)	330 (98.8)
FDC tablet low strength (500 AA/50 niraparib)	222 (9.5)	66 (19.8)
Total	2,331	334

AA=abiraterone acetate; FDC=fixed dose combination; PopPK=population pharmacokinetics
[a] Some participants switched formulations during the study; these study participants are counted for each formulation that they were treated with.

Previously, a PopPK analysis on niraparib was conducted including pooled PK data from participants with mCRPC enrolled in 5 clinical studies (64091742PCR1001, 64091742PCR2001, 64091742PCR2002, 67652000PCR1001, and MAGNITUDE). The PK of niraparib in mCRPC patients was adequately described by an open 2-compartment disposition model with linear elimination from central compartment and sequential zero-order input into the depot compartment and first-order absorption from depot to central compartments. The model was parameterized in terms of clearance and volumes. IIV was estimated on KA, CL/F, V3/F, D1, and F1. Two residual error models were introduced: 1 for rich PK sampling and 1 for sparse PK sampling. The identified covariate effects on PK model parameters were:

- FDC-LS on D1 and on F1 (12% and 13% decrease versus SAC, respectively).
- CRCL on CL/F (19% decrease when halving CRCL).

- HRR-negative on CL/F and HRR-positive non-BRCA on CL/F (12% and 8% decrease versus HRR-positive BRCA1 or BRCA2, respectively).
- Other races (ie, races other than White, Asian, or Hispanic/Latino) on KA and Hispanic/Latino race on KA (36% and 33% decrease versus White or Asian race, respectively).
- Asian race on Q/F and V3/F (39% decrease and 48% increase versus non-Asian race, respectively).

None of the covariates were deemed clinically relevant and therefore, no niraparib dose adjustment based on these covariates is warranted in mCRPC patients. The parameters of the previous niraparib PopPK model are summarized in Table *7*.

Table 7. Parameter Estimates in the Previously Developed Niraparib PopPK Model

Parameter	Estimate [a]
KA (1/h)	0.834 (6.46)
Other races on KA (vs White or Asian race)	-0.359 (16.2)
Hispanic/Latino race on KA (vs White or Asian race)	-0.334 (25.9)
CL/F (L/h)	16.7 (2.22)
CRCL on CL/F	0.305 (11.5)
HRR-negative on CL/F (vs HRR-positive BRCA1 or BRCA2)	-0.115 (22.0)
HRR-positive non-BRCA on CL/F (vs HRR-positive BRCA1 or BRCA2)	-0.0792 (34.1)
V2/F (L)	386 (4.30)
V3/F (L)	731 (5.03)
Asian race on V3/F (vs non-Asian race)	0.483 (31.9)
Q/F (L/h)	60.5 (6.13)
Asian race on Q/F (vs non-Asian race)	-0.389 (38.8)
D1 (h)	1.33 (3.22)
FDC-LS on D1 (vs SAC)	-0.118 (46.6)
F1 single-agent capsule	1 FIX
FDC-LS on F1 (vs SAC)	-0.131 (20.8)
IIV KA	0.364 (14.1) [47]
IIV CL/F	0.0683 (11.4) [26]
IIV V2/F	0 FIX
IIV V3/F	0.184 (13.5) [50]
IIV Q/F	0 FIX
IIV D1	0.530 (11.4) [42]
IIV F1	0.103 (8.39) [20]
Residual error rich PK sampling	0.0478 (6.34)
Residual error sparse PK sampling	0.117 (6.48)

BRCA=breast cancer gene; CL/F=oral clearance; CRCL=creatinine clearance; D1=duration of zero-order drug release; F1=apparent relative oral bioavailability; FDC-LS=low strength fixed-dose combination; HRR=homologous recombination repair; IIV=interindividual variability; KA=first-order absorption rate constant; NONMEM=nonlinear mixed effects modeling; PK=pharmacokinetic(s); PopPK=population PK; Q/F=apparent intercompartmental clearance; RSE=residual standard error; SAC=single-agent combination; V2/F=apparent volume of distribution of the central compartment; V3/F=apparent volume of distribution of the peripheral compartment; vs=versus.

[a] For (RSE%) [Shrinkage %] estimates by NONMEM. IIV and residual error, 100×sqrt(exp(var)-1), where var represents the variance estimate for the log-normally distributed random effects and residual errors. Participants who did not have observations and hence had estimated random effects equal to 0 were removed from shrinkage calculation.

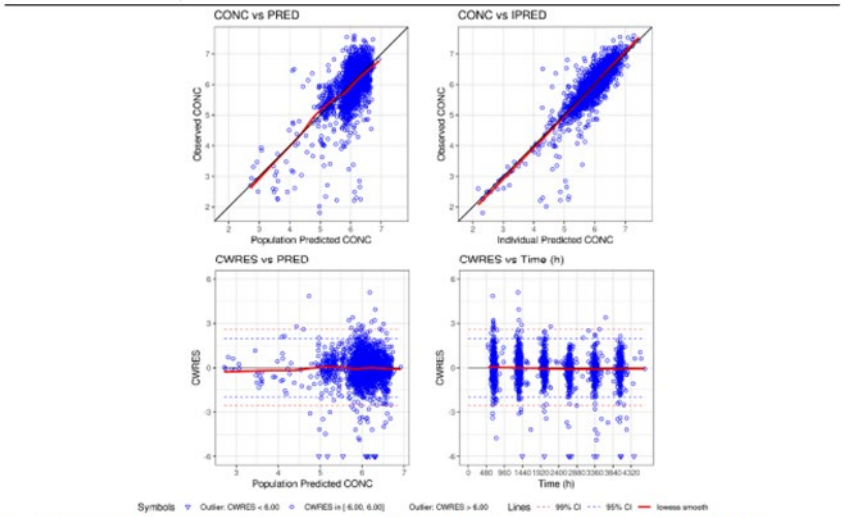
External evaluation

It was assumed that the disease state in prostate cancer would not affect the niraparib PK, and similar niraparib PK profiles were expected between participants with mHSPC and mCRPC. To confirm the assumption, an external evaluation using the previously developed model was performed to estimate post hoc individual parameters in participants with mCSPC in the AMPLITUDE study.

A "maximum a posteriori" (MAP) estimation was used to estimate the individual parameters for participants in the AMPLITUDE study. This analysis was conducted using the MAXEVAL=0 option in NONMEM.

The *Goodness-of-fit (*GOF) plots are shown in Figure *1*.

Figure 1. Goodness-of-fit Plots (Initial External Evaluation run05e_pcr3002, Including Outlier Data Points)



CI=confidence interval; CONC=concentration; CWRES=conditional weighted residual; IPRED=individual predictions; lowess=locally weighted scatterplot smoothing; PRED=population predictions; SD=standard deviation.; vs=versus.

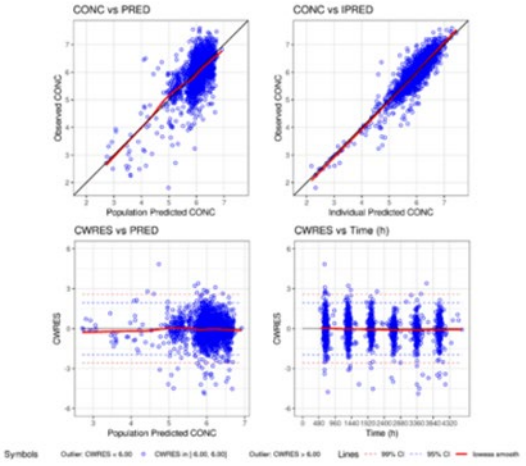
Units: observations or predictions=log ng/mL.

The black solid lines indicate the line of identity or the zero line. The blue and red dashed lines indicate 95% and 99% CI for a normally-distributed mean=0 and SD=1, respectively, and the red solid lines indicate the lowess smoothing line. The blue circles indicate observations. The time since first dose was used for CWRES vs TIME plot.

Data points with population prediction ≥15 ng/mL are excluded; 49 data points (out of total 2,341, ie, 2.1%) not shown for reasons of readability.

A total of 10 (0.4%) observations were identified as outliers (|CWRES| >6) following the external evaluation. Using the final analysis dataset excluding the outlier data points, the external evaluation was repeated. The GOF plots are shown in Figure 2. The pcVPC plots show that the model adequately captured the central tendency and the variability of the data, as attested by the general agreement between 5th, 50th, and 95th percentiles of the observed data and the respective 95% CIs obtained from the simulation (Figure 3).

Figure 2. Goodness-of-fit Plots for the Final External Evaluation Run run05e_pcr3002_noout)



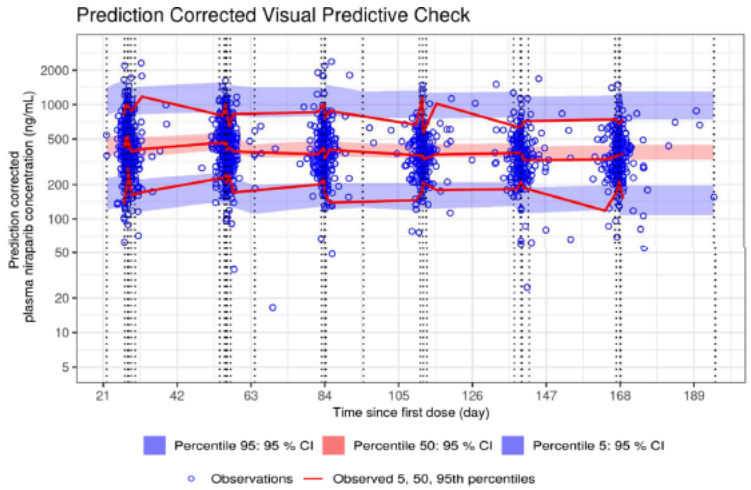
CI=confidence interval; CONC=concentration; CWRES=conditional weighted residual; IPRED=individual predictions; lowess=locally weighted scatterplot smoothing; PRED=population predictions; SD=standard deviation.; vs=versus.

Units: observations or predictions=log ng/mL.

The black solid lines indicate the line of identity or the zero line. The blue and red dashed lines indicate 95% and 99% CI for a normally-distributed mean=0 and SD=1, respectively, and the red solid lines indicate the lowess smoothing line. The blue circles indicate observations. The time since first dose was used for CWRES vs TIME plot.

Data points with population prediction ≥15 ng/mL are excluded; 49 data points (out of total 2,341, ie, 2.1%) not shown for reasons of readability.

Figure 3. Prediction-corrected Visual Predictive Check for the External Evaluation of the Previous Niraparib PopPK Model on Data From Participants With mCSPC (AMPLITUDE Study) (run05e_pcr3002_noout)



CI=confidence interval; mCSPC=metastatic castration-sensitive prostate cancer; PopPK=population pharmacokinetics.

Blue open circles and red solid lines indicate the observed data and the 5th, 50th, and 95th percentile lines. Blue and red ribbons indicate 95% CI of the 5th, 50th, and 95th percentiles of the simulated data. Vertical dotted lines indicate time bins used to calculate the percentiles. A total of 500 simulation replicates were generated to obtain the CIs.

Individual Steady-state Exposure Parameters for Niraparib

The descriptive statistics of the individual AUC0-24h,ss, Cavg,ss, Ctrough,ss, Cmax,ss, and terminal t1/2 in the participants with mCSPC in AMPLITUDE study, assuming the nominal 200 mg QD niraparib dose (Table *8*).

Table 8. Summary of Individual Steady-state Exposure Metrics Based on the Niraparib PopPK Model in Participants With mCSPC (AMPLITUDE study)

Parameter[a]	N[b]	Mean	SD	CV%	Min	5th%	Median	95th%	Max
$AUC_{0\text{-}24\ h,ss}$ (ng.h/mL)	334	12,814	4,651	36.3	4,057	7,059	12,067	21,301	39,597
$C_{avg,ss}$ (ng/mL)	334	534	194	36.3	169	294	503	888	1,649
$C_{max,ss}$ (ng/mL)	334	728	226	31.0	291	440	696	1,140	1,943
$C_{trough,ss}$ (ng/mL)	334	416	171	41.1	102	210	387	733	1,419
Terminal $t_{1/2}$ (h)	334	62.7	19.5	31.1	32.8	39.8	57.4	95.9	182

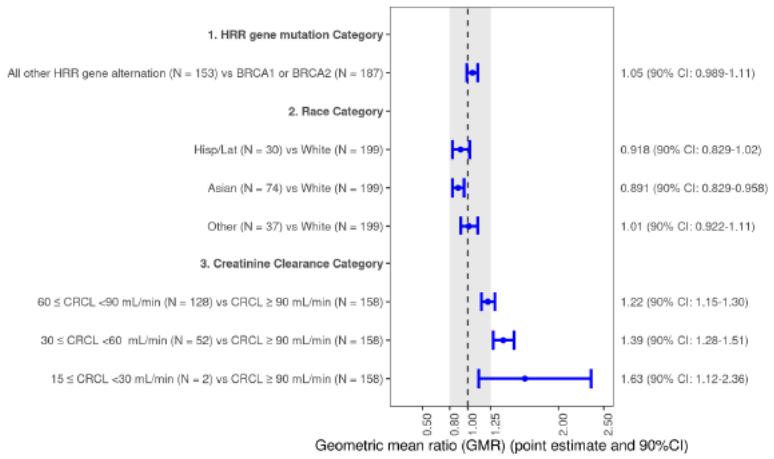
5th%=5th percentiles of the data; 95th%=95th percentiles of the data;$AUC_{0\text{-}24\ h,ss}$=area under the concentration-time curve during 24 hours after dose at steady-state; $C_{avg,ss}$=average plasma concentration at steady-state (calculated as $AUC_{0\text{-}24\ h,ss}$/24); $C_{max,ss}$=maximum plasma concentration at steady-state; $C_{trough,ss}$=plasma concentration at the end of a dose interval at steady-state; CV%=percentage coefficient of variation (ie, SD/mean×100); Max=maximum; mCSPC=metastatic castration-sensitive prostate cancer; Min=minimum; PK=pharmacokinetic(s); PopPK=population PK; QD=once a day; SD=standard deviation; $t_{1/2}$=half-life.

[a] Calculated based on the nominal 200 mg QD niraparib dose using the formulation used on Day 1 per participant.

[b] Derived values for participants with available observed concentration data are included in the summary.

Effects of the PK covariates were illustrated by a forest plot (Figure *4*).

Figure 4. Forest Plot Showing Extent of Covariate Effects on Cavg for the PopPK Analysis Dataset, Based on the Previously Developed PopPK Model



$AUC_{0\text{-}24h,ss}$=area under the curve during 24 hours dose interval at steady-state; BRCA=breast cancer gene; $C_{avg,ss}$=average plasma concentration at steady state (calculated as $AUC_{0\text{-}24h,ss}$/24); CI=confidence interval; CRCL=creatinine clearance; GMR=geometric mean ratio; Hisp/Lat=Hispanic/Latino race; HRR=homologous recombination repair; N=number of participants; PK= pharmacokinetic(s); QD=once daily; vs=versus.
All participants were assumed to receive niraparib 200 mg QD. Vertical dashed line represents the GMR of exposure at the reference level or category (=1) and the gray shaded region represents the equivalence range of 0.8 to 1.25, which translates to 20% difference from the reference level on the normal scale. The forest plot is based on multivariate regression model analysis.
It should be noted that the number of participants with creatinine clearance category 15 ≤ CRCL <30 mL/min was limited (N=2).
The effect of time-varying covariate formulation is not presented in the plot.

2.3.3. Pharmacodynamics

Not applicable.

2.3.4. PK/PD modelling

The ER analysis population is summarized in Table 8. In total, 688 participants with mCSPC (340 received niraparib and 348 received placebo) in the AMPLITUDE study were included in the ER analyses. The exposure-efficacy analysis was performed for 3 prespecified subgroups:

1. All HRR: overall population.
2. BRCA: participants with BRCA1 or BRCA2 gene alterations.
3. HRR effectors: the HRR effectors group is composed of eligible genes that serve as immediate effectors of HRR at the site of DNA double strand breaks (BRIP1, PALB2, RAD51B, and RAD54L, in addition to BRCA1 and BRCA2).

Table 9. Summary of Participants Included in the ER Analysis (Study AMPLITUDE)

	Total N[a] (niraparib arm:placebo arm)	Reference
Exposure-efficacy	All HRR group: 688 (340[b]:348) BRCA group: 383 (187:196) HRR effectors group: 450 (224:226)	FAS: All HRR group: 696 (348:348) BRCA group: 387 (191:196) HRR effectors group: 456 (230:226)
Exposure-safety	688 (340:348)	Safety Analysis Set: 695 (347:348)

BRCA=breast cancer gene; PopPK=population pharmacokinetics; ER=exposure-response; FAS=full analysis set; HRR=homologous recombination repair; N=number of participants.
[a] Participants included in the ER analysis dataset.
[b] 8 participants excluded due to missing dose time record.

Exposure-efficacy analysis

Exposure-efficacy analysis on rPFS

The primary endpoint of the AMPLITUDE study, rPFS, was defined as the time interval from the date of randomization to the first date of radiographic progression as assessed by investigator or death due to any cause, whichever occurs first.

Summaries of daily average dose up to the time of the first event of rPFS, Cavg,ss,200 mg, and Cavg,ss,DAV by niraparib exposure quartile group are presented in Table 10.

Table 10. Summary of Average Daily Dose Up to the Time of First rPFS Event, Cavg,ss,200 and Cavg,ss,DAV by Niraparib Exposure Quartile Group for the Niraparib-treated Participants in the ER Analysis Dataset

Parameter	Group	N	Mean	SD	CV%	Min	Median	Max
Average daily dose (mg) [a]	Q1	85	127	53.7	53.7	8.79	111	200
	Q2	85	163	44.9	44.9	81.8	195	200
	Q3	85	178	33.4	33.4	94.1	197	200
	Q4	85	189	20.3	20.3	100	198	201
$C_{avg,ss,200mg}$ (ng/mL)	Q1	85	336	52.8	15.7	169	343	403
	Q2	85	453	28.0	6.19	405	448	503
	Q3	85	562	33.5	5.96	504	559	619
	Q4	85	786	183	23.3	620	725	1,650
$C_{avg,ss,DAV}$ (ng/mL)	Q1	85	243	67.4	27.7	27.1	259	318
	Q2	85	365	24.4	6.68	323	369	406
	Q3	85	450	25.8	5.74	406	447	499
	Q4	85	615	111	18.1	501	584	1,046

$C_{avg,ss,200mg}$=steady-state average concentration at nominal niraparib 200 mg; $C_{avg,ss,DAV}$=average plasma concentration of a dosing interval at steady corrected for the average daily dose up to the time of first rPFS event; CV=coefficient of variation; ER=exposure-response; Max=maximum; Min=minimum; N=number of participants; Q1=lowest exposure quartile; Q2=second exposure quartile; Q3=third exposure quartile; Q4=highest exposure quartile; rPFS=radiographic progression-free survival; SD=standard deviation.

[a] Average daily dose up to the time of first rPFS event.

The correlations between Cavg,ss,200 mg and Cavg,ss,DAV were not high ($r^2 \leq 0.8$) for rPFS; therefore, Cavg,ss,DAV was also used in the ER analysis as sensitivity analysis.

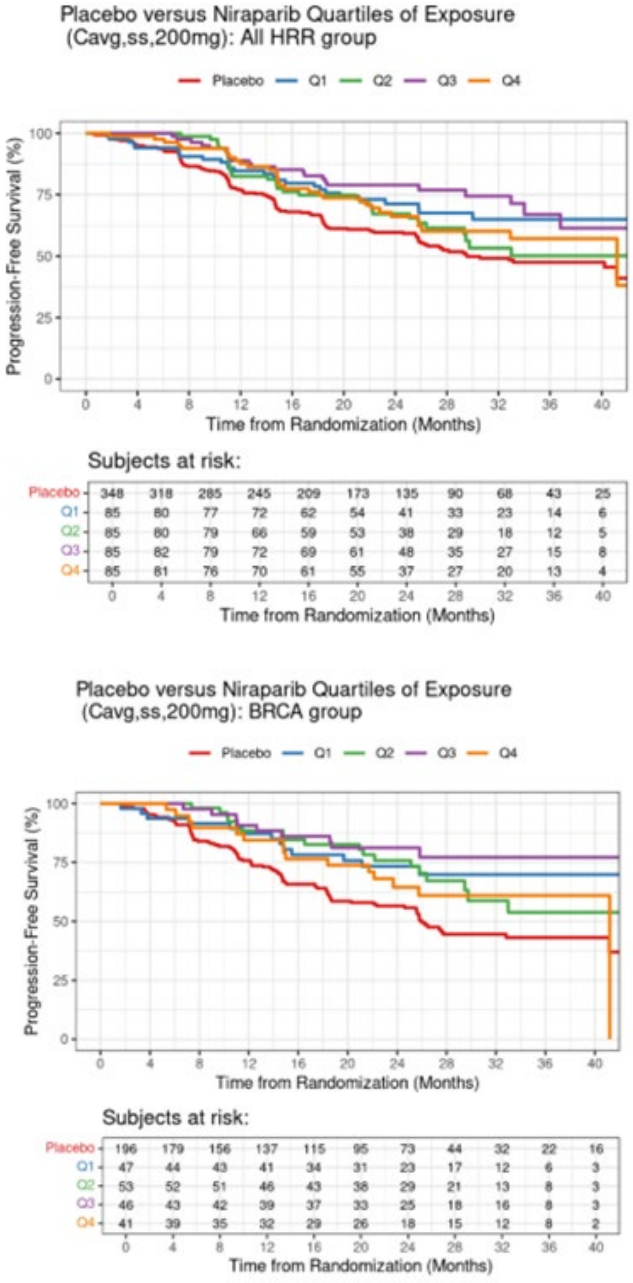
Summary statistics for the prognostic factors by treatment group and exposure quartile group are presented in Table 10.

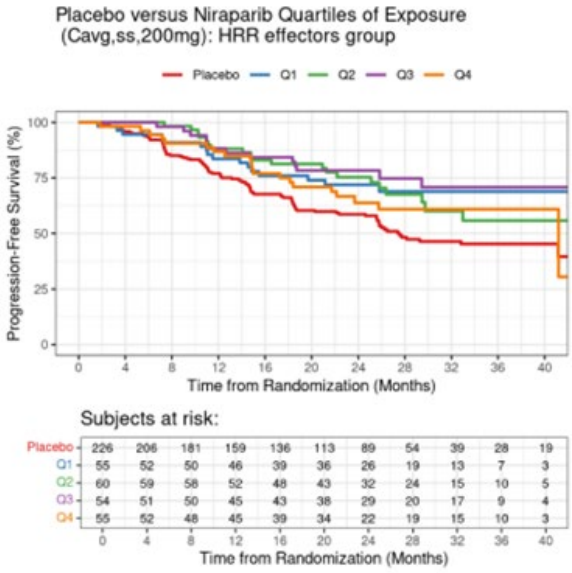
Table 11. Summary Statistics for Prognostic Factors by Treatment Group and Quartile of Niraparib Exposure (Cavg,ss,200mg) for the Participants in the ER Analysis Dataset

Variable	Labels	Placebo	Niraparib	Q1	Q2	Q3	Q4	Total
N		348	340	85	85	85	85	688
Baseline PSA above median, n(%)	No	166 (47.7)	177 (52.1)	37 (43.5)	45 (52.9)	45 (52.9)	50 (58.8)	343 (49.9)
	Yes	182 (52.3)	163 (47.9)	48 (56.5)	40 (47.1)	40 (47.1)	35 (41.2)	345 (50.1)
	N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Baseline LDH above median, n(%)	No	167 (48)	176 (51.8)	42 (49.4)	44 (51.8)	45 (52.9)	45 (52.9)	343 (49.9)
	Yes	179 (51.4)	162 (47.6)	43 (50.6)	41 (48.2)	39 (45.9)	39 (45.9)	341 (49.6)
	N missing (%)	2 (0.6)	2 (0.6)	0 (0)	0 (0)	1 (1.2)	1 (1.2)	4 (0.6)
Baseline ALP above median, n(%)	No	171 (49.1)	174 (51.2)	42 (49.4)	40 (47.1)	47 (55.3)	45 (52.9)	345 (50.1)
	Yes	176 (50.6)	166 (48.8)	43 (50.6)	45 (52.9)	38 (44.7)	40 (47.1)	342 (49.7)
	N missing (%)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Baseline pain score (BPI-SF Item 3), n(%)	0	152 (43.7)	147 (43.2)	31 (36.5)	44 (51.8)	36 (42.4)	36 (42.4)	299 (43.5)
	1 to 3	117 (33.6)	115 (33.8)	29 (34.1)	28 (32.9)	32 (37.6)	26 (30.6)	232 (33.7)
	>3	77 (22.1)	78 (22.9)	25 (29.4)	13 (15.3)	17 (20)	23 (27.1)	155 (22.5)
	N missing (%)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.3)
ECOG status, n(%)	Grade 0	218 (62.6)	239 (70.3)	60 (70.6)	58 (68.2)	59 (69.4)	62 (72.9)	457 (66.4)
	Grade ≥1	130 (37.4)	101 (29.7)	25 (29.4)	27 (31.8)	26 (30.6)	23 (27.1)	231 (33.6)
	N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total Gleason score, n(%)	≤7	68 (19.5)	57 (16.8)	12 (14.1)	12 (14.1)	17 (20)	16 (18.8)	125 (18.2)
	> 7	262 (75.3)	271 (79.7)	69 (81.2)	72 (84.7)	65 (76.5)	65 (76.5)	533 (77.5)
	Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N missing (%)	18 (5.2)	12 (3.5)	4 (4.7)	1 (1.2)	3 (3.5)	4 (4.7)	30 (4.4)
Volume of disease at screening, n(%)	Low	77 (22.1)	75 (22.1)	18 (21.2)	17 (20)	18 (21.2)	22 (25.9)	152 (22.1)
	High	271 (77.9)	265 (77.9)	67 (78.8)	68 (80)	67 (78.8)	63 (74.1)	536 (77.9)
	N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Baseline PSA (ng/mL)	Mean (SD)	38.4 (173)	58.9 (470)	55.3 (278)	38.9 (188)	30.5 (114)	111 (872)	48.5 (352)
	Median	3.56	2.79	4.08	2.83	3.1	1.77	3.3
	Range	(0.02; 2703)	(0.02; 8046)	(0.02; 2452)	(0.02; 1658)	(0.02; 844)	(0.02; 8046)	(0.02; 8046)
	N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Univariate Kaplan-Meier Analyses on rPFS

Figure 5. Kaplan-Meier Plot for rPFS Stratified by Niraparib Cavg,ss,200 mg Exposure Quartile Groups Versus Placebo Group (All HRR [Overall Population], BRCA, HRR effectors groups)





All HRR group=overall population; BRCA=breast cancer gene; BRCA group=participants with BRCA1 or BRCA2 gene alterations; $C_{avg,ss,200\ mg}$=steady-state average concentration at nominal niraparib 200 mg dose; HRR=homologous recombination repair; HRR effectors group=participants with eligible genes that serve as immediate effectors of HRR at the site of DNA double strand breaks (BRIP1, PALB2, RAD51B, RAD54L, in addition to BRCA1 and BRCA2); Q1=lowest exposure quartile; Q2=second exposure quartile; Q3=third exposure quartile; Q4=highest exposure quartile; rPFS=radiographic progression-free survival.

Multivariate Analysis on rPFS

Table 12. Summary of Influence of the Niraparib Exposure Metrics (Cavg,ss,200mg) on rPFS (Multivariate Cox Regression Model) (All HRR Group, BRCA Group, HRR Effectors Group)

Model	Parameters	HR (95% CI)	p-value	-2LL	VIF	AIC
All HRR:	Treatment (niraparib vs placebo)	0.627 (0.486-0.807)	0.0003	2,771	1.01	2,783
Model A	Baseline PSA[a]	1.07 (1.00-1.13)	0.039		1.3	
	Baseline ALP[a]	1.29 (1.10-1.50)	0.001		1.35	
	Pain score based on BPI-SF Item 3	1.07 (1.02-1.12)	0.005		1.04	
	Total Gleason score (≤7 vs >7)	0.62 (0.423-0.907)	0.014		1.02	
	Volume of disease (low vs high)	0.558 (0.375-0.831)	0.004		1.11	
Model B	Treatment (niraparib vs placebo)	0.603 (0.348-1.04)	0.07	2,771	4.71	2,785
	$C_{avg,ss,200mg}$	1.01 (0.921-1.10)	0.875		4.72	
	Baseline PSA[a]	1.07 (1.00-1.13)	0.038		1.31	
	Baseline ALP[a]	1.29 (1.10-1.50)	0.002		1.38	
	Pain score based on BPI-SF Item 3	1.07 (1.02-1.12)	0.005		1.05	
	Total Gleason score (≤7 vs >7)	0.62 (0.424-0.907)	0.014		1.02	
	Volume of disease (low vs high)	0.558 (0.374-0.83)	0.004		1.11	

Model C	$C_{avg,ss,200mg}$	0.933 (0.892-0.975)	0.002	2,775	1.01	2,787
	Baseline PSA[a]	1.06 (1.00-1.13)	0.049		1.29	
	Baseline ALP[a]	1.3 (1.12-1.52)	0.0007		1.34	
	Pain score based on BPI-SF Item 3	1.08 (1.02-1.13)	0.003		1.04	
	Total Gleason score (≤7 vs >7)	0.625 (0.427-0.914)	0.015		1.02	
	Volume of disease (low vs high)	0.562 (0.377-0.837)	0.005		1.11	
BRCA: Model A	Treatment (niraparib vs placebo)	0.487 (0.344-0.688)	<0.0001	1,426	1.01	1,440
	ECOG status (Grade 0 vs Grade ≥1)	0.719 (0.508-1.02)	0.064		1.03	
	Baseline PSA[a]	1.08 (1-1.16)	0.037		1.08	
	Baseline LDH[a]	1.87 (1-3.51)	0.05		1.03	
	Pain score based on BPI-SF Item 3	1.09 (1.02-1.16)	0.008		1.05	
	Total Gleason score (≤7 vs >7)	0.409 (0.225-0.744)	0.003		1.02	
	Volume of disease (low vs high)	0.573 (0.343-0.957)	0.033		1.07	
Model B	Treatment (niraparib vs placebo)	0.515 (0.205-1.3)	0.16	1,426	7.18	1,442
	$C_{avg,ss,200mg}$	0.989 (0.836-1.17)	0.895		7.18	
	ECOG status (Grade 0 vs Grade >=1)	0.719 (0.508-1.02)	0.064		1.03	
	Baseline PSA[a]	1.08 (1-1.16)	0.037		1.08	
	Baseline LDH[a]	1.88 (0.999-3.52)	0.05		1.03	
	Pain score based on BPI-SF Item 3	1.09 (1.02-1.16)	0.008		1.05	
	Total Gleason score (≤7 vs >7)	0.409 (0.225-0.743)	0.003		1.02	
	Volume of disease (low vs high)	0.573 (0.343-0.957)	0.033		1.07	
Model C	$C_{avg,ss,200mg}$	0.882 (0.825-0.941)	0.0002	1,428	1.01	1,442
	ECOG status (Grade 0 vs Grade ≥1)	0.72 (0.507-1.02)	0.065		1.04	
	Baseline PSA[a]	1.08 (1-1.16)	0.045		1.08	
	Baseline LDH[a]	1.92 (1.01-3.63)	0.046		1.03	
	Pain score based on BPI-SF Item 3	1.09 (1.02-1.16)	0.009		1.06	
	Total Gleason score (≤7 vs >7)	0.411 (0.226-0.747)	0.004		1.02	
	Volume of disease (low vs high)	0.563 (0.338-0.939)	0.028		1.06	
HRR effectors: Model A	Treatment (niraparib vs placebo)	0.56 (0.408-0.77)	0.0004	1,687	1.01	1,699
	Baseline PSA[a]	1.07 (0.989-1.15)	0.093		1.38	
	Baseline ALP[a]	1.24 (1.01-1.52)	0.043		1.47	
	Pain score based on BPI-SF Item 3	1.09 (1.03-1.16)	0.003		1.04	
	Total Gleason score (≤7 vs >7)	0.433 (0.249-0.754)	0.003		1.01	
	Volume of disease (low vs high)	0.584 (0.355-0.963)	0.035		1.13	
Model B	Treatment (niraparib vs placebo)	0.499 (0.221-1.13)	0.095	1,686	6.63	1,700
	$C_{avg,ss,200mg}$	1.02 (0.887-1.18)	0.761		6.61	
	Baseline PSA[a]	1.07 (0.99-1.15)	0.091		1.39	
	Baseline ALP[a]	1.24 (1.01-1.52)	0.043		1.47	
	Pain score based on BPI-SF Item 3	1.09 (1.03-1.16)	0.003		1.04	
	Total Gleason score (≤7 vs >7)	0.433 (0.249-0.754)	0.003		1.01	
	Volume of disease (low vs high)	0.586 (0.355-0.965)	0.036		1.13	
Model C	$C_{avg,ss,200mg}$	0.911 (0.86-0.966)	0.002	1,689	1.01	1,701
	Baseline PSA[a]	1.07 (0.988-1.15)	0.101		1.38	
	Baseline ALP[a]	1.23 (1-1.51)	0.044		1.46	
	Pain score based on BPI-SF Item 3	1.09 (1.03-1.16)	0.002		1.04	
	Total Gleason score (≤7 vs >7)	0.438 (0.252-0.761)	0.003		1.01	
	Volume of disease (low vs high)	0.577 (0.35-0.949)	0.03		1.12	

-2LL=-2loglikelihood; AIC=Akaike's information criterion; All HRR group=overall population; ALP=alkaline phosphatase; BRCA group=participants with BRCA1 or BRCA2 gene alterations; $C_{avg,ss,200mg}$=steady-state average concentration at nominal niraparib 200 mg dose; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; HRR effectors group=participants with eligible genes that serve as immediate effectors of HRR at the site of DNA double strand breaks (BRIP1, PALB2, RAD51B, RAD54L, in addition to BRCA1 and BRCA2); LDH=lactate dehydrogenase; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival; VIF=variance inflation factor; vs=versus.

[a] Continuous natural log-transformed.

The treatment effect and all the prognostic factors identified were incorporated simultaneously in the model (Model A). In Model B, niraparib exposure as continuous variable was added to Model A. In Model C, the treatment effect was removed from Model B.

Exposure-safety analysis

Based on the safety profile of niraparib and AA in patients with mCRPC (the MAGNITUDE study), Grade ≥3 anemia and hematological toxicity (anemia, thrombocytopenia, or neutropenia) were prespecified in the analysis plan. In addition, hypertension was included in the analysis, based on the prespecified criteria: (1) Grade ≥3 events with an overall incidence of ≥10% and (2) significant

difference between the incidences in the niraparib arm versus the placebo arm (nominal p<0.05). No other TEAE met the above-mentioned criteria. The selected TEAEs were dichotomized into presence or absence of the AEs, and the participants with multiple occurrences of events were only counted once, including the first event.

The purpose of the exposure-safety analysis was to assess the relationship between niraparib exposure and the incidence of the selected TEAEs (Grade ≥3 anemia, hematological toxicity, and hypertension) in the AMPLITUDE study.

Table 13. Distribution of TEAEs by Treatment Group and by Niraparib Cavg,ss,200mg Exposure Quartile Group for the ER Analysis Dataset

Categories	N	Anemia: n(%)	Hematological toxicity: n(%)	Hypertension: n(%)	Hypokalemia: n(%)
Overall	688	115 (16.7)	150 (21.8)	157 (22.8)	78 (11.3)
Placebo	348	16 (4.6)	22 (6.32)	64 (18.4)	38 (10.9)
Niraparib	340	99 (29.1)	128 (37.6)	93 (27.4)	40 (11.8)
Q1 - $C_{avg,ss,200mg}$	85	10 (11.8)	14 (16.5)	26 (30.6)	11 (12.9)
Q2 - $C_{avg,ss,200mg}$	85	21 (24.7)	26 (30.6)	25 (29.4)	9 (10.6)
Q3 - $C_{avg,ss,200mg}$	85	24 (28.2)	36 (42.4)	22 (25.9)	10 (11.8)
Q4 - $C_{avg,ss,200mg}$	85	44 (51.8)	52 (61.2)	20 (23.5)	10 (11.8)

$C_{avg,ss,200\ mg}$=steady-state average concentration at nominal niraparib 200 mg dose; N=number of subjects; n=number of subjects with an event; Q1=lowest exposure quartile; Q2=second exposure quartile; Q3=third exposure quartile; Q4=highest exposure quartile.

Table 14. Distribution of TEAEs by Treatment Group and by Niraparib Cavg,ss,DAV Exposure Quartile Group for the ER Analysis Dataset

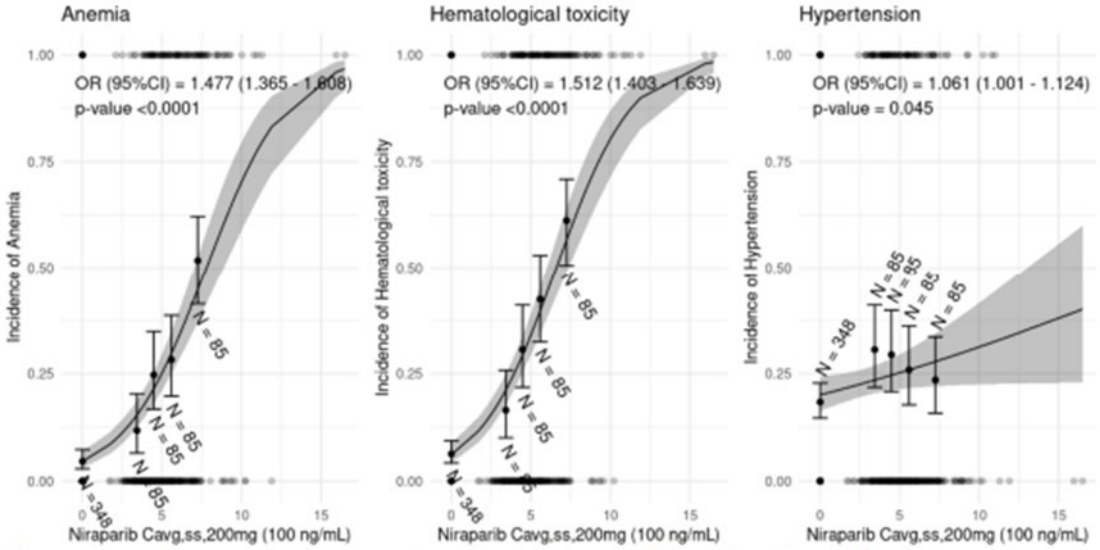
Categories	N	Anemia: n(%)	Hematological toxicity: n(%)	Hypertension: n(%)	Hypokalemia: n(%)
Overall	688	115 (16.7)	150 (21.8)	157 (22.8)	78 (11.3)
Placebo	348	16 (4.6)	22 (6.32)	64 (18.4)	38 (10.9)
Niraparib	340	99 (29.1)	128 (37.6)	93 (27.4)	40 (11.8)
Q1 - $C_{avg,ss,DAV}$	85	9 (10.6)	15 (17.6)	16 (18.8)	12 (14.1)
Q2 - $C_{avg,ss,DAV}$	85	19 (22.4)	25 (29.4)	22 (25.9)	4 (4.71)
Q3 - $C_{avg,ss,DAV}$	85	27 (31.8)	35 (41.2)	28 (32.9)	10 (11.8)
Q4 - $C_{avg,ss,DAV}$	85	44 (51.8)	53 (62.4)	27 (31.8)	14 (16.5)

$C_{avg,ss,DAV}$=average plasma concentration of a dosing interval at steady corrected for the average daily dose up to first event of interest; N=number of subjects; n=number of subjects with an event; Q1=lowest exposure quartile; Q2=second exposure quartile; Q3=third exposure quartile; Q4=highest exposure quartile.

Univariate and Multivariate Logistic Regression Analysis

Results of the univariate logistic regression showed that the probability of experiencing Grade ≥3 anemia and hematological toxicity increases with increasing niraparib exposure (Cavg,ss,200 mg) (Figure 6). In the multivariate logistic regression analyses, niraparib exposure (Cavg,ss,200 mg) was identified as a statistically significant predictor for anemia and hematological toxicity in the models with (Model A) or without (Model B) the treatment effect (Table 14).

Figure 6. Logistic Regression Representing the Probability of Experiencing Grade ≥3 Anemia, Hematological Toxicity, and Hypertension as a Function of Niraparib Cavg,ss,200 mg

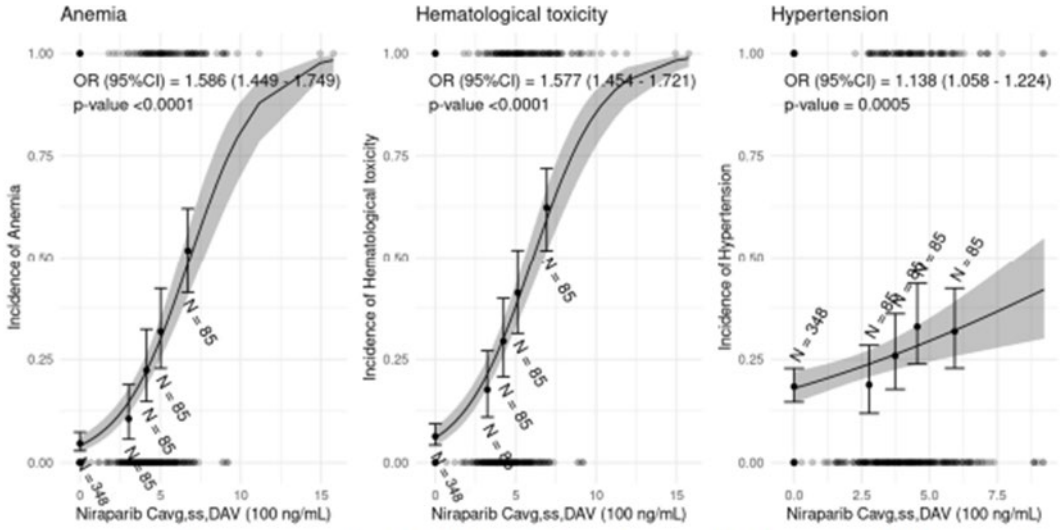


$C_{avg,ss,200\ mg}$=steady-state average concentration at nominal niraparib 200 mg dose; CI=confidence interval; N=number of participants; OR=odds ratio; TEAE=treatment-emergent adverse event.

The upper and lower open circles represent the presence (value=1) or absence (value=0) of a given TEAE across the range of the niraparib $C_{avg,ss,200\ mg}$. The dots depict the observed incidence for the placebo and the niraparib $C_{avg,ss,200\ mg}$ quartile groups (printed at median values), whereas the corresponding vertical bars represent the exact 95% CI calculated using Wilson's method. Finally, the middle line and its corresponding shaded area represent the model-based exposure-safety relationship and the 95% CI respectively.

Unit for odds ratio: per niraparib 100 ng/mL.

Figure 7. Logistic Regression Representing the Probability of Experiencing Grade ≥3 Anemia, Hematological Toxicity, and Hypertension as a Function of Niraparib Cavg,ss,DAV



$C_{avg,ss,DAV}$=average plasma concentration of a dosing interval at steady corrected for the average daily dose up to first event of interest; CI=confidence interval; N=number of participants; OR=odds ratio; TEAE=treatment-emergent adverse event.

The upper and lower open circles represent the presence (value =1) or absence (value=0) of a given TEAE across the range of the niraparib $C_{avg,ss,DAV}$. The dots depict the observed incidence for the placebo and the niraparib $C_{avg,ss,DAV}$ quartile groups (printed at median values), whereas the corresponding vertical bars represent the exact 95% CI calculated using Wilson's method. Finally, the middle line and its corresponding shaded area represent model-based exposure-safety relationship and the 95% CI respectively.

Unit for odds ratio: per niraparib 100 ng/mL

Table 15. Multivariate Logistic Regression Analyses for Grade ≥3 Anemia, Hematological Toxicity, and Hypertension Using Cavg,ss,200 mg as Exposure Metric

Model	Variable	OR (95% CI) (Unit: per niraparib 100 ng/mL)	p-value	-2LL	VIF
Anemia					
Model A	Treatment (niraparib vs placebo)	1.035 (0.391, 2.824)	0.946	505	3.1
	$C_{avg,ss,200\ mg}$ (per 100 ng/mL)	1.483 (1.291, 1.723)	<0.0001		
Model B	$C_{avg,ss,200\ mg}$ (per 100 ng/mL)	1.477 (1.365, 1.608)	<0.0001	505	
Hematological toxicity					
Model A	Treatment (niraparib vs placebo)	1.178 (0.469, 3.075)	0.732	572	3.65
	$C_{avg,ss,200\ mg}$ (per 100 ng/mL)	1.545 (1.341, 1.802)	<0.0001		
Model B	$C_{avg,ss,200\ mg}$ (per 100 ng/mL)	1.512 (1.403, 1.639)	<0.0001	572	
Hypertension					
Model A	Treatment (niraparib vs placebo)	0.419 (0.191, 0.902)	0.028	730	4.61
	$C_{avg,ss,200\ mg}$ (per 100 ng/mL)	0.935 (0.815, 1.061)	0.315		
Model B	$C_{avg,ss,200\ mg}$ (per 100 ng/mL)	1.061 (1.001, 1.124)	0.045	735	

-2LL=-2loglikelihood; Cavg,ss,200 mg=steady-state average concentration at nominal niraparib 200 mg dose; CI=confidence interval; OR=odds ratio; VIF=variance inflation factor; vs=versus.
The treatment effect and all the prognostic factors identified were incorporated simultaneously in the model (Model A). In Model B, niraparib exposure as a continuous variable was added to Model A. In Model C, the treatment effect was removed from Model B.

Table 16. Multivariate Logistic Regression Analyses for Grade ≥3 Anemia, Hematological Toxicity, and Hypertension Using Cavg,ss,DAV as Exposure Metric

Model	Variable	OR (95% CI) (Unit: per niraparib 100 ng/mL)	p-value	-2LL	VIF
Anemia					
Model A	Treatment (niraparib vs placebo)	1.643 (0.596 - 4.723)	0.345	491	3.37
	$C_{avg,ss,DAV}$ (per 100 ng/mL)	1.695 (1.441 - 2.021)	<0.0001		
Model B	$C_{avg,ss,\ DAV}$ (per 100 ng/mL)	1.586 (1.449 - 1.749)	<0.0001	492	.
Hematological toxicity					
Model A	Treatment (niraparib vs placebo)	1.428 (0.561 - 3.796)	0.464	564	3.75
	$C_{avg,ss,DAV}$ (per 100 ng/mL)	1.659 (1.421 - 1.965)	<0.0001		
Model B	$C_{avg,ss,\ DAV}$ (per 100 ng/mL)	1.577 (1.454 - 1.721)	<0.0001	565	.
Hypertension					
Model A	Treatment (niraparib vs placebo)	1.265 (0.580 - 2.821)	0.559	727	4.74
	$C_{avg,ss,DAV}$ (per 100 ng/mL)	1.187 (1.014 - 1.391)	0.033		
Model B	$C_{avg,ss,\ DAV}$ (per 100 ng/mL)	1.138 (1.058 - 1.224)	0.0005	727	.

$C_{avg,ss,DAV}$=average plasma concentration of a dosing interval at steady corrected for the average daily dose up to first event of interest; CI=confidence interval; OR=odds ratio; VIF=variance inflation factor; vs=versus; -2LL=-2loglikelihood.

2.3.5. Discussion on clinical pharmacology

Clinical pharmacology data is based on the new PK data of the pivotal study AMPLITUDE in patients with mHSPC and HRR gene alterations and a population PK and exposure-response analysis based on the pivotal study to support the proposed indication and posology.

In this procedure, sample analysis was carried out to quantify niraparib and its major metabolite, M1 in samples from study AMPLITUDE. Two different analytical methods were employed (PRA-NL-SML-2194 and SHBTM-2077) as samples were analysed in two different laboratories (ICON

Bioanalytical laboratories and Frontage laboratories). The validation of these analytical methods as well as the cross-validation between them, were previously assessed and found acceptable in the initial procedure (EMEA/H/C/005932).

Sample analysis was assessed and considered consistent with the validated analytical methods and complies with the ICHM10 Guideline on bioanalytical method validation and study sample analysis (EMA/CHMP ICH/172948/2019).

Sparse sampling for niraparib PK was performed in the AMPLITUDE study before the first dose and 1 to 3 hours postdose on day 1 of cycles 2 and 3 and at ≥3 hours postdose on Day 1 of Cycles 4 to 7. Therefore, it was not possible to perform non compartmental analysis (NCA).

A previous population PK analysis was developed for niraparib based on a pooled dataset from five studies, which includes data of niraparib as monotherapy from phase 2 study GALAHAD, data of niraparib in combination with abiraterone acetate from phase 1b BEDIVERE study, phase 1b-2 QUEST study, FDC BA/BE study, and phase 3 MAGNITUDE study with patients with mCRPC. Considering that the proposed indication is not dissimilar to the approved indication in patients with mCRPC, and that the dosage and dosing intervals are the same, it can be acceptable to perform an external evaluation using the previous model to estimate post hoc individual parameters in participants with mHSPC in the AMPLITUDE study to confirm this assumption. Overall, GOF showed agreement between observed concentration and population predicted concentration and observed concentration and individual predicted concentrations values. In addition, residual plots showed the absence of model misfit. The predictive ability of the model was demonstrated using pcVPC.

A forest plot has been provided to assess the clinical relevance of the covariates selected based on the change on the exposure metric (Cavg). No relevant exposure changes were predicted across the statistically selected covariates, except for renally impaired patients, who showed a trend to increase exposure as renal function decreases with the proposed dosing regimen. The SmPC states that no dose adjustment is necessary for patients with mild to moderate renal impairment, and close monitoring of safety events should be conducted with moderate renal impairment due to the potential for increased niraparib exposure. The limited number of patients with severe renal impairment impedes to establish a dose recommendation currently.

The MAH has compared observed exposures of niraparib at C2D1 predose and 1 to 3 hours post dose (steady state) from AMPLITUDE study with those previously observed in MAGNITUDE study (mCRPC) cohort 1 and cohort 3 to justify that disease state in prostate cancer would not affect the PK. Both studies used the same starting dose. The results showed that observed niraparib exposure were comparable between indications. Based on data in the mCRPC, the exposures of abiraterone administered in combination with 200 mg of niraparib were consistent with the exposures observed in previously conducted monotherapy studies. Additionally, a published population PK analysis of abiraterone monotherapy showed that abiraterone exposure at steady state was similar in chemotherapy-naïve vs. chemotherapy-pretreated mCRPC participants at 1000 mg QD. Furthermore, abiraterone as monotherapy has been approved for both indications mCRPC and mHSPC at the same dose. This may suggest that disease status in prostate cancer may not impact abiraterone PK.

The relationship between niraparib exposure and rPFS in the AMPLITUDE study was evaluated for All HRR group, BRCA group, and HRR effectors group. Cavg,ss,200mg and Cavg,ss,DAV derived from the PPK analysis were used as measure of exposure. The Kaplan-Meier analysis identified a statistically significant improvement in the niraparib plus AAP group with a reduction in the risk of rPFS compared to the placebo plus AAP group. When the exposure of niraparib was categorised by quartiles, no consistent ER relationship was observed across the exposure quartile groups. The

results were consistent in all efficacy subgroups. Multivariate Cox analysis supports the benefit of the combination treatment, additionally, when adding niraparib exposure, the exposure effect was not statistically significant. The results were consistent with all subgroups. Therefore, differences in niraparib exposure within the evaluated dose regimen are not expected to be associated with clinically relevant differences in rPFS.

The relationship between niraparib exposure and the incidence of the selected TEAEs (Grade ≥3 anaemia, haematological toxicity, and hypertension) in the AMPLITUDE study were evaluated in the exposure-safety analysis. Cavg,ss,200 mg and Cavg,ss,DAV were used as the exposure metric. The results of the analysis showed an increase in the probability of Grade ≥3 anaemia and haematological toxicity with increasing niraparib Cavg,ss,200mg and an increase in the probability of Grade ≥3 anaemia, haematological toxicity and hypertension with increase Cavg,ss,DAV. Probabilities of anaemia and haematological toxicity >50% were predicted in patients with high exposure of niraparib (Q4). Currently, the SmPC provides dose adjustment recommendations for anaemia, thrombocytopenia and neutropenia.

For Grade ≥ 3 hypertension, a statistically significant exposure-response relationship was only seen for Cavg,ss,DAV. As niraparib Cavg,ss,DAV increased from Q1 to Q4, the incidence of Grade ≥ 3 hypertension increased slowly (16%, 22%, 28%, and 27% for Q1 to Q4) with overlapping 95% confidence intervals. Considering that Grade 3 hypertension is generally managed with supportive care including anti-hypertensive medication and that hypertension initially occurs within the first 2-3 cycles, the recommendations in the SmPC of close monitoring of blood pressure are considered sufficient for managing hypertension.

The MAH has compared the baseline characteristics of participants, including demographics and disease characteristics, across the 4 quartiles of niraparib steady state average concentration (Cavg,ss) to identify specific sub-groups of patients with higher exposures. The results showed that patients with ≥ 75 years or moderate renal impairment (CRCL 30 to <60 mL/min) appear to have higher exposure. The higher exposure in patients ≥ 75 years was likely due to high correlation with creatinine clearance (CRCL). This is consistent with the information provided in the SmPC recommending close monitoring of safety events for patients with moderate renal impairment due to the potential increase in niraparib exposure.

2.3.6. Conclusions on clinical pharmacology

No issues were found regarding sample analysis as it was carried out in accordance with the validation of the analytical methods employed and ICHM10 Guideline.

The previously developed PopPK model for niraparib adequately described the time course of niraparib plasma concentration in participants with mHSPC in the AMPLITUDE study. Observed exposures of niraparib at C2D1 predose and 1 to 3 hours post dose (steady state) from AMPLITUDE study and those previously observed in MAGNITUDE study (mCRPC) cohort 1 and cohort 3 were comparable. Furthermore, based on data in the mCRPC, the exposures of abiraterone administered in combination with 200 mg of niraparib were consistent with the exposures observed in previously conducted monotherapy studies.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose-response studies have been submitted.

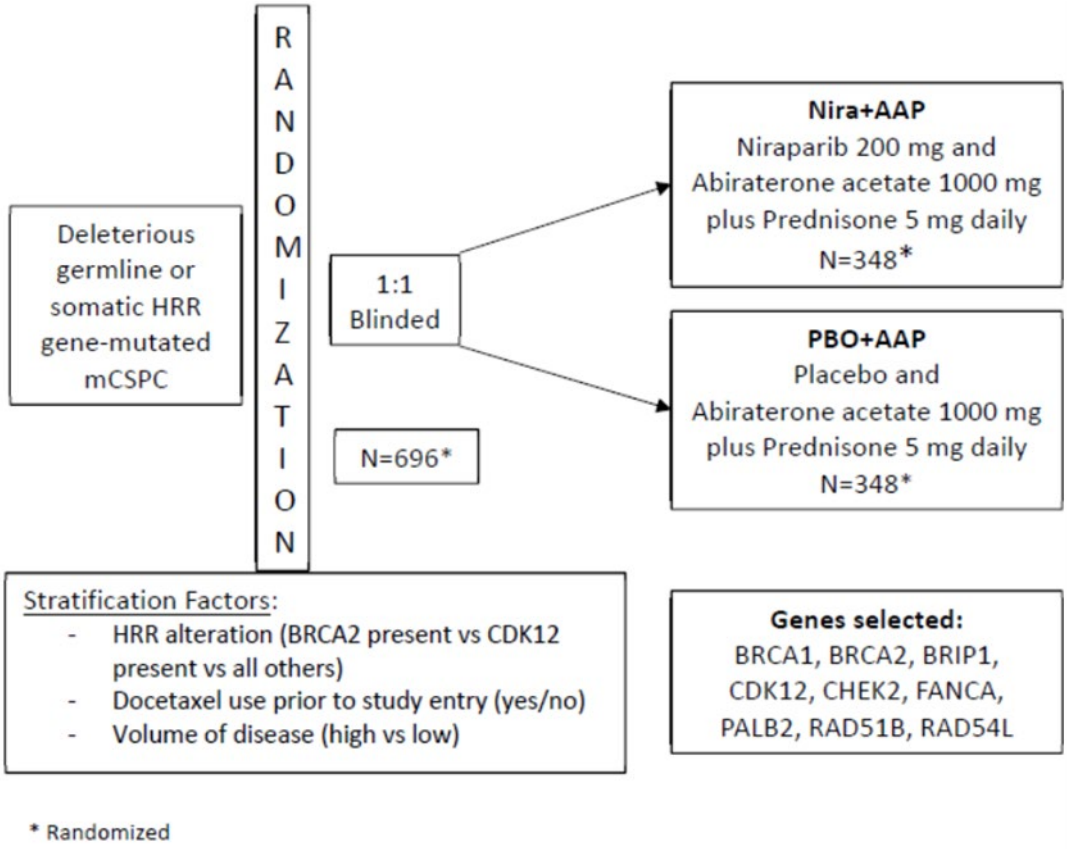
2.4.2. Main study

AMPLITUDE: a Phase 3 randomized, placebo-controlled, double-blind study of niraparib in combination with abiraterone acetate and prednisone versus abiraterone acetate and prednisone for the treatment of participants with deleterious germline or somatic homologous recombination repair gene-mutated metastatic castration-sensitive prostate cancer

Methods

AMPLITUDE is an ongoing, randomized, double-blind, placebo-controlled, multinational Phase 3 interventional study to evaluate the safety and efficacy of nira+AAP compared with PBO+AAP in men over the age of 18 years with deleterious germline or somatic HRR gene mutated mHSPC receiving ADT (i.e., GnRHa [agonist or antagonist], or surgical castration).

Figure 8. Schematic overview of the study



Study participants

According to the last protocol amendment (Amendment 4; 28-Aug-2023):

Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. >18 years of age (or the local legal age of consent).
2. Pathological diagnosis of prostate adenocarcinoma.

3. Metastatic disease documented by conventional imaging with CT or MRI (for soft tissue lesions) or 99mTc bone scan (for bone lesions). Participants with a single bone lesion on 99mTc bone scan with no other non-nodal metastatic disease must have confirmation of bone metastasis by CT or MRI.
    a. Participants with lymph node-only disease are not eligible.
4. Must have at least one of the following deleterious germline or somatic HRR gene alterations: BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, RAD54L.
5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) Grade <2.
6. Androgen deprivation therapy (either medical or surgical castration) must have been started >14 days prior to randomization and participants be willing to continue ADT through the treatment phase. Participants who start a GnRH agonist <28 days prior to randomization will be required to take a first-generation anti-androgen for >14 days prior to randomization. The anti-androgen must be discontinued prior to randomization.
7. Participants who have received prior docetaxel treatment must meet the following criteria:
    a. Received a maximum of 6 cycles of docetaxel therapy for mCSPC
    b. Received the last dose of docetaxel ≤3 months prior to randomization
    c. Maintained a response to docetaxel of stable disease or better, by investigator assessment of imaging and/or PSA, prior to randomization.
8. Other allowed prior therapy for mCSPC:
    a. Maximum of 1 course of radiation and 1 surgical intervention for symptomatic control of prostate cancer (e.g., uncontrolled pain, impending spinal cord compression or obstructive symptoms). Participants with radiation or surgical interventions to all known sites of metastatic disease will be excluded from trial participation. Radiation must be completed prior to randomization.
    b. Up to a maximum of 6 months of ADT prior to randomization.
    c. Up to a maximum of 45 days of AAP prior to randomization.
    d. Up to a maximum of 2 weeks of ketoconazole for prostate cancer prior to randomization.
9. Allowed prior treatments for localized prostate cancer include radical prostatectomy (with or without lymph node dissection), radiation therapy, and other locally directed treatments to the prostate per institutional standards of care.
    a. Participants who received ADT or first-generation anti-androgens for the treatment of localized prostate cancer
        i. ADT: must have had < 3 years total and must have completed ≥1 year prior to randomization
        ii. ii. First-generation anti-androgen: must have had ≤3 years total and must have completed ≥1 year prior to randomization.
10. Clinical laboratory values at Screening:
    a. Absolute neutrophil count ≥1.5 x 109/L

b. Hemoglobin ≥9.0 g/dL, independent of transfusions for at least 28 days

c. Platelet count ≥100 x 109/L

d. Creatinine <2 x upper limit of normal (ULN)

e. Serum potassium ≥3.5 mmol/L

f. Serum total bilirubin ≤1.5× ULN or direct bilirubin ≤1 x ULN (Note: In participants with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin, and if direct bilirubin is ≤1.5 × ULN, participant may be eligible)

g. AST or ALT ≤3 × ULN

Exclusion Criteria

Any potential participant who met any of the following criteria were excluded from participating in the study:

1. Pathological finding consistent with small cell or neuroendocrine carcinoma of the prostate.
2. Prior treatment with a PARP inhibitor.
3. Prior AR-targeted therapy (e.g., apalutamide, enzalutamide, darolutamide), immunotherapy, or radiopharmaceutical agents for prostate cancer with the Exception: allowed prior therapies in inclusion criteria.
4. History of adrenal dysfunction
5. Long-term use of systemically administered corticosteroids (>5 mg of prednisone or the equivalent) during the study was not allowed. Short-term use (≤4 weeks, including taper) and locally administered steroids (e.g., inhaled, topical, ophthalmic, and intra-articular) were allowed, if clinically indicated.
6. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions were:
    a. non-muscle invasive bladder cancer;
    b. skin cancer (non-melanoma or melanoma) treated within the last 24 months that was considered completely cured;
    c. breast cancer –adequately treated lobular carcinoma in situ or ductal carcinoma in situ;
    d. malignancy that wasconsidered cured with minimal risk of recurrence.
7. History or current diagnosis of MDS/AML.
8. Current evidence within 6 months prior to randomization of any of the following: severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, clinically significant arterial or venous thromboembolic events (ie. Pulmonary embolism), or clinically significant ventricular arrhythmias.
9. Presence of sustained uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg). Participants with a history of hypertension were allowed, provided that blood pressure was controlled to within these limits by an antihypertensive treatment.

10. Known allergies, hypersensitivity, or intolerance to the excipients of niraparib, AA, or niraparib/AA FDC (refer to the IBs for niraparib and AA).
11. Current evidence of any medical condition that would make prednisone use contraindicated.
12. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study medication.
13. Participants who have had the following ≤28 days prior to randomization:
    a. A transfusion (platelets or red blood cells);
    b. Hematopoietic growth factors;
    c. Major surgery (sponsor should be consulted regarding what constitutes major surgery).
14. Human immunodeficiency virus positive participants with 1 or more of the following:
    a. Not receiving highly active antiretroviral therapy or on antiretroviral therapy for less than 4 weeks.
    b. Receiving antiretroviral therapy that may interfere with the study medication (consult the sponsor for review of medication prior to enrollment).
    c. A change in antiretroviral therapy within 6 months of the start of screening (except if, after consultation with the sponsor on exclusion criterion 16.b, a change is made to avoid a potential drug-drug interaction with the study medication).
    d. CD4 count <350 at screening.
    e. An acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of the start of screening.
    f. Human immunodeficiency virus load >400 copies/mL.
15. Active or symptomatic viral hepatitis or chronic liver disease; encephalopathy, ascites or bleeding disorders secondary to hepatic dysfunction.
16. Moderate or severe hepatic impairment (Class B and C per Child-Pugh classification system.

Treatments

Participants were randomized to one of the following two treatment arms:

- In the experimental arm (nira+AAP), participants received a starting dose of niraparib 200 mg/AA 1,000 mg:
    - Niraparib and abiraterone acetate as 2 FDC tablets (nira 100 mg/AA 500 mg per tablet)
    - A placebo formulation of abiraterone acetate
    - Prednisone (or prednisolone)

- In the active comparator control arm (PBO+AAP), participants received a starting dose of AA 1,000 mg:
    - A placebo formulation of the FDC tablet
    - Abiraterone acetate
    - Prednisone (or prednisolone)

The 5 mg dose of prednisone (or prednisolone) is in accordance with the SmPC for AA in mHSPC.

Low-strength FDC (nira 50 mg/AA 500 mg per tablet) and single-agent niraparib (or placebo) were provided when applicable to allow dose reductions for management of TEAEs.

Participants received study medication daily on an outpatient basis until disease progression, unacceptable toxicity, death, withdrawal of consent, or termination of the study by the MAH. Treatment was continuous; however, a treatment cycle was defined as 28 days. Participants with radiographic progression could remain on therapy if still receiving clinical benefit.

Participants were followed until death or termination of the study. In addition to survival follow-up, data was collected to evaluate the secondary and other endpoints.

The study consisted of 4 phases: a Prescreening Phase for biomarker evaluation for eligibility only, a Screening Phase, a Treatment Phase, and a Follow-up Phase.

Table *17. Description of treatment arms*

Treatment arm	Participants Received	Abbreviation Throughout Text
Experimental: (nira+AAP) Niraparib 200 mg and AA 1,000 mg plus prednisone 5 mg daily	nira/AA FDC (active) AA (PBO) prednisone (active)	nira+AAP
Active comparator control: (PBO+AAP) Placebo and AA 1,000 mg plus prednisone 5 mg daily	nira/AA FDC (PBO) AA (active) prednisone (active)	PBO+AAP

AA=abiraterone acetate; AAP=AA plus prednisone; FDC=fixed-dose combination; nira=niraparib; PBO=placebo

Objectives

Table *18. Objectives and endpoints of the study AMPLITUDE*

Objectives	Endpoints
Primary	
• To determine if nira+AAP compared with AAP in participants with deleterious germline or somatic HRR gene-mutated mCSPC provides superior efficacy in improving rPFS	• rPFS[a], as determined by investigator (based on RECIST 1.1 for soft tissue disease and PCWG3 for bone disease)
Secondary	
• To assess the clinical benefit of nira+AAP compared with AAP in participants with deleterious germline or somatic HRR gene-mutated mCSPC	• OS[b] • Time to symptomatic progression[c] • Time to subsequent therapy[d]
• To characterize the safety profile of nira+AAP compared with AAP in participants with deleterious germline or somatic HRR gene-mutated mCSPC	• Incidence and severity of AEs
Other	
• To evaluate other efficacy assessments and determine the clinical benefit of nira+AAP compared with AAP in participants with deleterious germline or somatic HRR gene-mutated mCSPC	• PFS2[e] • Objective response[f] • Time to PSA progression[g]
• To characterize the PK of niraparib when administered as nira+AAP	• Observed plasma concentrations of niraparib and estimated population PK and exposure parameters for niraparib
• To show the effect of nira+AAP is similar to AAP on HRQoL	• The FACT-P, the EQ-5D-5L, BPI-SF, and the PRO-CTCAE
• To evaluate biomarkers predictive of response	• Objective response, rPFS, and PSA response across deleterious germline or somatic HRR gene alterations

a. Radiographic progression-free survival (rPFS): defined as the time interval from the date of randomization to the first date of radiographic progression as assessed by investigator or death due to any cause, whichever occurs first.

b. Overall survival (OS): defined as the time from date of randomization to date of death due to any cause.

c. Time to symptomatic progression (TSP): defined as time from the date of randomization to the date of first of the following:

   - The use of external beam radiation therapy for skeletal or pelvic symptoms. Note: Only radiation planned prior to randomization will not be considered as symptomatic progression
   - The need for tumour-related orthopedic surgical intervention
   - Other cancer-related procedures (eg, nephrostomy insertion, bladder catheter insertion, external beam radiation therapy, or surgery for tumour symptoms)
   - Cancer-related morbid events (ie, fracture [symptomatic and/or pathologic], cord compression, urinary obstructive events)
   - Initiation of a new systemic anti-cancer therapy because of cancer symptoms.

d. Time to Subsequent Therapy (TST): defined as the time from date of randomization to the date of initiation of subsequent therapy for prostate cancer.

e. PFS2: defined as time from date of randomization to date of first occurrence of disease progression (radiographic, clinical, or PSA progression) on first subsequent therapy for prostate cancer or death, whichever comes first.

f. Objective response (ORR): defined as achieving a complete or partial response according to modified RECIST 1.1.

g. Time to PSA progression: defined as the time from the date of randomization to the date of PSA progression based on PCWG3 criteria.

Sample size

The planned total sample size was approximately 692 participants to be randomized in a 1:1 ratio to receive niraparib + AAP or AAP, and it was estimated that approximately half of all enrolled participants would have BRCA mutations. The primary endpoint of rPFS was assumed to follow an exponential distribution with a constant hazard rate. It was estimated that approximately 261 rPFS events were required in the All HRR population to provide 91% power for detecting a HR of 0.64 (median rPFS of 33 months for the AAP treatment arm versus 51.6 months for the niraparib + AAP treatment arm) at a 2-sided significance level of 0.025. With a 33-month accrual period and an additional 15 months of follow up, the study duration to reach the required number of rPFS events is projected to be approximately 48 months.

Additionally, at the planned sample size and study duration:

- Approximately 146 rPFS events were projected to be observed in the target subgroup of participants with BRCA mutations at the time of rPFS primary analysis, which would provide 95% power to detect a HR of 0.55 for rPFS (33 versus 60 months) at a 2-sided significance level of 0.05.
- Approximately 185 rPFS events were projected to be observed in the target subgroup of participants with HRR effector gene mutations, which would provide 96% power to detect a HR of 0.55 (33 vs 60 months) at a 2-sided significance level of 0.025.

Table *19. rPFS power justification summary*

Population	rPFS events	Significance level (2-sided)	HR assumption	Power
BRCA	146 expected	0.05	0.55	95%
HRR effectors	185 expected	0.025	0.55	96%
All HRR	261 required	0.025	0.64	91%

Number of events for secondary endpoints

In the All HRR population, 389 OS events are expected at the time of final OS analysis after a study duration of approximately 79 months, with 80% power to detect an underlying true HR of 0.75 for OS (53 versus 70.7 months) at a 2-sided significance level of 0.05.

Approximately 170 OS events are expected to be observed at the time of the rPFS primary analysis (i.e., the first OS interim analysis).

The second interim analysis is planned to occur after 255 OS events are observed in the All HRR population with 199 TSP events projected to be observed at that time.

Randomisation

Central randomization 1:1 was implemented in this study. Participants were randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule.

The randomization was balanced by using randomly permuted blocks and was stratified based on 3 factors: HRR gene alterations (BRCA2 alteration present vs. CDK12 alteration present vs. all other pathogenic alterations), prior docetaxel use (yes vs. no), and volume of disease at screening (high vs. low).

High-volume mHSPC is defined as visceral metastases; or at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis.

Blinding (masking)

This study was double-blinded: the study design included sponsor trial team, investigator, site staff, caregiver, and participant blinding/masking. An IDMC evaluated unblinded safety data from the study at prespecified intervals.

Statistical methods

Analysis sets

Table 20. Definition of analysis sets

Analysis Sets	Definition	
Full Analysis Set (FAS)	The FAS includes all randomized participants classified according to their assigned treatment arm, regardless of the actual treatment received.	Demographics and baseline disease characteristics, Disposition, efficacy, and PRO analysis
Safety Analysis Set	The safety analysis set includes all randomized participants who received at least 1 dose of study medication	Safety, treatment compliance, and exposure analyses
Pharmacokinetics Analysis Set	The PK analysis set is defined as participants who received at least 1 dose of study medication and have at least 1 valid blood sample drawn for PK analysis.	PK/PD analyses

Interim analyses

There is no interim analysis for the primary endpoint of rPFS.

Two interim analyses and a final analysis for the secondary endpoint of OS were planned based on number of OS events in the All HRR population. The first interim analysis (IA1) would coincide with the primary analysis of rPFS (hereafter referred to as 'PA-IA1').

Formal analyses for TSP were to be performed at IA1 and IA2 only.

The group-sequential design was to be used for TSP and OS, respectively. The corresponding alpha spending function was αtρ, with t denoting the information fraction. The overall family-wise Type-1 error was to be controlled at 0.05.

Table 21. Operating characteristics of OS and TSP analysis with a maximum overall alpha of 0.05*

		IA1	IA2	FA
OS	Number of events expected in HRR full analysis set (info fraction)	~170 (~43.7%)	~255 (65.6%)	389 (100%)
	Efficacy exit boundary**	HR<0.658	HR<0.736	HR<0.814
	P value boundary	0.0063	0.0144	0.0424
TSP	Number of events expected in HRR full analysis set (info fraction)	~133 (66.8%)	~199 (100%)	
	Efficacy exit boundary**	HR<0.672	HR<0.747	
	P value boundary	0.0219	0.0392	

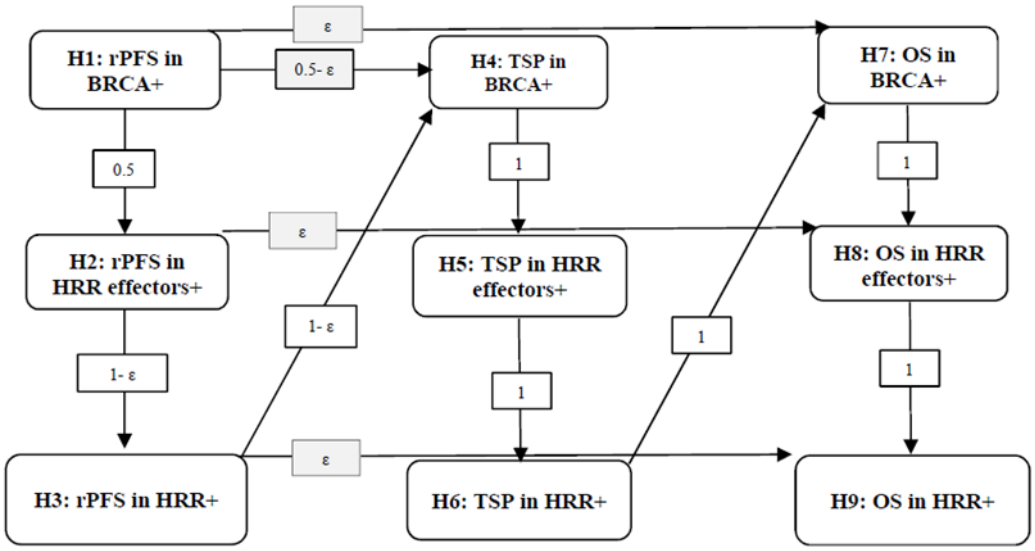
*If the overall alpha is less than 0.05 (see Section 4.1.1.1, for details), cumulative alpha spent at IAs and the final analysis will be reduced, and the efficacy boundary will be adjusted accordingly.
**HR exit boundary values are approximate; the testing results will be based on the corresponding p-value boundary values

Multiplicity adjustment for testing of primary and key secondary endpoints

To preserve the overall family-wise type I error rate at the 2-sided 0.05 level, the multiple comparison testing procedure in a group sequential design using the graphical approach was to be applied. The procedure was to take into account both sources of multiplicity, multiple hypothesis tests (e.g., across primary and secondary endpoints) and multiple analyses planned for the study (e.g., two interim analyses and a final analysis for OS).

There were two key components that define this approach, testing algorithm for multiple hypotheses specified by the graphical representation and repeated testing of some hypotheses using the alpha spending function methodology. The testing algorithm codes a series of graph transformations which happen at each successful clearing of a hypothesis as described in Maurer (2013). During execution of the procedure, different scenarios for local significance levels emerged in an iterative manner.

Figure 9 ***Graphical approach for testing key efficacy endpoints***



A given transition weight, written to the directed edge on the graph, specifies the fraction of the local significance level transferred from the initial node to the connected edge terminal node, if the null hypothesis corresponding to the initial node is successfully rejected.

The hypothesis testing started with H1 at 2-sided alpha=0.05. If rPFS was to meet statistical significance in BRCA, then half of the alpha (0.025) would have been passed to H2 and the other half would have been splitted between H4 and H7, with 0.5-ε and ε weights, respectively. The overall family-wise type I error rate was preserved at the pre-specified 2-sided 0.05 level.

Table 22. Operating characteristics for rPFS, TSP and OS analysis with planned graphical procedure

Endpoint		Alpha Level Available	Significance Level (2-sided) at Each IA and FA*		
			IA1	IA2	FA
rPFS	H1: BRCA	0.05	0.05	-	-
	H2: HRR effectors	0.025	0.025	-	-
	H3: All HRR	0.0247	0.0247	-	-
TSP	H4: BRCA (only H1 meets statistical significance)	0.0245	0.0108	0.0190	
	H4: BRCA (H1, H2, and H3 meet statistical significance)	0.049	0.0216	0.0393	-
	H5: HRR effectors (H1 and H4 meet statistical significance)	0.0245	0.0110	0.0189	-
	H5: HRR effectors (H1, H2, H3, H4 meet statistical significance)	0.049	0.0219	0.0392	-
	H6: All HRR (H1, H4, and H5 meet statistical significance)	0.0245	0.0109	0.0189	-
	H6: All HRR (H1, H2, H3, H4, and H5 meet statistical significance)	0.049	0.0219	0.0392	-
OS	H7: BRCA (H1, H4, H5, and H6 meet statistical significance)	0.025	0.0031	0.0069	0.0207
	H7: BRCA (H1 to H6 meet statistical significance)	0.0495	0.0061	0.0139	0.0421
	H8: HRR effectors (H1, H4, H5, H6, and H7 meet statistical significance)	0.025	0.0031	0.0069	0.0207
	H8: HRR effectors (H1, H2, H4, H5, H6, and H7 meet statistical significance)	0.0253	0.0031	0.0070	0.0209
	H8: HRR effectors (H1 to H7 meet statistical significance)	0.0498	0.0061	0.0141	0.0423
	H9: All HRR (H1, H4, H5, H6, H7, and H8 meet statistical significance)	0.025	0.0032	0.0070	0.0206
	H9: All HRR (H1, H2, H4, H5, H6, H7, and H8 meet statistical significance)	0.0253	0.0032	0.0071	0.0208
	H9: All HRR (H1 to H8 meet statistical significance)	0.05	0.0063	0.0144	0.0424

* The significance level for TSP and OS might change depending on the number of events that are observed at the time of the analysis.

Note: ε is set to 0.01. The OS operating characteristics are only presented for scenarios where the available alpha is at least 0.025.

Censoring rules

rPFS for the participants without radiographic progression or death were to be censored at the last disease assessment date if subsequent anti-cancer therapy was never received or censored at the last disease assessment date prior to the start of the subsequent anti-cancer therapy if the participant started subsequent anti-cancer therapy.

Table 23. rPFS censoring rules

Scenario	Censoring Rule
No disease assessment at baseline or No disease assessment after baseline and no death	Censored on the date of randomization
Participants who are lost to follow-up or withdraw from study	Censored on the date of the last disease assessment
Participants who receive new systemic anti-cancer therapy known or intended for the treatment of mPC during the study prior to documented disease progression or death	Censored on the date of the last disease assessment prior to the start of the new systemic anti-cancer therapy
Participants with no evidence of radiographic progressive disease or death	Censored on the date of the last disease assessment
Participants with progression or death immediately following ≥2 consecutive missed or unevaluable planned radiographic scans	Censored on the date of the last disease assessment before the missed/unevaluable scans.

Estimands

The primary estimand, the main clinical quantity of interest to be estimated in this study, is defined by the following four components [ICH E9 (R1) 2017]:

- Population: Men >18 years of age with deleterious germline or somatic HRR gene-mutated mHSPC as defined by the inclusion/exclusion criteria to reflect the targeted patient population for treatment
- Variable: rPFS by investigator
- Intercurrent event: use of subsequent anti-cancer therapy, treatment discontinuation due to AE or other reasons than AE or worsening of disease
- Population-level summary: hazard ratio (niraparib + AAP compared with AAP), median rPFS and its 95% CI, rPFS rates at selected time points for each treatment arm.

Table 24. Intercurrent events and the corresponding strategies

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Treatment discontinuation due to AE or other reasons than AE or worsening of disease	**Treatment Policy Strategy**: Use time to PD or death, regardless of whether or not this intercurrent event had occurred.
Initiation of subsequent anti-cancer therapy prior to the documented disease progression or death	**Hypothetical strategy**: subjects are censored at the last disease assessment showing no evidence of PD before the use of subsequent anti-cancer therapy.

As described for the primary estimand, a description of the Intercurrent events (ICEs) and strategies for addressing ICEs for secondary endpoints are as follows:

Table *25. Intercurrent events and the corresponding strategies for the Secondary Endpoints*

Intercurrent Events: Overall Survival	Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation	**Treatment Policy Strategy**: targeting the effect of the treatment assignment, regardless of the occurrence of treatment discontinuation. Use time to death, regardless of whether or not this intercurrent event had occurred.

Initiation of subsequent anti-cancer therapy prior to death	**Treatment Policy Strategy**: targeting the effect of the treatment assignment, regardless of the initiation of subsequent anti-cancer therapy. Use time to death, regardless of whether or not this intercurrent event had occurred.
Intercurrent Events: Time to Symptomatic Progression	**Strategy for Addressing Intercurrent Events and Its Description**
Study treatment discontinuation for reason other than those (incl. AE) which qualifies as a Symptomatic Progression Event (SPE)	**Treatment Policy Strategy**: targeting the effect of the treatment assignment, regardless of the occurrence of treatment discontinuation (other than for AE or reasons which qualify as SPE). Use time to first SPE regardless of whether or not this intercurrent had occurred.
Initiation of subsequent anti-cancer therapy other than those which qualify as SPE	**Treatment Policy Strategy**: targeting the effect of the treatment assignment, regardless of the initiation of subsequent anti-cancer therapy (other than those which qualifies as SPE). Use time to first SPE regardless of whether or not this intercurrent had occurred.
Intercurrent Events: Time to Subsequent Therapy	**Strategy for Addressing Intercurrent Events and Its Description**
Study treatment discontinuation	**Treatment Policy Strategy**: targeting the effect of the treatment assignment, regardless of the occurrence of treatment discontinuation. Use time to subsequent therapy for prostate cancer, regardless of whether or not this intercurrent event had occurred.
Intercurrent Events: Objective Response Rate	**Strategy for Addressing Intercurrent Events and Its Description**
Treatment discontinuation	**Treatment Policy Strategy**: targeting the effect of the treatment assignment, regardless of the occurrence of treatment discontinuation. Use objective response assessments, regardless of whether or not this intercurrent event had occurred.
Initiation of subsequent anti-cancer therapy (prior to documented objective response)	**While prior to ICE**: targeting the treatment effect prior to initiation of subsequent anti-cancer therapy. Objective response assessments after initiation of subsequent anti-cancer therapy are not considered for reporting objective response rate; by protocol/study design scan/imaging assessments were not collected after the subsequent anti-cancer therapy initiation.
Intercurrent Events: Time to PSA Progression	**Strategy for Addressing Intercurrent Events and Its Description**
Treatment discontinuation	**Treatment Policy Strategy**: targeting the effect of the treatment assignment, regardless of the occurrence of treatment discontinuation. Use time to PSA measurements, regardless of whether or not this intercurrent event had occurred.
Initiation of subsequent anti-cancer therapy (prior to documented PSA progression)	**Hypothetical strategy**: targeting a treatment effect in a hypothetical scenario in which patients would continue treatment as assigned, without initiation of subsequent anti-cancer therapy. Subjects are censored at the last PSA assessment showing no evidence of PSA progression before the use of subsequent anti-cancer therapy; by protocol/study design PSA measurements were not collected after the subsequent anti-cancer therapy initiation.
Intercurrent Events: PSA Response Rate	**Strategy for Addressing Intercurrent Events and Its Description**
Treatment discontinuation	**Treatment Policy Strategy**: targeting the effect of the treatment assignment, regardless of the occurrence of treatment discontinuation. Use PSA measurements, regardless of whether or not this intercurrent event had occurred.
Initiation of subsequent anti-cancer therapy (prior to documented PSA response)	**While prior to ICE**: targeting the treatment effect prior to initiation of subsequent anti-cancer therapy. PSA response assessments after initiation of subsequent anti-cancer therapy are not considered for reporting PSA response rate; by

	protocol/study design PSA measurements were not collected after the subsequent anti-cancer therapy initiation.
Intercurrent Events: Progression-free Survival on first subsequent therapy	**Strategy for Addressing Intercurrent Events and Its Description**
1st subsequent anti-cancer therapy discontinuation due to AE, or due to other reasons than AE or worsening of disease	**Treatment Policy Strategy**: targeting the effect of the treatment assignment and 1st subsequent anti-cancer therapy, regardless of the occurrence of 1st subsequent anti-cancer therapy discontinuation. Use time to PD or death, regardless of whether or not this intercurrent event had occurred.
Initiation of 2nd subsequent anti-cancer therapy prior to documented disease progression on 1st subsequent therapy or death	**Hypothetical strategy**: targeting a treatment effect in a hypothetical scenario in which patients would continue treatment as assigned, without initiation of 2nd subsequent anti-cancer therapy. Subjects are censored at initiation of 2nd subsequent anti-cancer therapy minus 1 day.

Analysis methods

The primary analysis of rPFS were to be performed after approximately 261 rPFS events were observed in the All HRR population and would have been tested using stratified log-rank test at the overall 2-sided significance level of 0.05. The Kaplan-Meier product limit method and a stratified Cox model were to be used to estimate the median rPFS and to obtain the HR estimate along with the associated 95% confidence intervals, respectively.

Sensitivity analysis using non-stratified log rank test were also to be performed as supportive analyses.

The proportional hazard assumption was to be assessed graphically by plotting log (-log [estimated survival distribution function]) against log (survival time). The resulting graphs should have had approximately parallel lines when the assumption holds. If the proportional hazards assumption was reasonably met, then the HR would have been used as an estimate of treatment effect. If the proportional hazards assumption was violated, then the inference remains statistically valid for testing equality in survival distributions, but treatment effect would have only be estimated using the median time to event in each treatment arm. Sensitivity analysis such as piecewise constant hazards model could be performed as appropriate.

To assess the consistency of treatment benefit across important subgroups, forest plots were to be provided for subgroups. The comparison between the two treatment arms were to be evaluated using the hazard ratio with its 95% CI from a univariate non-stratified Cox regression model in each subgroup.

Multivariate Cox regression analysis, adjusting for important selected prognostic factors, would have also be performed as supportive analysis, if appropriate. The adjusted HR and its 95% confidence interval for treatment and each factor would have be provided.

Sensitivity analysis would have be performed using all progression or death events, whichever occurs first, regardless of change of therapy or missed/unevaluable scans for 2 or more consecutive visits.

The symmetry of disease assessment schedules between treatment arms would also be examined. Reasons for censoring would be summarized by treatment arm to check for informative censoring.

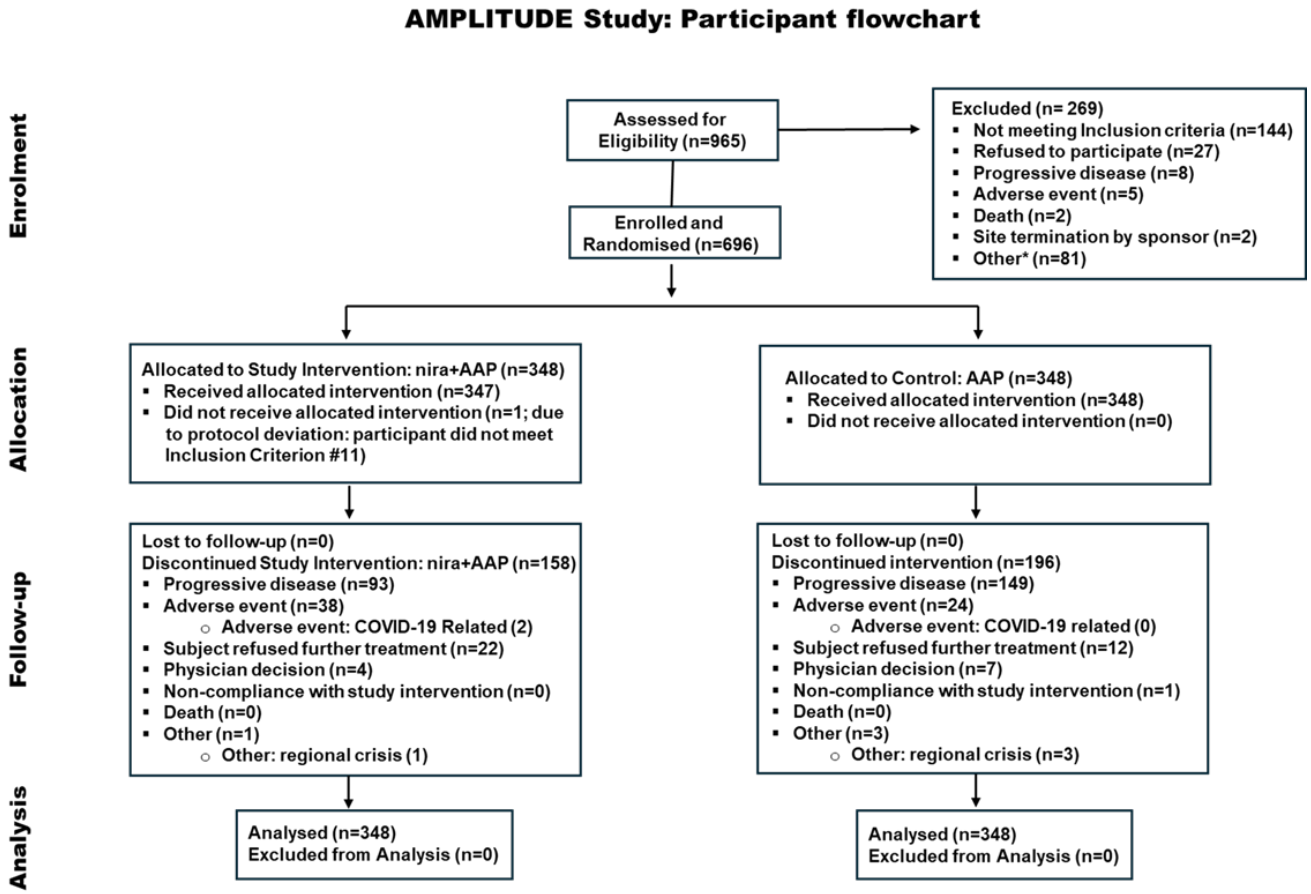
Stratified log-rank test and Cox proportional-hazard model by excluding subjects with major protocol (MPD) deviations (including COVID-19 or/and regional crisis Ukraine/Russia/Israel MPD) will be performed as sensitivity analysis if MPD>20%.

Missing disease assessment due to COVID-19 were to be summarized to evaluate COVID-19 impact on disease assessment. Sensitivity analysis will be performed as needed by censoring death event due to COVID- 19 at last disease assessment date.

The strength of association between rPFS and OS was be evaluated using Spearman's correlation coefficient taking censoring into account.

Results

Participant flow



Disposition

Table 26. Treatment disposition; safety analysis set (All HRR population)

	Placebo + AAP	Nira + AAP	Total
Analysis set: Safety	348	347	695
Subjects ongoing	152 (43.7%)	189 (54.5%)	341 (49.1%)
Discontinued study treatment	196 (56.3%)	158 (45.5%)	354 (50.9%)
Reason for discontinuation			
Progressive disease	149 (42.8%)	93 (26.8%)	242 (34.8%)
Adverse event	24 (6.9%)	38 (11.0%)	62 (8.9%)
Adverse event - COVID-19 related	0	2 (0.6%)	2 (0.3%)
Subject refused further study treatment	12 (3.4%)	22 (6.3%)	34 (4.9%)
Physician decision	7 (2.0%)	4 (1.2%)	11 (1.6%)
Non-Compliance with study drug	1 (0.3%)	0	1 (0.1%)
Death	0	0	0
Death - COVID-19 related	0	0	0
Other	3 (0.9%)	1 (0.3%)	4 (0.6%)
Other - COVID-19 related	0	0	0
Other - regional crisis	3 (0.9%)	1 (0.3%)	4 (0.6%)

Key: AAP = abiraterone acetate plus prednisone.

Treatment and study disposition for the BRCA and HRR effector populations were similar to the All HRR population.

Biomarker pre-screening

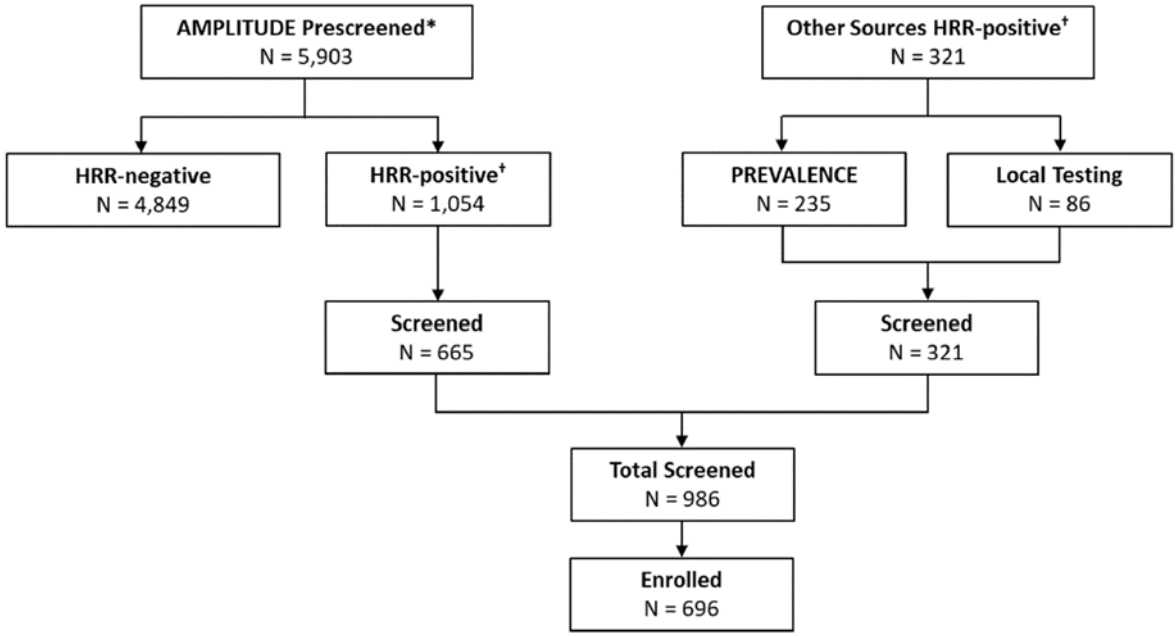
A total of 5,903 participants were pre-screened for biomarkers by one of the central assays in the AMPLITUDE study and had valid results. Of these, 1054 were positive for at least 1 protocol-defined HRR gene alteration:

- 965 participants exhibited single gene alterations
- 89 had co-occurring gene alterations, of whom, 60 had BRCA1 and/or BRCA2 co-occurring gene alterations.

A total of 665 participants pre-screened for AMPLITUDE entered screening.

In addition, 321 biomarker-positive participants were identified from other sources and approved by the MAH to be screened for eligibility, including 235 participants from the PREVALENCE study and 86 from local testing. Overall, 986 biomarker-positive participants screened for eligibility and 696 were enrolled in the study.

Figure *10. Participant pre-screening and eligibility*



*Includes patients with a valid result (ie, HRR-negative and HRR-positive per protocol)
†HRR positivity based on assay results and presence of protocol-defined HRR alterations in BRCA1/2, BRIP1, CHEK2, CDK12, FANCA, PALB2, RAD51B, RAD54L

Table 27. Summary of single- and co-occurring gene alterations in pre-screened HRR participants by central assays (N=5,903)

Single Gene Alterations	N	Percent of total
Total	**965**	**16.35%**
BRCA2	351	5.95%
CHEK2	232	3.93%
CDK12	190	3.22%
BRCA1	51	0.86%
FANCA	41	0.69%
PALB2	37	0.63%
RAD54L	28	0.47%
BRIP1	21	0.36%
RAD51B	14	0.24%
Co-Occurring Gene Alterations		
Total	**89**	**1.51%**
BRCA1 and/or BRCA2 co-occurring gene alterations	60	1.02%
Non BRCA co-occurring gene alterations	29	0.49%

Recruitment

This study was conducted at 400 centers that enrolled participants in Argentina, Australia, Belarus, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, France, Hungary, Germany, Israel, Italy, Malaysia, Mexico, Netherlands, New Zealand, Poland, Portugal, Korea, Russia, Spain, South Africa, Sweden, Taiwan, Thailand, Turkey, Ukraine, UK, and US.

First patient enrolled (FPI): 03 December 2020

Data cut-off: 07 January 2025. Ongoing.

Conduct of the study

Protocol amendments

There were four protocol amendments to the original protocol, dated 10-Jun-2020.

- Protocol amendment 1 (21-Dec-2020) was implemented to update safety monitoring and guidance based on updated to niraparib core safety information.
- Protocol amendment 2 (25-Oct-2021) was implemented to modify eligibility criteria based on investigator feedback to facilitate enrolment, to allow additional forms of testing for HRR alterations, and to clarify toxicity management guidelines.
- Protocol amendment 3 (09-Feb-2023) was implemented to revise the sample size based on emerging data from results of clinical trials with PARPi in prostate cancer.
- Protocol amendment 4 (28-Aug-2023) was implemented to modify the secondary efficacy endpoint from "symptomatic progression-free survival" to "time to symptomatic progression".

A tabular summary with the most relevant amendments is included in below.

Table 28: Summary of Changes to AMPLITUDE Protocol Amendments

AMPLITUDE (67652000PCR3002) Protocol Amendment			
Rationale	**Section Number and Name**	**Description of Change**	**Brief Rationale**
Protocol Amendment 3 (09 February 2023) **Overall Rationale**: To revise the sample size based on emerging data from results of clinical trials with PARP inhibitors in prostate cancer.			
To revise the sample size based on emerging data from results of clinical trials with PARP inhibitors in prostate cancer.	1.1. Synopsis (Number of Participants, Efficacy); 1.2. Schema; 4.1. Overall Design; 9.2. Sample Size Determination	The number of participants was updated from '788' to '692'.	To revise the sample size based on emerging data from other recent clinical trials with PARP inhibitors in prostate cancer.
	9.2. Sample Size Determination	Text added: "Long term survival follow-up will continue until approximately 480 OS events have been observed. Approximately 193 OS events are expected at the time of the rPFS analysis assuming the HR of 0.79 for OS."	To update timing of efficacy analysis based on emerging data.
	9.5. Interim Analysis for Overall Survival	The number of planned formal interim analyses was updated.	To revise the number of analyses based on emerging data.
Updates to gene alterations	2.2.3. Summary of Available Clinical Data for Niraparib and AA Plus	Added language regarding Study 64091742PCR3001	Updated with emerging data from PARP inhibitor trials in prostate cancer. Also

permitted for eligibility to reflect stopping enrollment of participants with CDK12-only gene alterations.	Prednisone in Prostate Cancer; 2.3. Benefit-Risk Assessment; 4.3. Justification for Dose	(MAGNITUDE) and the Phase 3 PROpel study.	provides rationale for stopping enrollment of participants with CDK12-only alterations.
	2.3. Benefit-Risk Assessment;	Text was added to indicate that participants with CDK12-only alterations are no longer being enrolled in Study 67652000PCR3002.	Updates to gene alterations permitted for eligibility allowed in prior version of the protocol and specific language is added to reflect this change for CDK12-only alterations.
Protocol Amendment 4 (28 August 2023) **Overall Rationale**: The overall rationale for this amendment is to modify the secondary efficacy endpoint from "Symptomatic progression free survival" to "Time to symptomatic progression". In addition, this amendment consolidates the protocol for European Clinical Trial Regulation (EU CTR) transition.			
Updates to reflect changes to the secondary efficacy endpoint from "Symptomatic progression free survival" to "Time to symptomatic progression"	3. Objectives and Endpoints; 9.4.3. Secondary Endpoints	Modify the secondary efficacy endpoint from "Symptomatic progression free survival" to "Time to symptomatic progression".	To capture a patient-centered endpoint. As death for any cause is captured in radiographic progression-free survival (rPFS) and overall survival, it was removed from the endpoint related to symptomatic progression. No changes were made to the corresponding objective.
		Footnote "b": "Death from any cause" removed from definition of endpoint.	Updated to correspond to the secondary endpoint modification.

Protocol deviations

Table *29. Summary of Subjects with Major Protocol Deviations; Full Analysis Set (Study AMPLITUDE)*

	Placebo + AAP	Nira + AAP	Total
Analysis set: Full	348	348	696
Subjects with major protocol deviations	20 (5.7%)	24 (6.9%)	44 (6.3%)
Received wrong treatment or incorrect dose	5 (1.4%)	16 (4.6%)	21 (3.0%)
Entered but did not satisfy criteria	11 (3.2%)	4 (1.1%)	15 (2.2%)
Received a disallowed concomitant treatment	4 (1.1%)	3 (0.9%)	7 (1.0%)
Other	0	1 (0.3%)	1 (0.1%)
Other - Regional Crisis	0	1 (0.3%)	1 (0.1%)
Other - COVID-19	0	0	0

Key: AAP = abiraterone acetate plus prednisone.
Note: Subjects may appear in more than one category.
[tsidev01.rtf] [PROD/jnj-67652000/pcr3002/dbr_csr/re_csr/tsidev01.sas] 19FEB2025, 14:43

Participant received wrong treatment or incorrect dose

A total of 16 (4.6%) participants in the nira+AAP arm received wrong treatment or incorrect dose. Of these, 9 participants did not receive the correct IP dose following an AE (ie, drug was not reduced or interrupted per protocol or restarted at the wrong dose). Compliance issues were reported for 5 participants. These included compliance ≤50% with no recorded reason and insufficient drug dispensed. In 2 participants, no additional details were available for receipt or intake of wrong treatment or incorrect dose.

In the PBO+AAP arm, 5 (1.4%) participants received wrong treatment or incorrect dose; 3 participants did not receive the correct IP dose following an AE, 1 participant self-administered from the wrong bottle for 2 weeks, and 1 participant received an expired kit. In addition, after database lock, it was discovered one participant in the PBO+AAP arm was dispensed a kit from the nira+AAP treatment arm and received 2 cycles of nira+AAP. Based on medical review of safety data for this participant before and after incorrect dosing, it was determined that there was no impact on safety, and no to low impact on efficacy (data on file).

Participant entered but did not satisfy criteria

In the nira+AAP arm, 4 (1.1%) participants entered without meeting all eligibility criteria. This included 3 participants who received disallowed medications prior to randomization (red blood cell transfusion, a GnRH agonist, and AAP for more than 45 days, respectively); 1 participant had screening laboratory values outside of limits.

In the PBO+AAP arm, 11 (3.2%) participants entered without meeting all eligibility criteria; 9 participants received disallowed medications, or received medications outside of the prespecified window prior to randomization (including docetaxel, GnRH, ADT, CSF, AAP, and filgrastim); 2 participants had deviation around histological confirmation of prostate cancer (the inclusion criterion was subsequently removed at Protocol Amendment 1), and documentation of metastatic disease (no additional details provided).

Participant received disallowed concomitant treatment

In the nira+AAP arm, 3 (0.9%) participants received disallowed medication, including spironolactone (2 participants), and an unspecified medication in 1 participant. In the PBO+AAP arm, 4 (1.1%) participants received an unspecified disallowed medication during treatment.

Baseline data

Gene alterations

Table *30. Summary of subjects gene alterations; full analysis set (All HRR population)*

	Placebo + AAP	Nira + AAP	Total
Analysis set: Full	348	348	696
Single Gene Alterations			
BRCA1	25 (7.2%)	25 (7.2%)	50 (7.2%)
BRCA2	144 (41.4%)	148 (42.5%)	292 (42.0%)
BRIP1	4 (1.1%)	9 (2.6%)	13 (1.9%)
CDK12	28 (8.0%)	28 (8.0%)	56 (8.0%)
CHEK2	76 (21.8%)	72 (20.7%)	148 (21.3%)
FANCA	15 (4.3%)	15 (4.3%)	30 (4.3%)
PALB2	13 (3.7%)	9 (2.6%)	22 (3.2%)
RAD51B	5 (1.4%)	4 (1.1%)	9 (1.3%)
RAD54L	6 (1.7%)	12 (3.4%)	18 (2.6%)
Subtotal single gene alterations	316 (90.8%)	322 (92.5%)	638 (91.7%)
Co-occurring Gene Alterations			
BRCA Co-occurring			
BRCA1/BRCA2	3 (0.9%)	3 (0.9%)	6 (0.9%)
BRCA1/BRIP1	1 (0.3%)	0	1 (0.1%)
BRCA1/CDK12	3 (0.9%)	1 (0.3%)	4 (0.6%)
BRCA1/CHEK2	2 (0.6%)	2 (0.6%)	4 (0.6%)
BRCA1/FANCA	1 (0.3%)	0	1 (0.1%)
BRCA1/PALB2	1 (0.3%)	0	1 (0.1%)
BRCA2/BRIP1	1 (0.3%)	0	1 (0.1%)
BRCA2/CDK12	2 (0.6%)	1 (0.3%)	3 (0.4%)
BRCA2/CHEK2	13 (3.7%)	5 (1.4%)	18 (2.6%)
BRCA2/FANCA	0	2 (0.6%)	2 (0.3%)
BRCA2/RAD51B	0	1 (0.3%)	1 (0.1%)
BRCA2/CDK12/PALB2	0	1 (0.3%)	1 (0.1%)
BRCA2/CDK12/RAD51B	0	1 (0.3%)	1 (0.1%)
BRCA2/CHEK2/FANCA	0	1 (0.3%)	1 (0.1%)
Subtotal BRCA Co-occurring	27 (7.8%)	18 (5.2%)	45 (6.5%)
Non-BRCA Co-occurring			
BRIP1/CDK12	0	1 (0.3%)	1 (0.1%)
CDK12/CHEK2	2 (0.6%)	3 (0.9%)	5 (0.7%)
CDK12/PALB2	0	1 (0.3%)	1 (0.1%)
CDK12/RAD54L	1 (0.3%)	2 (0.6%)	3 (0.4%)
CHEK2/FANCA	1 (0.3%)	0	1 (0.1%)
CHEK2/PALB2	1 (0.3%)	0	1 (0.1%)
CHEK2/RAD51B	0	1 (0.3%)	1 (0.1%)
Subtotal non-BRCA Co-occurring	5 (1.4%)	8 (2.3%)	13 (1.9%)

Key: AAP = abiraterone acetate plus prednisone.
Key: BRCA1=Breast Cancer gene 1; BRCA2=Breast Cancer gene 2; BRIP1=BRCA1 Interacting Protein C-terminal Helicase 1 gene; CDK12=Cyclin-Dependent Kinase 12; CHEK2=Checkpoint Kinase 2 gene; FANCA=Fanconi Anemia Complementation Group A gene; PALB2=Partner and Localizer of BRCA2 gene; RAD51B=RAD51 paralog B; RAD54L=RAD54-Like.

Demographic characteristics

Table *31. Summary of demographics; full analysis set (All HRR population)*

	Placebo + AAP	Nira + AAP	Total
Analysis set: Full	348	348	696
Age, years			
N	348	348	696
Mean (SD)	66.7 (8.84)	67.8 (8.75)	67.3 (8.81)
Median	67.0	68.0	68.0
Range	(40; 92)	(40; 88)	(40; 92)
< 65	135 (38.8%)	116 (33.3%)	251 (36.1%)
≥ 65 to <75	139 (39.9%)	148 (42.5%)	287 (41.2%)
≥ 75	74 (21.3%)	84 (24.1%)	158 (22.7%)
Sex			
N	348	348	696
Male	348 (100.0%)	348 (100.0%)	696 (100.0%)
Race			
N	348	348	696
American Indian or Alaska Native	3 (0.9%)	1 (0.3%)	4 (0.6%)
Asian	67 (19.3%)	77 (22.1%)	144 (20.7%)
Black or African American	10 (2.9%)	18 (5.2%)	28 (4.0%)
Native Hawaiian or Other Pacific Islander	1 (0.3%)	0	1 (0.1%)
White	257 (73.9%)	246 (70.7%)	503 (72.3%)
Multiple	2 (0.6%)	2 (0.6%)	4 (0.6%)
Not Reported	6 (1.7%)	3 (0.9%)	9 (1.3%)
Unknown	2 (0.6%)	1 (0.3%)	3 (0.4%)
Ethnicity			
N	348	348	696
Hispanic or Latino	43 (12.4%)	40 (11.5%)	83 (11.9%)
Not Hispanic or Latino	292 (83.9%)	287 (82.5%)	579 (83.2%)
Not Reported	7 (2.0%)	10 (2.9%)	17 (2.4%)
Unknown	6 (1.7%)	11 (3.2%)	17 (2.4%)
Weight, kg			
N	348	348	696
Mean (SD)	82.0 (17.46)	79.6 (16.18)	80.8 (16.87)
Median	80.0	77.9	78.8
Range	(43; 160)	(36; 155)	(36; 160)
Height, cm			
N	348	348	696
Mean (SD)	172.8 (7.95)	171.6 (8.26)	172.2 (8.12)
Median	173.0	171.0	172.0
Range	(153; 195)	(130; 196)	(130; 196)

Key: AAP = abiraterone acetate plus prednisone.
Note: N's for each parameter reflect non-missing values.
Note: Unknown category includes missing data.

Baseline disease characteristics

Table 32. Summary of prostate cancer baseline clinical disease characteristics; full analysis set (All HRR population)

	Placebo + AAP	Nira + AAP	Total
Analysis set: Full	348	348	696
Time from initial diagnosis to randomization (months)			
N	348	348	696
Mean (SD)	13.20 (30.826)	10.30 (25.549)	11.75 (28.328)
Median	4.16	4.14	4.14
Range	(1.3; 260.6)	(1.1; 249.6)	(1.1; 260.6)
Time from metastatic diagnosis to randomization (months)			
N	348	348	696
Mean (SD)	3.87 (2.762)	4.51 (5.764)	4.19 (4.528)
Median	3.12	3.65	3.37
Range	(0.7; 40.7)	(0.4; 68.1)	(0.4; 68.1)
Tumor stage at initial diagnosis			
N	348	348	696
T0	0	2 (0.6%)	2 (0.3%)
T1	8 (2.3%)	15 (4.3%)	23 (3.3%)
T2	63 (18.1%)	75 (21.6%)	138 (19.8%)
T3	134 (38.5%)	117 (33.6%)	251 (36.1%)
T4	77 (22.1%)	85 (24.4%)	162 (23.3%)
TX	45 (12.9%)	39 (11.2%)	84 (12.1%)
Unknown	21 (6.0%)	15 (4.3%)	36 (5.2%)
Lymph node stage at initial diagnosis			
N	348	348	696
N0	101 (29.0%)	90 (25.9%)	191 (27.4%)
N1	183 (52.6%)	200 (57.5%)	383 (55.0%)
NX	46 (13.2%)	42 (12.1%)	88 (12.6%)
Unknown	18 (5.2%)	16 (4.6%)	34 (4.9%)
Metastasis stage at initial diagnosis			
N	348	348	696
M0	36 (10.3%)	32 (9.2%)	68 (9.8%)
M1	302 (86.8%)	301 (86.5%)	603 (86.6%)
Unknown	10 (2.9%)	15 (4.3%)	25 (3.6%)
Gleason score at initial diagnosis			
N	348	348	696
<7	6 (1.7%)	5 (1.4%)	11 (1.6%)
7	62 (17.8%)	55 (15.8%)	117 (16.8%)
3+4	20 (5.7%)	19 (5.5%)	39 (5.6%)
4+3	41 (11.8%)	36 (10.3%)	77 (11.1%)
Unknown	1 (0.3%)	0	1 (0.1%)
≥8	262 (75.3%)	276 (79.3%)	538 (77.3%)
Unknown	18 (5.2%)	12 (3.4%)	30 (4.3%)
ECOG performance status score			
N	348	348	696
0	218 (62.6%)	242 (69.5%)	460 (66.1%)
1	124 (35.6%)	97 (27.9%)	221 (31.8%)

2	6 (1.7%)	9 (2.6%)	15 (2.2%)
Histology at study entry			
N	348	348	696
Adenocarcinoma	346 (99.4%)	347 (99.7%)	693 (99.6%)
Adenocarcinoma with small-cell or neuroendocrine features	2 (0.6%)	1 (0.3%)	3 (0.4%)
Extent of disease at study entry[a]			
N	347	348	695
Bone	339 (97.7%)	344 (98.9%)	683 (98.3%)
Bone only	154 (44.4%)	146 (42.0%)	300 (43.2%)
Visceral	54 (15.6%)	57 (16.4%)	111 (16.0%)
Adrenal gland	3 (0.9%)	3 (0.9%)	6 (0.9%)
Liver	16 (4.6%)	9 (2.6%)	25 (3.6%)
Lung	42 (12.1%)	49 (14.1%)	91 (13.1%)
Lymph nodes	161 (46.4%)	173 (49.7%)	334 (48.1%)
Soft tissue[b]	28 (8.1%)	32 (9.2%)	60 (8.6%)
Number of bone lesions at study entry			
N	348	348	696
≤ 10 lesions[c]	159 (45.7%)	176 (50.6%)	335 (48.1%)
> 10 lesions[d]	189 (54.3%)	172 (49.4%)	361 (51.9%)
BPI-SF pain score (item 3)			
N	346	348	694
Mean (SD)	1.92 (2.434)	1.98 (2.373)	1.95 (2.402)
Median	1.00	1.00	1.00
Range	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)
0	152 (43.9%)	149 (42.8%)	301 (43.4%)
1 to 3	117 (33.8%)	118 (33.9%)	235 (33.9%)
> 3	77 (22.3%)	81 (23.3%)	158 (22.8%)
PSA at initial diagnosis (ng/mL)			
N	275	258	533
Mean (SD)	537.00 (1424.151)	545.97 (1451.565)	541.34 (1436.140)
Median	101.60	112.25	110.00
Range	(0.1; 15900.0)	(0.1; 17475.0)	(0.1; 17475.0)
Disease volume of mCSPC (eCRF)[e]			
N	348	348	696
High	271 (77.9%)	269 (77.3%)	540 (77.6%)
Low	77 (22.1%)	79 (22.7%)	156 (22.4%)

Key: AAP = abiraterone acetate plus prednisone, BPI-SF = Brief Pain Inventory - Short Form, PSA = prostate-specific antigen, mCSPC = metastatic castration sensitive prostate cancer, eCRF = electronic case report form.
[a] Subjects having multiple lesions within each category are counted only once in the category and may be represented in more than one category.
[b] Soft tissue lesions are lesions reported in locations other than categories of visceral, lymph node, and bone.
[c] Includes subjects with no bone lesion.
[d] Superscan is counted in > 10 lesions bone category.
[e] Data is based on eCRF data. High-volume mCSPC is defined as 1) visceral metastases or 2) at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis or 3) when a Superscan is present. Low-volume mCSPC is defined as not meeting the definition of high-volume mCSPC.

Table 33. Summary of Demographics and Other Baseline Characteristics BRCA Full Analysis Set (AMPLITUDE Study)

	Placebo + AAP N=196	Nira + AAP N=191	Total N=387
Age, years			
Median	66.0	67.0	67.0
Range	(44; 92)	(41; 88)	(41; 92)
< 65	82 (41.8%)	74 (38.7%)	156 (40.3%)
≥ 65 to <75	81 (41.3%)	69 (36.1%)	150 (38.8%)
≥ 75	33 (16.8%)	48 (25.1%)	81 (20.9%)
Race			
Asian	43 (21.9%)	49 (25.7%)	92 (23.8%)
Black or African American	4 (2.0%)	10 (5.2%)	14 (3.6%)
White	144 (73.5%)	125 (65.4%)	269 (69.5%)
Ethnicity			
Hispanic or Latino	27 (13.8%)	18 (9.4%)	45 (11.6%)
Not Hispanic or Latino	162 (82.7%)	156 (81.7%)	318 (82.2%)
Type of prior ADT for mHSPC			
Medical Castration	183 (93.4%)	186 (97.4%)	369 (95.3%)
Surgical Castration	16 (8.2%)	9 (4.7%)	25 (6.5%)
Previous prostate cancer therapy			
Prostatectomy or radiotherapy	40 (20.4%)	47 (24.6%)	87 (22.5%)
Prostatectomy only	11 (5.6%)	14 (7.3%)	25 (6.5%)
Radiotherapy only	24 (12.2%)	25 (13.1%)	49 (12.7%)
Both prostatectomy and radiotherapy	5 (2.6%)	8 (4.2%)	13 (3.4%)
Androgen deprivation therapy	196 (100.0%)	191 (100.0%)	387 (100.0%)
GnRHa	183 (93.4%)	186 (97.4%)	369 (95.3%)
Bilateral Orchiectomy	16 (8.2%)	9 (4.7%)	25 (6.5%)
First generation anti-androgen	97 (49.5%)	99 (51.8%)	196 (50.6%)
Abiraterone acetate	14 (7.1%)	30 (15.7%)	44 (11.4%)
Docetaxel	33 (16.8%)	29 (15.2%)	62 (16.0%)
Time from metastatic diagnosis to randomization (months)			
N	196	191	387
Mean (SD)	3.79 (2.069)	4.05 (5.652)	3.92 (4.231)
Median	3.04	3.09	3.06
Range	(1.1; 14.9)	(0.4; 68.1)	(0.4; 68.1)
Tumor stage at initial diagnosis			
N	196	191	387
T1	5 (2.6%)	9 (4.7%)	14 (3.6%)
T2	33 (16.8%)	37 (19.4%)	70 (18.1%)
T3	68 (34.7%)	64 (33.5%)	132 (34.1%)
T4	48 (24.5%)	46 (24.1%)	94 (24.3%)
TX	32 (16.3%)	24 (12.6%)	56 (14.5%)
Unknown	10 (5.1%)	11 (5.8%)	21 (5.4%)
Lymph node stage at initial diagnosis			
N	196	191	387
N0	50 (25.5%)	44 (23.0%)	94 (24.3%)
N1	108 (55.1%)	110 (57.6%)	218 (56.3%)
NX	29 (14.8%)	27 (14.1%)	56 (14.5%)
Unknown	9 (4.6%)	10 (5.2%)	19 (4.9%)
Metastasis stage at initial diagnosis			
N	196	191	387
M0	16 (8.2%)	14 (7.3%)	30 (7.8%)
M1	175 (89.3%)	167 (87.4%)	342 (88.4%)
Unknown	5 (2.6%)	10 (5.2%)	15 (3.9%)
Gleason score at initial diagnosis			
N	196	191	387
<7	1 (0.5%)	3 (1.6%)	4 (1.0%)
7	29 (14.8%)	22 (11.5%)	51 (13.2%)
3+4	10 (5.1%)	4 (2.1%)	14 (3.6%)
4+3	19 (9.7%)	18 (9.4%)	37 (9.6%)
≥ 8	158 (80.6%)	160 (83.8%)	318 (82.2%)
8	54 (27.6%)	43 (22.5%)	97 (25.1%)
9	74 (37.8%)	96 (50.3%)	170 (43.9%)
10	30 (15.3%)	21 (11.0%)	51 (13.2%)
Unknown	8 (4.1%)	6 (3.1%)	14 (3.6%)
ECOG performance status score			
N	196	191	387
0	130 (66.3%)	133 (69.6%)	263 (68.0%)
1	65 (33.2%)	55 (28.8%)	120 (31.0%)
2	1 (0.5%)	3 (1.6%)	4 (1.0%)
Histology at study entry			
N	196	191	387
Adenocarcinoma	195 (99.5%)	190 (99.5%)	385 (99.5%)
Adenocarcinoma with small-cell or neuroendocrine features	1 (0.5%)	1 (0.5%)	2 (0.5%)

ECOG performance status score			
0	130 (66.3%)	133 (69.6%)	263 (68.0%)
1	65 (33.2%)	55 (28.8%)	120 (31.0%)
2	1 (0.5%)	3 (1.6%)	4 (1.0%)
Extent of disease at study entry[a]			
Bone	191 (97.4%)	189 (99.0%)	380 (98.2%)
Bone only	77 (39.3%)	81 (42.4%)	158 (40.8%)
Visceral	31 (15.8%)	33 (17.3%)	64 (16.5%)
Lymph nodes	100 (51.0%)	92 (48.2%)	192 (49.6%)
Soft tissue[b]	19 (9.7%)	17 (8.9%)	36 (9.3%)
PSA at initial diagnosis (ng/mL)			
Median	100.00	134.50	107.00
Range	(0.1; 15900.0)	(1.3; 7206.0)	(0.1; 15900.0)
Disease volume of mHSPC (eCRF)[c]			
High	155 (79.1%)	151 (79.1%)	306 (79.1%)
Low	41 (20.9%)	40 (20.9%)	81 (20.9%)
Bone sparing agents			
Received bone sparing agents	45 (23.0%)	46 (24.1%)	91 (23.5%)
Did not receive bone sparing agents	151 (77.0%)	145 (75.9%)	296 (76.5%)

Prior, concomitant and post-treatment therapy

Prior prostate cancer therapy

Table 34. Summary of prior prostate cancer therapy and related information; full analysis set (All HRR population)

	Placebo + AAP	Nira + AAP	Total
Analysis set: Full	348	348	696
Type of prior ADT for mCSPC			
N	348	348	696
Medical Castration	323 (92.8%)	334 (96.0%)	657 (94.4%)
Surgical Castration	28 (8.0%)	18 (5.2%)	46 (6.6%)
Time from initiation of ADT for mCSPC to randomization (months)			
N	348	348	696
Mean (SD)	2.70 (1.518)	2.79 (1.578)	2.74 (1.548)
Median	2.30	2.46	2.33
Range	(0.1; 6.2)	(0.2; 6.2)	(0.1; 6.2)
< 3 months	246 (70.7%)	217 (62.4%)	463 (66.5%)
≥ 3 months	102 (29.3%)	131 (37.6%)	233 (33.5%)
Previous prostate cancer therapy			
N	348	347	695
Prostatectomy or radiotherapy	81 (23.3%)	86 (24.8%)	167 (24.0%)
Prostatectomy only	17 (4.9%)	24 (6.9%)	41 (5.9%)
Radiotherapy only	48 (13.8%)	51 (14.7%)	99 (14.2%)
Both prostatectomy and radiotherapy	16 (4.6%)	11 (3.2%)	27 (3.9%)
Androgen deprivation therapy	348 (100.0%)	347 (100.0%)	695 (100.0%)
GnRHa	324 (93.1%)	333 (96.0%)	657 (94.5%)
Bilateral Orchiectomy	28 (8.0%)	18 (5.2%)	46 (6.6%)
First generation anti-androgen	165 (47.4%)	169 (48.7%)	334 (48.1%)
Abiraterone acetate	27 (7.8%)	46 (13.3%)	73 (10.5%)
Docetaxel	56 (16.1%)	54 (15.6%)	110 (15.8%)
Other	2 (0.6%)	4 (1.2%)	6 (0.9%)

Key: AAP = abiraterone acetate plus prednisone.
GnRHa = gonadotropin releasing hormone analog.
Note: Prior hormonal therapy Other category includes CYPROTERONE and CYPROTERONE ACETATE.

Prior and concomitant medication

Prior and concomitant treatment use was consistent with an elderly prostate cancer population and similar between treatment arms. The most common prior medication class received was endocrine therapy (95.3%), as participants were required to be treated with medical or surgical castration prior to randomization. Other common (≥30%) prior medication classes were vaccines (54.7%),

analgesics (36.0%), and agents acting on the renin-angiotensin system (34.5%). Similarly, endocrine therapy (92.5%) was the most common class of concomitant medication in the study, indicating continuance of medical castration as required by protocol. Other common concomitant medication classes were analgesics (66.9%), agents acting on the renin-angiotensin system (55.8%), drugs for acid-related disorders (45.8%), antibacterials for systemic use (45.6%), mineral supplements (41.7%), calcium channel blockers (40.3%), urologicals (39.1%), lipid-modifying agents (36.3%), anti-inflammatory and antirheumatic products (35.1%), vitamins (35.0%), and beta-blocking agents (30.5%).

Numbers analysed

Table 35. Number of subjects in each analysis set; Full analysis set (study AMPLITUDE)

	Placebo + AAP	Nira + AAP	Total
Full analysis set	348	348	696
Safety analysis set	348 (100.0%)	347 (99.7%)	695 (99.9%)
PK analysis set	0	335 (96.3%)	335 (48.1%)

Outcomes and estimation

BRCA subgroup

Radiographic Progression-free survival (rPFS) by Investigator - Primary endpoint

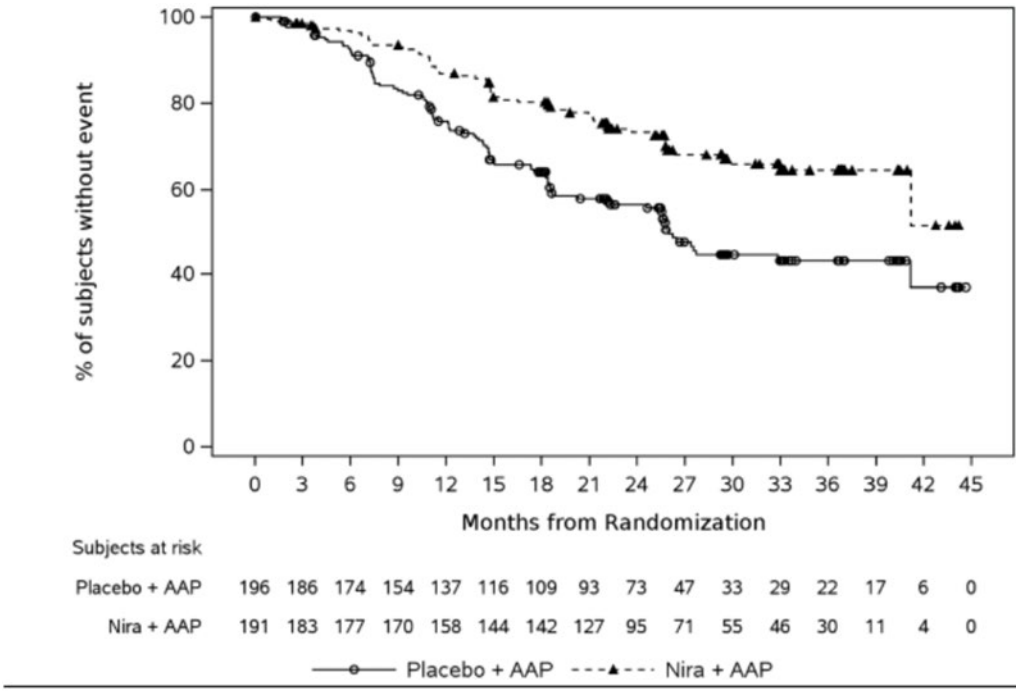
As per the SAP, the primary endpoint of investigator-assessed rPFS was tested first in the BRCA subgroup.

Table 36. IA1: Summary of Radiographic Progression-free Survival by Investigator Review - Stratified Analysis; BRCA Full Analysis Set (Study 67652000PCR3002)

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Event	93 (47.4%)	57 (29.8%)
Radiographic progression	88 (44.9%)	46 (24.1%)
Death	5 (2.6%)	11 (5.8%)
Censored	103 (52.6%)	134 (70.2%)
Time to event (months)		
25th percentile (95% CI)	12.19 (10.41, 14.65)	22.14 (14.98, 26.38)
Median (95% CI)	25.99 (22.11, 41.17)	NE (41.20, NE)
75th percentile (95% CI)	NE (41.17, NE)	NE (NE, NE)
Range	(0.0+, 44.6+)	(0.0+, 44.2+)
6-month event-free rate (95% CI)	0.926 (0.879, 0.956)	0.968 (0.930, 0.985)
12-month event-free rate (95% CI)	0.759 (0.690, 0.814)	0.869 (0.811, 0.910)
18-month event-free rate (95% CI)	0.640 (0.566, 0.705)	0.802 (0.736, 0.853)
24-month event-free rate (95% CI)	0.565 (0.488, 0.635)	0.732 (0.660, 0.792)
30-month event-free rate (95% CI)	0.445 (0.362, 0.525)	0.658 (0.575, 0.729)
36-month event-free rate (95% CI)	0.431 (0.346, 0.513)	0.645 (0.558, 0.718)
p-value [a]		<.0001
Hazard ratio (95% CI) [b]		0.515 (0.370,0.717)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Figure 11. Kaplan-Meier Plot of Radiographic Progression-free Survival by Investigator Review; BRCA Full Analysis Set Cut-off date 07 January 2025



Key: AAP = abiraterone acetate plus prednisone.

Time to Symptomatic Progression – Key secondary endpoint

TSP evaluated the treatment effect of nira+AAP on the development of clinically meaningful symptoms that impact the patient experience, including the need for palliative radiotherapy, tumor-related orthopedic intervention, other cancer-related morbidity (eg, spinal cord compression) or procedures (eg, nephrostomy), or initiation of new antineoplastic systemic therapy due to cancer-related symptoms.

Table 37: Summary of time to symptomatic progression - stratified analysis; BRCA full analysis set Cut-off date 07 January 2025

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Event	66 (33.7%)	31 (16.2%)
Censored	130 (66.3%)	160 (83.8%)
Time to event (months)		
25th percentile (95% CI)	18.56 (13.01, 24.61)	NE (25.99, NE)
Median (95% CI)	NE (39.72, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.8, 46.4+)	(0.7+, 46.7+)
6-month event-free rate (95% CI)	0.954 (0.913, 0.976)	0.984 (0.951, 0.995)
12-month event-free rate (95% CI)	0.834 (0.774, 0.880)	0.957 (0.915, 0.978)
18-month event-free rate (95% CI)	0.761 (0.694, 0.815)	0.911 (0.859, 0.945)
24-month event-free rate (95% CI)	0.693 (0.622, 0.754)	0.833 (0.767, 0.882)
30-month event-free rate (95% CI)	0.652 (0.576, 0.718)	0.816 (0.746, 0.869)
36-month event-free rate (95% CI)	0.635 (0.552, 0.706)	0.803 (0.728, 0.859)

p-value [a]	0.0001
Hazard ratio (95% CI) [b]	0.444 (0.290,0.681)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Figure 12. Kaplan-Meier plot of time to symptomatic progression; BRCA full analysis set Cut-off date 07 January 2025

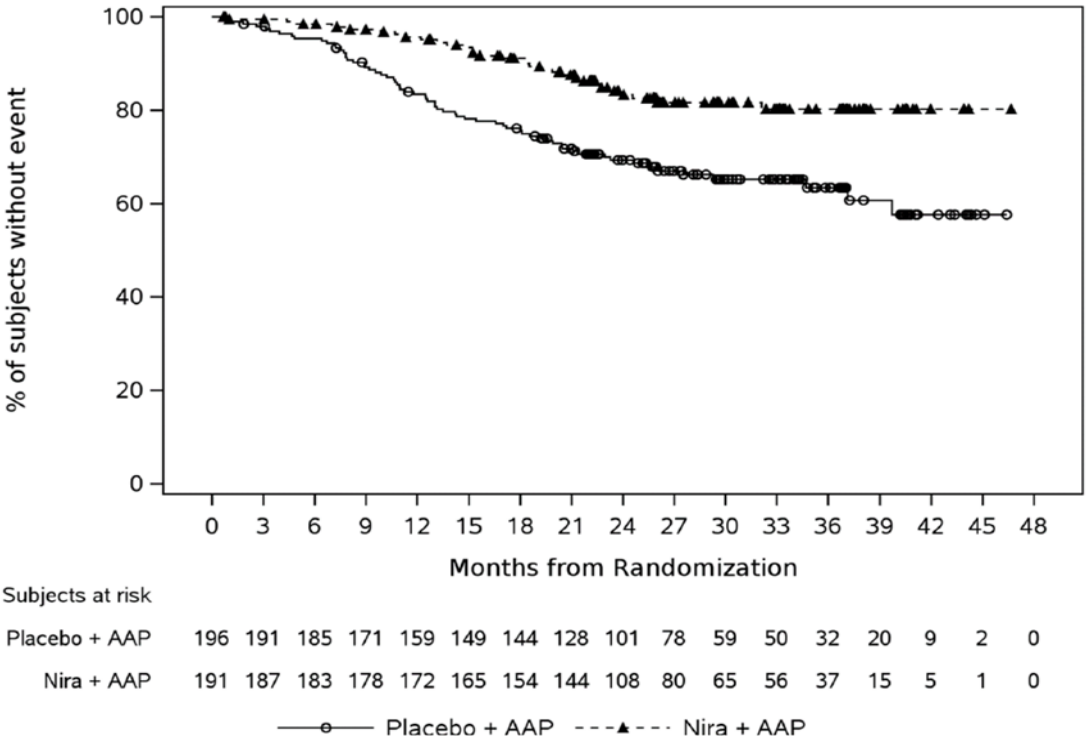


Table 38: Number of Subjects who reported Symptomatic Progression Events and Bone Sparing Agents; BRCA Safety Analysis Set

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Subjects who received bone sparing agents	45 (23.0%)	46 (24.1%)
Subjects with symptomatic progression event	16 (8.2%)	5 (2.6%)
Subjects who did not receive bone sparing agents	151 (77.0%)	145 (75.9%)
Subjects with symptomatic progression event	50 (25.5%)	26 (13.6%)
Subjects with symptomatic progression event	66 (33.7%)	31 (16.2%)
Subjects who received bone sparing agents prior to the first event[a]	13 (6.6%)	2 (1.0%)
Subjects who did not receive bone sparing agents prior to the first event	53 (27.0%)	29 (15.2%)
Subjects with no symptomatic progression event	130 (66.3%)	160 (83.8%)
Subjects who received bone sparing agents	29 (14.8%)	41 (21.5%)

Key: AAP = abiraterone acetate plus prednisone.
[a] Received bone-sparing agent up to and including 1 day prior to symptomatic progression event.
Included bone sparing agents as prior therapy or concomitant medication.

[tefbsaspr01brca.rtf] [PROD/jnj-67652000/pcr3002/dbr_csr/re_eureg/tefbsaspr01brca.sas] 13NOV2025, 23:58

Overall survival – Key secondary endpoint

At the first interim analysis for OS (IA1), the median follow-up in the BRCA subgroup was 30.7 months; 44 (23.0%) participants in the nira+AAP arm and 61 (31.1%) participants in the PBO+AAP arm had died. Statistical significance was not met at PA-IA1. HR point estimate was 0.750 (95% CI: 0.509, 1.106).

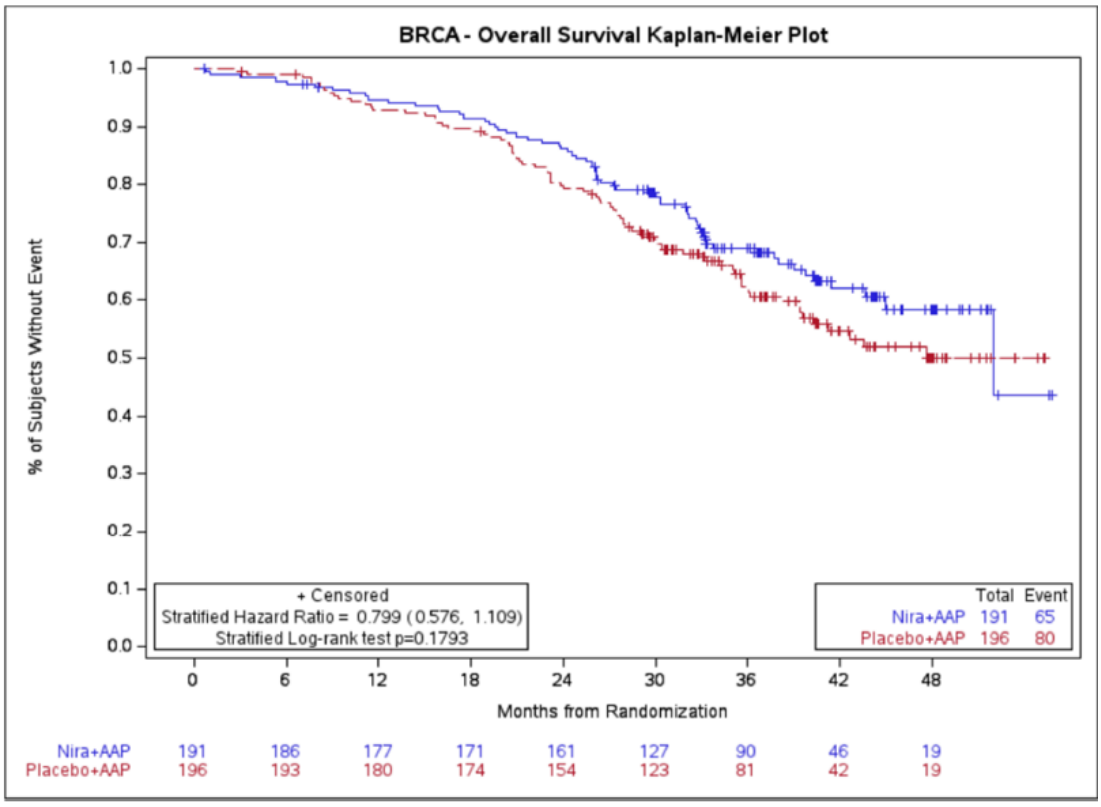
At the second interim analysis for OS (IA2), with a DCO of 03-Oct-2025 and median follow-up in All HRR population of 40.5 months. HR point estimate was 0.799 (95% CI: 0.576, 1.109) with a p-value above the prespecified significance boundary.This analysis was performed with 65 (34%) events in the Nira+AAP arm and 80 (40.8%) in the Pbo+AAP treatment arm.

Table 39. Summary of Overall Survival – Stratified Analysis; BRCA Full Analysis Set (IA2) Cut-off date 03-Oct-2025

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Event	80 (40.8%)	65 (34.0%)
Censored	116 (59.2%)	126 (66.0%)
Time to event (months)		
25th percentile (95% CI)	27.53 (23.20, 30.42)	32.10 (26.15, 36.44)
Median (95% CI)	47.61 (39.36, NE)	52.01 (44.98, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (52.01, NE)
Range	(2.7, 55.4+)	(0.7+, 55.8+)
6-month event-free rate (95% CI)	0.990 (0.960, 0.997)	0.979 (0.945, 0.992)
12-month event-free rate (95% CI)	0.928 (0.881, 0.957)	0.947 (0.904, 0.971)
18-month event-free rate (95% CI)	0.897 (0.845, 0.932)	0.915 (0.865, 0.947)
24-month event-free rate (95% CI)	0.798 (0.735, 0.848)	0.861 (0.803, 0.903)
30-month event-free rate (95% CI)	0.704 (0.634, 0.763)	0.779 (0.713, 0.833)
36-month event-free rate (95% CI)	0.622 (0.546, 0.689)	0.689 (0.615, 0.753)
42-month event-free rate (95% CI)	0.546 (0.462, 0.623)	0.620 (0.535, 0.694)
48-month event-free rate (95% CI)	0.499 (0.406, 0.585)	0.583 (0.487, 0.667)
p-value [a]		0.1793
Hazard ratio (95% CI) [b]		0.799 (0.576,1.109)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Figure 13. BRCA – Overall Survival (IA2) Cut-off date 03-Oct-2025



- **Secondary endpoints**

Results of all secondary end point are based on the Cut-off date 07 January 2025 analysis

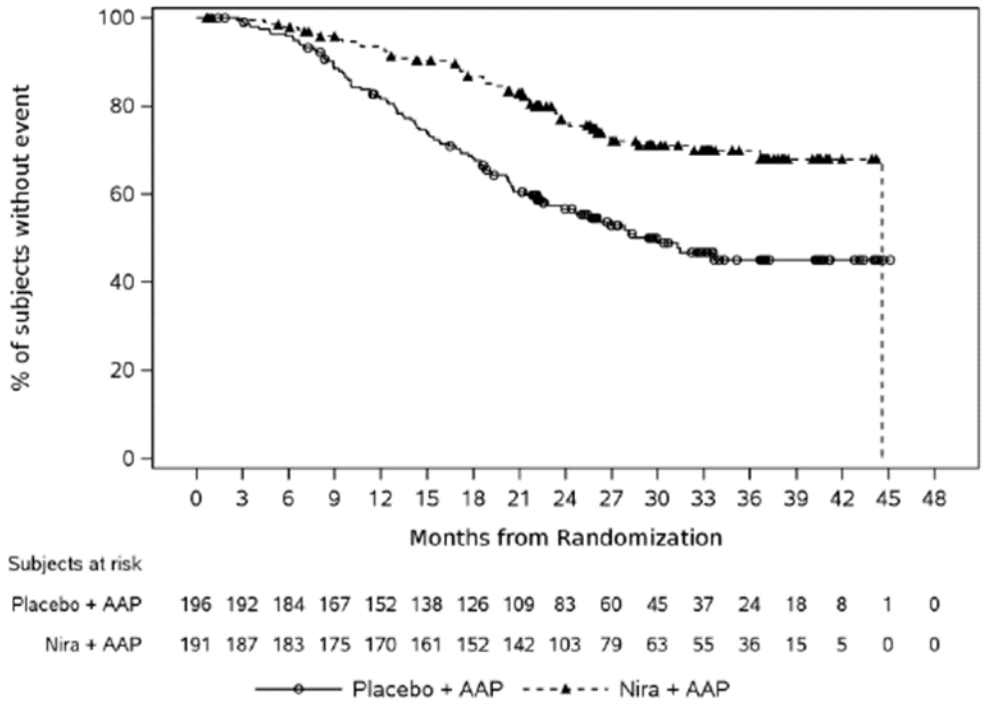
Time to subsequent therapy

Table 40. Summary of time to subsequent therapy – stratified analysis; BRCA full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Event	92 (46.9%)	50 (26.2%)
Censored	104 (53.1%)	141 (73.8%)
Time to event (months)		
25th percentile (95% CI)	14.49 (12.35, 17.68)	25.79 (21.65, NE)
Median (95% CI)	29.96 (22.80, NE)	44.55 (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	44.55 (NE, NE)
Range	(1.4+, 45.1+)	(0.7+, 44.6)
6-month event-free rate (95% CI)	0.958 (0.919, 0.979)	0.979 (0.944, 0.992)
12-month event-free rate (95% CI)	0.816 (0.753, 0.864)	0.935 (0.888, 0.963)
18-month event-free rate (95% CI)	0.681 (0.610, 0.743)	0.868 (0.809, 0.910)
24-month event-free rate (95% CI)	0.567 (0.491, 0.635)	0.762 (0.690, 0.819)
30-month event-free rate (95% CI)	0.490 (0.409, 0.565)	0.710 (0.631, 0.776)
36-month event-free rate (95% CI)	0.451 (0.365, 0.532)	0.699 (0.617, 0.766)
p-value [a]		<.0001
Hazard ratio (95% CI) [b]		0.467 (0.330,0.659)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Figure 14. Kaplan-Meier plot of time to subsequent therapy; BRCA full analysis set



Objective response rate (ORR)

Table 41. Summary of objective response rate based on RECIST version 1.1 criteria in subjects with measurable disease at baseline by Investigator review – Non-stratified Analysis; BRCA Full Analysis Set

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Number of subjects with measurable disease at baseline[a]	72	63
Responder	53 (73.6%)	48 (76.2%)
Non-responder	19 (26.4%)	15 (23.8%)
p-value[b]		0.731
Relative Risk (95% CI)[c]		1.035 (0.851,1.258)
Best Overall Response		
Complete Response (CR)	12 (16.7%)	16 (25.4%)
Partial Response (PR)	41 (56.9%)	32 (50.8%)
Stable Disease (SD)	18 (25.0%)	12 (19.0%)
Progressive Disease (PD)	1 (1.4%)	1 (1.6%)
Not Evaluable (NE)	0	2 (3.2%)

Key: AAP = abiraterone acetate plus prednisone.
[a] No progression by PCWG3.
[b] p-value is from chi-square test.
[c] Relative Risk >1 favors Nira + AAP treatment.
Note: Response is a CR or PR. CR and PR do not have to be confirmed.
Note: Percent of Responder/Non-responder is based on the number of subjects with measurable disease at baseline.

Duration of response (DoR)

Table 42. Summary of duration of response by Investigator review based on subjects with measurable disease at baseline – Non-stratified analysis; responders in BRCA full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Responders in Full	53	48
Event	32 (60.4%)	20 (41.7%)
Censored	21 (39.6%)	28 (58.3%)
Time to event (months)		
25th percentile (95% CI)	6.74 (4.14, 11.99)	13.14 (9.23, 18.37)
Median (95% CI)	16.79 (11.50, 23.85)	27.63 (16.89, NE)
75th percentile (95% CI)	NE (23.72, NE)	NE (NE, NE)
Range	(0.2+, 42.3+)	(0.0+, 39.2+)
6-month event-free rate (95% CI)	0.787 (0.649, 0.876)	0.934 (0.809, 0.978)
12-month event-free rate (95% CI)	0.622 (0.472, 0.740)	0.796 (0.645, 0.889)
18-month event-free rate (95% CI)	0.478 (0.328, 0.613)	0.648 (0.485, 0.772)
24-month event-free rate (95% CI)	0.310 (0.174, 0.455)	0.530 (0.362, 0.673)
30-month event-free rate (95% CI)	0.275 (0.145, 0.423)	0.486 (0.313, 0.639)
36-month event-free rate (95% CI)	0.275 (0.145, 0.423)	0.486 (0.313, 0.639)
p-value [a]		0.0361
Hazard ratio (95% CI) [b]		0.554 (0.316,0.970)

Duration of response in participants with measurable disease at baseline is defined as time from documented response (CR or PR whichever occurred first) post baseline and before PD identified by RECIST to the first date of documented disease progression.
Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a nonstratified log-rank test.
[b] Hazard ratio is from nonstratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment
Note: + = censored observation, NE = not estimable.

Time to PSA progression

Table 43: Summary of time to PSA progression - Stratified analysis; BRCA full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Event	93 (47.4%)	47 (24.6%)
Censored	103 (52.6%)	144 (75.4%)
Time to event (months)		
25th percentile (95% CI)	9.53 (7.36, 12.91)	22.18 (14.92, NE)
Median (95% CI)	25.53 (16.66, NE)	NE (41.36, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (41.36, NE)
Range	(0.0+, 44.3+)	(0.0+, 44.2+)
6-month event-free rate (95% CI)	0.837 (0.776, 0.882)	0.929 (0.881, 0.958)
12-month event-free rate (95% CI)	0.707 (0.635, 0.768)	0.856 (0.795, 0.899)
18-month event-free rate (95% CI)	0.568 (0.491, 0.638)	0.792 (0.724, 0.844)
24-month event-free rate (95% CI)	0.516 (0.438, 0.588)	0.737 (0.663, 0.797)
30-month event-free rate (95% CI)	0.442 (0.358, 0.522)	0.728 (0.652, 0.789)
36-month event-free rate (95% CI)	0.428 (0.343, 0.510)	0.728 (0.652, 0.789)
p-value [a]		<.0001
Hazard ratio (95% CI) [b]		0.414 (0.291,0.589)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

PSA response rate

Table 44: Summary of PSA response rate (decline ≥50%) – Non-stratified analysis; BRCA full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Subjects with PSA Response	176 (89.8%)	177 (92.7%)
Confirmed	168 (85.7%)	169 (88.5%)
Unconfirmed	8 (4.1%)	8 (4.2%)
p-value[a]		0.417
Relative Risk (95% CI)[b]		1.032 (0.956,1.115)

Key: AAP = abiraterone acetate plus prednisone.
PSA response is defined as a PSA decline of ≥50% according to PCWG3 criteria.
[a] p-value is based on confirmed response from chi-square test.
[b] Relative Risk is based on confirmed response. Relative Risk >1 favors Nira + AAP treatment.

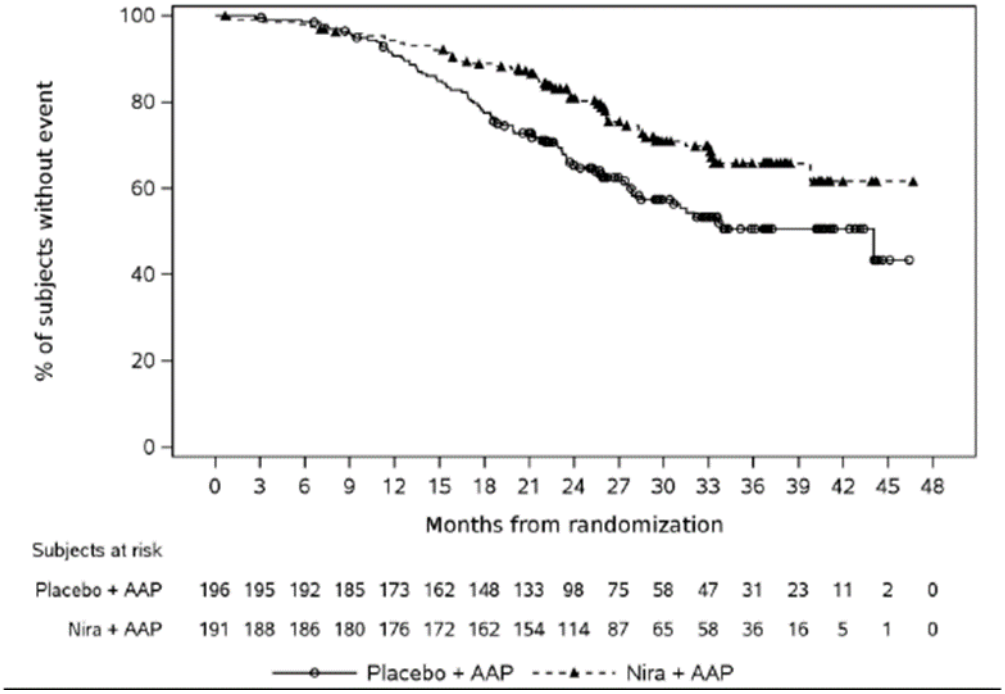
Progression-free survival on first subsequent therapy (PFS2)

Table 45: Summary of progression-free survival 2 – stratified analysis; BRCA full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Event	81 (41.3%)	51 (26.7%)
Censored	115 (58.7%)	140 (73.3%)
Time to event (months)		
25th percentile (95% CI)	18.76 (16.89, 23.20)	27.27 (23.69, 33.18)
Median (95% CI)	44.02 (28.45, NE)	NE (39.79, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(2.7, 46.4+)	(0.7+, 46.7+)
6-month event-free rate (95% CI)	0.985 (0.953, 0.995)	0.979 (0.945, 0.992)
12-month event-free rate (95% CI)	0.907 (0.856, 0.940)	0.942 (0.897, 0.967)
18-month event-free rate (95% CI)	0.776 (0.710, 0.828)	0.888 (0.833, 0.925)
24-month event-free rate (95% CI)	0.654 (0.579, 0.718)	0.809 (0.743, 0.860)
30-month event-free rate (95% CI)	0.574 (0.494, 0.647)	0.708 (0.627, 0.775)
36-month event-free rate (95% CI)	0.506 (0.417, 0.587)	0.657 (0.566, 0.734)
p-value [a]		0.0026
Hazard ratio (95% CI) [b]		0.587 (0.413,0.834)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Figure 15. Kaplan-Meier plot of progression-free survival 2; BRCA full analysis set



Time to initiation of cytotoxic chemotherapy

Table 46: Time to initiation of cytotoxic chemotherapy – stratified analysis; BRCA full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Event	62 (31.6%)	41 (21.5%)
Censored	134 (68.4%)	150 (78.5%)
Time to event (months)		
25th percentile (95% CI)	22.18 (17.12, 27.86)	28.62 (23.49, NE)
Median (95% CI)	45.54 (34.07, NE)	NE (NE, NE)
75th percentile (95% CI)	45.54 (NE, NE)	NE (NE, NE)
Range	(1.4+, 45.5)	(0.7+, 46.7+)
6-month event-free rate (95% CI)	0.974 (0.939, 0.989)	0.979 (0.944, 0.992)
12-month event-free rate (95% CI)	0.894 (0.840, 0.930)	0.946 (0.902, 0.970)
18-month event-free rate (95% CI)	0.796 (0.730, 0.847)	0.901 (0.847, 0.936)
24-month event-free rate (95% CI)	0.721 (0.648, 0.781)	0.795 (0.724, 0.850)
30-month event-free rate (95% CI)	0.666 (0.586, 0.735)	0.745 (0.666, 0.807)
36-month event-free rate (95% CI)	0.592 (0.494, 0.676)	0.745 (0.666, 0.807)
p-value [a]		0.0145
Hazard ratio (95% CI) [b]		0.614 (0.414,0.911)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

HRR effector subgroup

Radiographic Progression-free survival (rPFS) by Investigator - Primary endpoint

Per the SAP, the HRR effector subgroup was tested next in the hierarchy, after the BRCA subgroup.

Table 47: Summary of Radiographic Progression-free Survival by Investigator Review - Stratified Analysis; HRR Effectors Full Analysis Set Cut-off date 07 January 2025

	Placebo + AAP	Nira + AAP
Analysis set: Full	226	230
Event	102 (45.1%)	71 (30.9%)
Radiographic progression	95 (42.0%)	57 (24.8%)
Death	7 (3.1%)	14 (6.1%)
Censored	124 (54.9%)	159 (69.1%)
Time to event (months)		
25th percentile (95% CI)	13.14 (10.74, 14.75)	21.16 (14.82, 25.79)
Median (95% CI)	27.56 (25.59, NE)	NE (41.20, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 44.6+)	(0.0+, 44.5+)
6-month event-free rate (95% CI)	0.936 (0.894, 0.961)	0.969 (0.936, 0.985)
12-month event-free rate (95% CI)	0.770 (0.708, 0.821)	0.859 (0.806, 0.899)
18-month event-free rate (95% CI)	0.662 (0.593, 0.722)	0.785 (0.724, 0.834)
24-month event-free rate (95% CI)	0.586 (0.515, 0.651)	0.718 (0.651, 0.773)
30-month event-free rate (95% CI)	0.464 (0.386, 0.539)	0.645 (0.568, 0.711)
36-month event-free rate (95% CI)	0.453 (0.372, 0.529)	0.633 (0.554, 0.702)
p-value [a]		0.0003
Hazard ratio (95% CI) [b]		0.571 (0.421,0.774)

Key: AAP = abiraterone acetate plus prednisone.

[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).

[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.

Note: + = censored observation, NE = not estimable.

Time to Symptomatic Progression – Key secondary endpoint

Table 48 Summary of time to symptomatic progression – stratified analysis; HRR effector full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Full	226	230
Event	69 (30.5%)	37 (16.1%)
Censored	157 (69.5%)	193 (83.9%)
Time to event (months)		
25th percentile (95% CI)	19.94 (14.29, 29.24)	41.40 (32.10, NE)
Median (95% CI)	NE (NE, NE)	NE (41.40, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.8, 47.5+)	(0.7+, 46.7+)
6-month event-free rate (95% CI)	0.955 (0.919, 0.976)	0.987 (0.959, 0.996)
12-month event-free rate (95% CI)	0.847 (0.792, 0.888)	0.959 (0.923, 0.979)
18-month event-free rate (95% CI)	0.783 (0.722, 0.832)	0.907 (0.859, 0.939)
24-month event-free rate (95% CI)	0.719 (0.653, 0.774)	0.836 (0.776, 0.881)
30-month event-free rate (95% CI)	0.683 (0.613, 0.743)	0.821 (0.759, 0.869)
36-month event-free rate (95% CI)	0.668 (0.594, 0.733)	0.810 (0.743, 0.861)
p-value [a]		0.0004
Hazard ratio (95% CI) [b]		0.495 (0.332,0.738)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Overall survival – Key secondary endpoint

Table 49: Summary of Overall Survival IA2 – Stratified Analysis; HRR Effectors Full Analysis Set *Cut-off date* 03 October 2025

	Placebo + AAP	Nira + AAP
Analysis set: Full	226	230
Event	88 (38.9%)	79 (34.3%)
Censored	138 (61.1%)	151 (65.7%)
Time to event (months)		
25th percentile (95% CI)	27.89 (23.20, 32.33)	32.07 (26.15, 35.65)
Median (95% CI)	NE (41.26, NE)	52.01 (44.98, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (52.01, NE)
Range	(2.7, 55.4+)	(0.7+, 55.8+)
6-month event-free rate (95% CI)	0.987 (0.959, 0.996)	0.978 (0.948, 0.991)
12-month event-free rate (95% CI)	0.929 (0.886, 0.956)	0.952 (0.914, 0.973)
18-month event-free rate (95% CI)	0.897 (0.850, 0.931)	0.894 (0.846, 0.927)
24-month event-free rate (95% CI)	0.803 (0.745, 0.850)	0.840 (0.786, 0.882)
30-month event-free rate (95% CI)	0.717 (0.652, 0.771)	0.768 (0.707, 0.818)
36-month event-free rate (95% CI)	0.641 (0.571, 0.703)	0.687 (0.619, 0.745)
42-month event-free rate (95% CI)	0.575 (0.498, 0.645)	0.613 (0.536, 0.681)
48-month event-free rate (95% CI)	0.536 (0.451, 0.613)	0.584 (0.500, 0.659)
p-value [a]		0.3493
Hazard ratio (95% CI) [b]		0.865 (0.638,1.172)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

All HRR population

Radiographic Progression-free survival (rPFS) by Investigator - Primary endpoint

Table 50: Summary of Radiographic Progression-free Survival by Investigator Review - Stratified Analysis; All HRR Full Analysis Set Cut-off date 07 January 2025

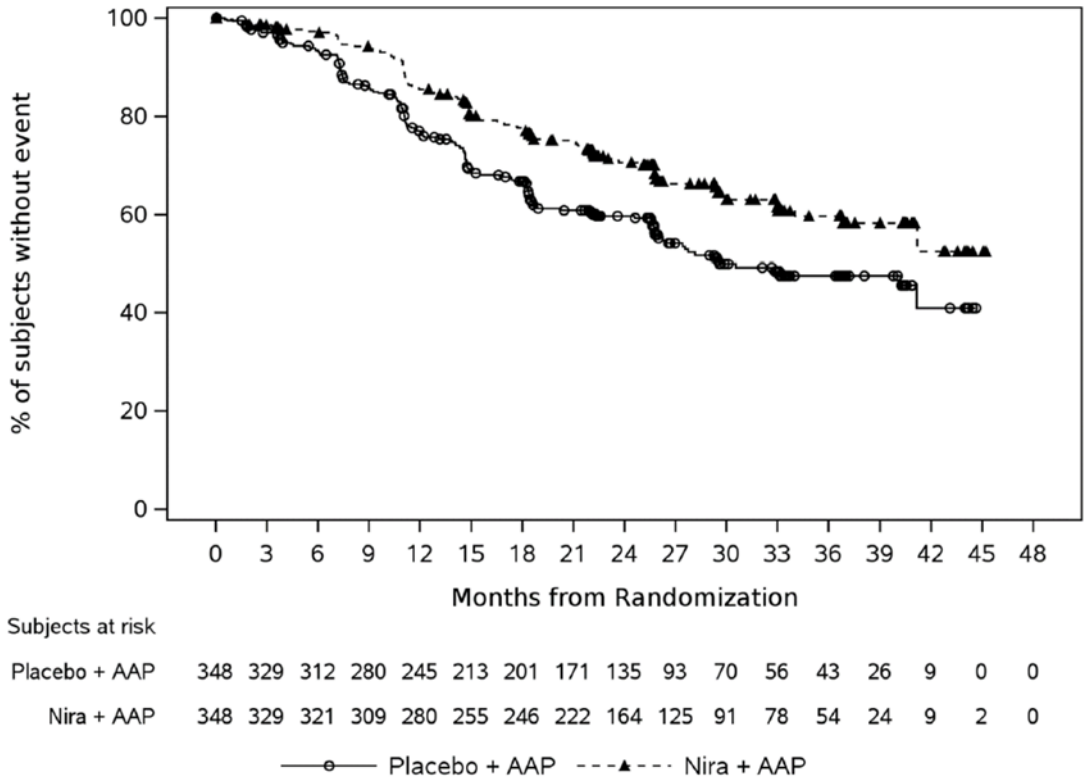
	Placebo + AAP	Nira + AAP
Analysis set: Full	348	348
Event	151 (43.4%)	113 (32.5%)
Radiographic progression	139 (39.9%)	92 (26.4%)
Death	12 (3.4%)	21 (6.0%)
Censored	197 (56.6%)	235 (67.5%)
Time to event (months)		
25th percentile (95% CI)	13.86 (11.10, 14.75)	20.93 (15.41, 25.10)
Median (95% CI)	29.54 (25.82, NE)	NE (41.20, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 44.6+)	(0.0+, 45.2+)
6-month event-free rate (95% CI)	0.935 (0.903, 0.957)	0.973 (0.949, 0.986)
12-month event-free rate (95% CI)	0.770 (0.721, 0.812)	0.854 (0.811, 0.888)
18-month event-free rate (95% CI)	0.667 (0.613, 0.716)	0.776 (0.727, 0.818)
24-month event-free rate (95% CI)	0.597 (0.540, 0.649)	0.706 (0.651, 0.753)
30-month event-free rate (95% CI)	0.499 (0.436, 0.559)	0.630 (0.568, 0.686)
36-month event-free rate (95% CI)	0.475 (0.409, 0.538)	0.596 (0.528, 0.658)
p-value [a]		0.0001
Hazard ratio (95% CI) [b]		0.625 (0.490,0.799)

	Placebo + AAP	Nira + AAP

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low), gene status (BRCA2 versus all other pathogenic alterations).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

[tefrpfs01.rtf] [PROD/jnj-67652000/pcr3002/dbr_csr/re_csr/tefrpfs01.sas] 17FEB2025, 13:54
And event type extracted from: [tefrpfs06.rtf] [PROD/jnj-67652000/pcr3002/dbr_csr/re_csr/tefrpfs06.sas] 19FEB2025, 15:54

Figure 16. Kaplan-Meier plot of radiographic progression-free survival by investigator review; full analysis set (All HRR population) Cut-off date 07 January 2025



Time to Symptomatic Progression – Key secondary endpoint

Table 51. Summary of time to symptomatic progression – stratified analysis; full analysis set (All HRR population) Cut-off date 07 January 2025

	Placebo + AAP	Nira + AAP
Analysis set: Full	348	348
Event	104 (29.9%)	57 (16.4%)
Censored	244 (70.1%)	291 (83.6%)
Time to event (months)		
25th percentile (95% CI)	20.40 (15.57, 26.87)	41.40 (32.10, NE)
Median (95% CI)	NE (43.14, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.5+, 47.5+)	(0.7+, 46.7+)
6-month event-free rate (95% CI)	0.965 (0.939, 0.980)	0.988 (0.969, 0.996)
12-month event-free rate (95% CI)	0.855 (0.813, 0.888)	0.961 (0.933, 0.977)
18-month event-free rate (95% CI)	0.783 (0.734, 0.823)	0.912 (0.876, 0.939)
24-month event-free rate (95% CI)	0.724 (0.672, 0.769)	0.847 (0.801, 0.884)
30-month event-free rate (95% CI)	0.685 (0.629, 0.734)	0.805 (0.751, 0.848)
36-month event-free rate (95% CI)	0.669 (0.609, 0.722)	0.787 (0.728, 0.835)
p-value [a]		<.0001
Hazard ratio (95% CI) [b]		0.503 (0.364,0.695)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low), gene status (BRCA2 versus all other pathogenic alterations).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Figure 17. Kaplan-Meier plot of time to symptomatic progression – full analysis set (All HRR population) Cut-off date 07 January 2025

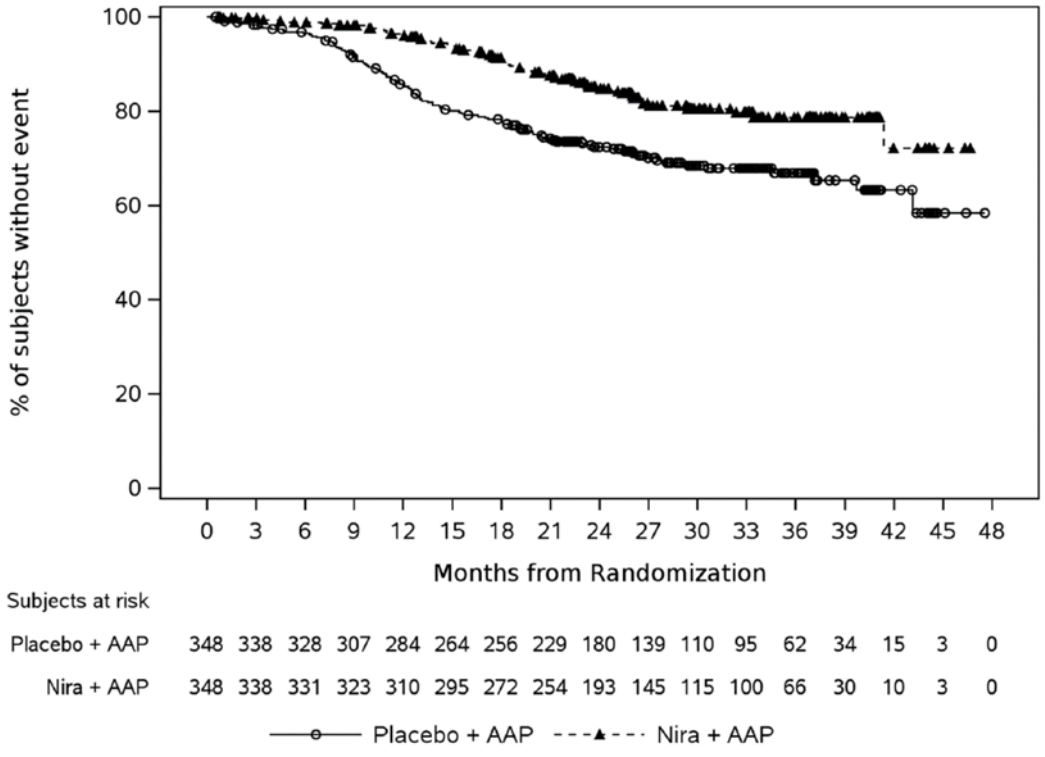


Table 52: Number of Subjects With or Without Symptomatic Progression Events and Bone Sparing Agents; Full Analysis Set

	Placebo + AAP	Nira + AAP
Analysis set: Full	348	348
Subjects who received bone sparing agents	70 (20.1%)	84 (24.1%)
Subjects with symptomatic progression event	21 (6.0%)	12 (3.4%)
Subjects who did not receive bone sparing agents	278 (79.9%)	264 (75.9%)
Subjects with symptomatic progression event	83 (23.9%)	45 (12.9%)
Subjects with symptomatic progression event	104 (29.9%)	57 (16.4%)
Subjects who received bone sparing agents prior to the first event[a]	17 (4.9%)	7 (2.0%)
Subjects who did not receive bone sparing agents prior to the first event	87 (25.0%)	50 (14.4%)
Subjects with no symptomatic progression event	244 (70.1%)	291 (83.6%)
Subjects who received bone sparing agents	49 (14.1%)	72 (20.7%)

Key: AAP = abiraterone acetate plus prednisone.
[a] Received bone-sparing agent (bisphosphonates or denosumab) up to and including 1 day prior to symptomatic progression event.
Included bone sparing agents as prior therapy or concomitant medication.

[tefbsaspr01eu.rtf] [PROD/jnj-67652000/pcr3002/dbr_csr/re_eureg/tefbsaspr01eu.sas] 06OCT2025, 08:16

Overall survival – Key secondary endpoint

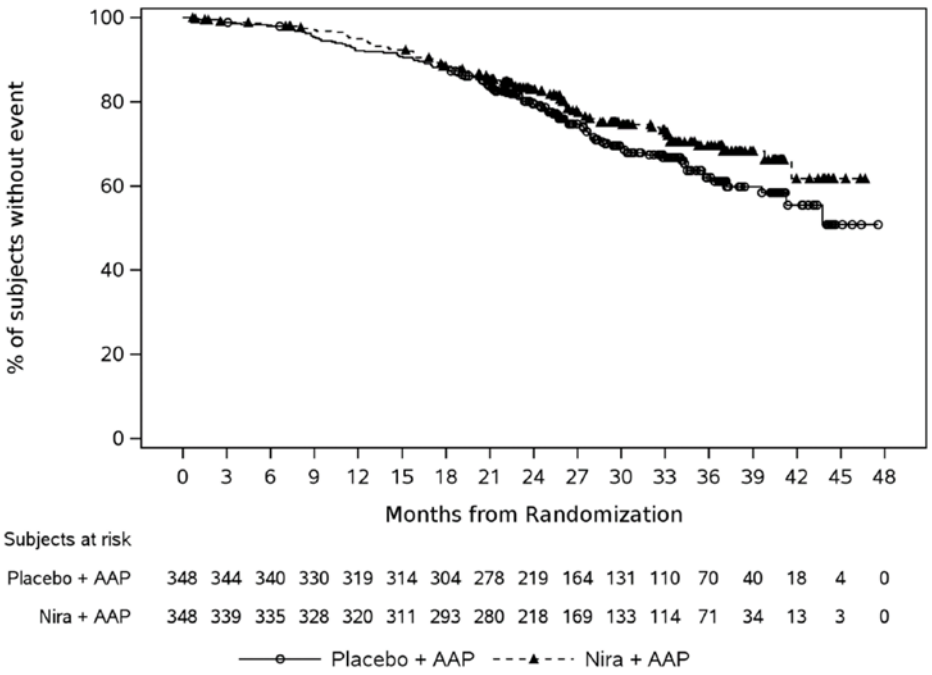
Table 53: Summary of Overall Survival (IA2) – Stratified Analysis; Full Analysis Set *Cut-off date* 03-Oct-2025

	Placebo + AAP	Nira + AAP
Analysis set: Full	348	348
Event	140 (40.2%)	121 (34.8%)
Censored	208 (59.8%)	227 (65.2%)
Time to event (months)		
25th percentile (95% CI)	27.40 (24.05, 29.93)	30.72 (26.18, 33.25)
Median (95% CI)	48.36 (41.33, NE)	52.01 (45.31, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (53.03, NE)
Range	(0.5, 55.4+)	(0.7+, 55.8+)
6-month event-free rate (95% CI)	0.980 (0.958, 0.990)	0.983 (0.962, 0.992)
12-month event-free rate (95% CI)	0.922 (0.888, 0.946)	0.950 (0.921, 0.969)
18-month event-free rate (95% CI)	0.879 (0.839, 0.909)	0.885 (0.845, 0.914)
24-month event-free rate (95% CI)	0.797 (0.751, 0.836)	0.831 (0.787, 0.867)
30-month event-free rate (95% CI)	0.703 (0.651, 0.748)	0.761 (0.712, 0.804)
36-month event-free rate (95% CI)	0.632 (0.576, 0.683)	0.686 (0.631, 0.734)
42-month event-free rate (95% CI)	0.562 (0.500, 0.619)	0.615 (0.553, 0.671)
48-month event-free rate (95% CI)	0.513 (0.443, 0.578)	0.570 (0.500, 0.634)
p-value [a]		0.1206
Hazard ratio (95% CI) [b]		0.825 (0.647,1.052)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low), gene status (BRCA2 versus all other pathogenic alterations).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

[tefos01.rtf] [PROD/jnj-67652000/pcr3002/dbr_ia2/re_ia2/tefos01.sas] 05NOV2025, 09:43

Figure 18. Kaplan-Meier plot of overall survival (IA1); full analysis set (All HRR population) Cut-off date 03-Oct-2025



Post-treatment therapy

Table 54. Summary of subsequent therapies for prostate cancer in subjects who discontinued treatment; full analysis set (All HRR population)

	Placebo + AAP	Nira + AAP
Analysis set: Full subjects who discontinued treatment	196	159
Number of subjects with subsequent therapy for prostate cancer	149 (76.0%)	94 (59.1%)
Chemotherapy	102 (52.0%)	71 (44.7%)
Docetaxel	84 (42.9%)	59 (37.1%)
Cabazitaxel	27 (13.8%)	18 (11.3%)
Carboplatin	15 (7.7%)	11 (6.9%)
Cisplatin	3 (1.5%)	2 (1.3%)
Etoposide	4 (2.0%)	2 (1.3%)
Cyclophosphamide	3 (1.5%)	1 (0.6%)
Mitoxantrone	1 (0.5%)	1 (0.6%)
Imifoplatin	1 (0.5%)	0
Paclitaxel	2 (1.0%)	0
AR Pathway Inhibitors	52 (26.5%)	36 (22.6%)
Enzalutamide	36 (18.4%)	23 (14.5%)
Abiraterone acetate	15 (7.7%)	11 (6.9%)
Apalutamide	3 (1.5%)	3 (1.9%)
Darolutamide	2 (1.0%)	1 (0.6%)
Rezvilutamide	1 (0.5%)	0
Other	33 (16.8%)	22 (13.8%)
Prednisone	14 (7.1%)	9 (5.7%)
Zoledronic acid	3 (1.5%)	4 (2.5%)
Capivasertib	6 (3.1%)	2 (1.3%)
Dexamethasone	3 (1.5%)	2 (1.3%)
ODM 208	1 (0.5%)	2 (1.3%)
Abemaciclib	0	1 (0.6%)
AMG 509	0	1 (0.6%)
Denosumab	2 (1.0%)	1 (0.6%)
Fludrocortisone	1 (0.5%)	1 (0.6%)
Leuprorelin	2 (1.0%)	1 (0.6%)
Prednisolone	0	1 (0.6%)
Vobramitamab duocarmazine	0	1 (0.6%)
ZEN 3694	0	1 (0.6%)
Cabozantinib	1 (0.5%)	0
Datopotamab deruxtecan	1 (0.5%)	0
Enfortumab vedotin	1 (0.5%)	0
Investigational antineoplastic drugs	3 (1.5%)	0
NUV 868	1 (0.5%)	0

Testosterone	1 (0.5%)	0
Traditional Chinese medicine	1 (0.5%)	0
Zanzalintinib	1 (0.5%)	0
PARPi	47 (24.0%)	10 (6.3%)
Olaparib	42 (21.4%)	10 (6.3%)
Saruparib	2 (1.0%)	0
Talazoparib	3 (1.5%)	0
Radiopharmaceutical	10 (5.1%)	8 (5.0%)
Lutetium (177lu) vipivotide tetraxetan	3 (1.5%)	6 (3.8%)
Radium Ra 223 dichloride	7 (3.6%)	2 (1.3%)
First generation antiandrogen	3 (1.5%)	2 (1.3%)
Bicalutamide	3 (1.5%)	2 (1.3%)
Immunotherapy	7 (3.6%)	2 (1.3%)
Pembrolizumab	0	2 (1.3%)
Atezolizumab	1 (0.5%)	0
Dostarlimab	1 (0.5%)	0
Durvalumab	1 (0.5%)	0
Nivolumab	2 (1.0%)	0
Sipuleucel-T	1 (0.5%)	0
Tislelizumab	1 (0.5%)	0

Key: AAP = abiraterone acetate plus prednisone.
Note: Recurrent medications are counted only once per subject.
Medications are coded using UMC Drug Dictionary Version 202409.

Table 55. Summary of Subjects who Stayed on Treatment after Radiographic Disease Progression by Investigator Review; Full Analysis Set

	Placebo + AAP	Nira + AAP
Analysis set: Full	348	348
Subjects experienced radiographic progression	139 (39.9%)	92 (26.4%)
Subjects with study treatment continued beyond radiographic progression [a]	118 (33.9%)	82 (23.6%)
Duration of exposure (months) beyond radiographic progression [b]		
N	118	82
Mean (SD)	3.47 (5.726)	3.28 (4.979)
Median	1.74	1.77
Range	(0.1; 32.2)	(0.1; 28.6)
Duration of exposure (months) beyond radiographic progression category [b]		
≤ 1 month	42 (35.6%)	32 (39.0%)
> 1 - ≤ 2 months	27 (22.9%)	12 (14.6%)
> 2 - ≤ 3 months	14 (11.9%)	17 (20.7%)
> 3 - ≤ 6 months	18 (15.3%)	7 (8.5%)
> 6 - ≤ 12 months	10 (8.5%)	11 (13.4%)
> 12 months	7 (5.9%)	3 (3.7%)

Key: AAP = abiraterone acetate plus prednisone.
[a] Events are counted for soft tissue progression (RECIST1.1), confirmed bone progression (PCWG3), or the presence of both.
[b] Treatment duration is calculated as the duration from the date of soft tissue progression or from the date of the confirmatory bone scan (whichever occurred first) to the date of last dose of study drug+1 divided by 30.4375.

[tefrpfs05aeu.rtf] [PROD/jnj-67652000/pcr3002/dbr_csr/re_eureg/tefrpfs05aeu.sas] 30SEP2025, 12:05

Ancillary analyses

- **Sensitivity analyses**

Analysis by central review

Table 56: Summary of radiographic progression-free survival by central review - stratified analysis; BRCA full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Event	88 (44.9%)	54 (28.3%)
Censored	108 (55.1%)	137 (71.7%)
Time to event (months)		
25th percentile (95% CI)	11.10 (7.85, 14.65)	22.11 (14.98, 31.70)
Median (95% CI)	26.25 (19.91, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 44.6+)	(0.0+, 44.2+)
6-month event-free rate (95% CI)	0.921 (0.872, 0.952)	0.973 (0.937, 0.989)
12-month event-free rate (95% CI)	0.714 (0.643, 0.774)	0.884 (0.828, 0.923)
18-month event-free rate (95% CI)	0.645 (0.570, 0.709)	0.814 (0.749, 0.864)
24-month event-free rate (95% CI)	0.530 (0.452, 0.603)	0.724 (0.650, 0.786)
30-month event-free rate (95% CI)	0.483 (0.401, 0.560)	0.685 (0.604, 0.753)
36-month event-free rate (95% CI)	0.464 (0.377, 0.546)	0.659 (0.572, 0.732)
p-value [a]		<.0001
Hazard ratio (95% CI) [b]		0.514 (0.366,0.723)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Table 57 Summary of radiographic progression-free survival by investigator review not censored for subsequent therapy - stratified analysis; BRCA full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Full	196	191
Event	104 (53.1%)	62 (32.5%)
Censored	92 (46.9%)	129 (67.5%)
Time to event (months)		
25th percentile (95% CI)	12.19 (10.41, 14.55)	21.26 (14.82, 25.79)
Median (95% CI)	25.63 (18.63, 27.73)	41.20 (41.20, NE)
75th percentile (95% CI)	NE (41.17, NE)	NE (NE, NE)
Range	(0.0+, 44.6+)	(0.0+, 44.2+)
6-month event-free rate (95% CI)	0.928 (0.881, 0.957)	0.963 (0.924, 0.982)
12-month event-free rate (95% CI)	0.756 (0.688, 0.810)	0.860 (0.802, 0.903)
18-month event-free rate (95% CI)	0.617 (0.544, 0.682)	0.789 (0.722, 0.841)
24-month event-free rate (95% CI)	0.524 (0.449, 0.593)	0.716 (0.644, 0.777)
30-month event-free rate (95% CI)	0.416 (0.338, 0.493)	0.637 (0.555, 0.708)
36-month event-free rate (95% CI)	0.404 (0.325, 0.482)	0.624 (0.539, 0.698)
p-value [a]		<.0001
Hazard ratio (95% CI) [b]		0.515 (0.375,0.706)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Table 58. Summary of radiographic progression-free survival by central review – stratified analysis; full analysis set (All HRR population)

	Placebo + AAP	Nira + AAP
Analysis set: Full	348	348
Event	140 (40.2%)	103 (29.6%)
Censored	208 (59.8%)	245 (70.4%)
Time to event (months)		
25th percentile (95% CI)	12.19 (11.04, 15.01)	21.06 (15.31, 25.82)
Median (95% CI)	40.21 (26.25, NE)	NE (40.41, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 44.6+)	(0.0+, 45.2+)
6-month event-free rate (95% CI)	0.926 (0.893, 0.950)	0.982 (0.961, 0.992)
12-month event-free rate (95% CI)	0.751 (0.700, 0.794)	0.871 (0.829, 0.903)
18-month event-free rate (95% CI)	0.681 (0.627, 0.729)	0.788 (0.739, 0.829)
24-month event-free rate (95% CI)	0.597 (0.539, 0.650)	0.713 (0.659, 0.760)
30-month event-free rate (95% CI)	0.527 (0.463, 0.587)	0.673 (0.613, 0.726)
36-month event-free rate (95% CI)	0.507 (0.439, 0.570)	0.650 (0.586, 0.706)
p-value [a]		0.0001
Hazard ratio (95% CI) [b]		0.612 (0.474,0.791)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low), gene status (BRCA2 versus all other pathogenic alterations).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Table 59. Summary of radiographic progression-free survival by investigator review not censored for subsequent therapy – stratified analysis; full analysis set (All HRR population)

	Placebo + AAP	Nira + AAP
Analysis set: Full	348	348
Event	172 (49.4%)	120 (34.5%)
Censored	176 (50.6%)	228 (65.5%)
Time to event (months)		
25th percentile (95% CI)	13.14 (11.07, 14.65)	18.56 (15.31, 22.80)
Median (95% CI)	27.56 (24.61, 34.40)	NE (41.20, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 44.6+)	(0.0+, 45.2+)
6-month event-free rate (95% CI)	0.933 (0.901, 0.955)	0.970 (0.946, 0.984)
12-month event-free rate (95% CI)	0.765 (0.716, 0.807)	0.850 (0.807, 0.884)
18-month event-free rate (95% CI)	0.639 (0.585, 0.688)	0.765 (0.715, 0.807)
24-month event-free rate (95% CI)	0.556 (0.500, 0.608)	0.694 (0.640, 0.741)
30-month event-free rate (95% CI)	0.463 (0.402, 0.521)	0.617 (0.556, 0.672)
36-month event-free rate (95% CI)	0.433 (0.369, 0.494)	0.584 (0.518, 0.645)
p-value [a]		<.0001
Hazard ratio (95% CI) [b]		0.594 (0.470,0.751)

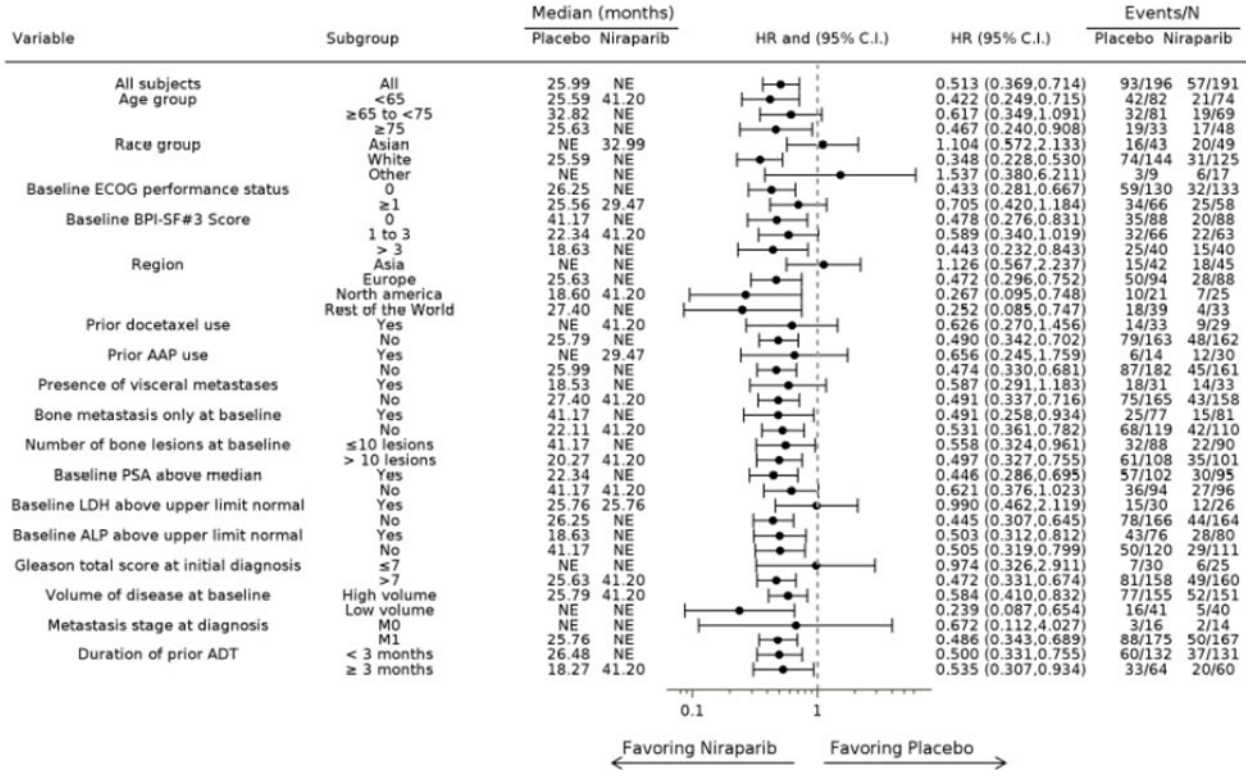
Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low), gene status (BRCA2 versus all other pathogenic alterations).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation. NE = not estimable.

Subgroup analyses

BRCA

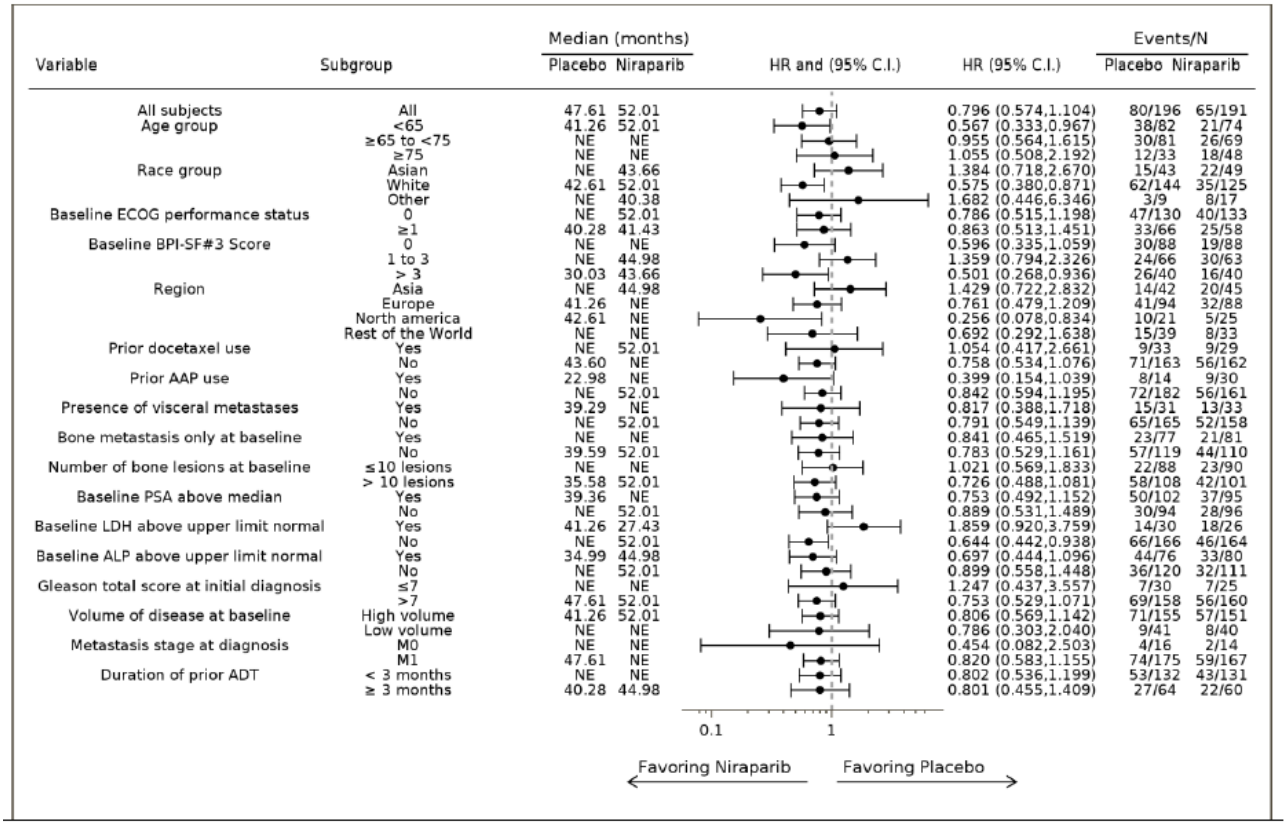
rPFS (BRCA subgroup)

Figure 19. Forest plot of radiographic Progression-Free survival by investigator for subgroups defined by baseline characteristics; BRCA Full analysis set



OS (BRCA subgroup)

Figure 20. Overall survival (IA2) for subgroups defined by baseline characteristics; BRCA full analysis set



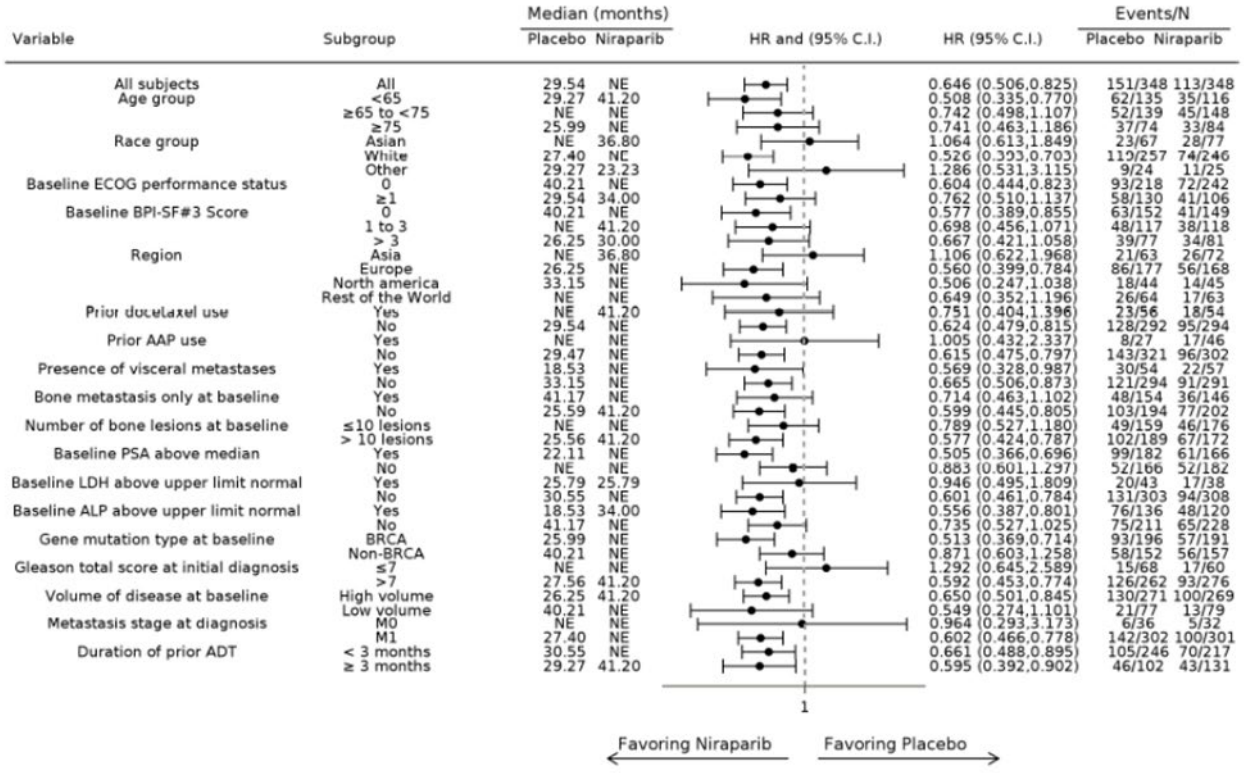
Key: ECOG = Eastern Cooperative Oncology Group, BPI-SF = Brief Pain Inventory-Short Form, AAP = abiraterone acetate plus prednisone, PSA = prostate-specific antigen, LDH = lactate dehydrogenase, ALP = alkaline phosphatase, ADT = androgen deprivation therapy.
Note: Subjects with missing baseline disease characteristics are not included in the subgroup analysis.
Hazard ratio is from nonstratified proportional hazards model.

[gefos02brca.rtf] [PROD/jnj-67652000/pcr3002/dbr_ia2/re_ia2/gefos02.sas] 05NOV2025, 09:44

All HRR population

rPFS (All HRR population)

Figure 21. Forest plot of radiographic Progression-Free survival by investigator for subgroups defined by baseline characteristics; full analysis set (All HRR population)



Efficacy by gene alteration and gene grouping

By gene alteration

Table 60: Key efficacy endpoints by gene alteration (single genes) - stratified analysis; full analysis set

		rPFS			TSP			OS		
Gene	Treatment group	N (events)	Median (95% CI)	HR(95% CI)	N (events)	Median (95% CI)	HR(95% CI)	N (events)	Median (95% CI)	HR(95% CI)
BRCA total (single gene)	PBO+AAP	169(80)	26.25 (22.11, 41.17)		169(56)	NE (37.13, NE)		169(53)	NE (35.58, NE)	
	Nira+AAP	173(54)	NE (41.20, NE)	0.559 (0.395,0.791)	173(29)	NE (NE, NE)	0.475 (0.303,0.745)	173(43)	NE (NE, NE)	0.837 (0.559,1.252)
BRCA1	PBO+AAP	25(6)	41.17 (NE, NE)		25(5)	NE (37.13, NE)		25(4)	NE (39.59, NE)	
	Nira+AAP	25(8)	NE (21.26, NE)	1.495 (0.488,4.581)	25(4)	NE (NE, NE)	0.862 (0.229,3.245)	25(7)	NE (26.15, NE)	2.450 (0.633,9.490)
BRCA2	PBO+AAP	144(74)	25.63 (18.27, 27.73)		144(51)	NE (39.72, NE)		144(49)	NE (34.27, NE)	
	Nira+AAP	148(46)	NE (41.20, NE)	0.493 (0.341,0.714)	148(25)	NE (NE, NE)	0.444 (0.275,0.717)	148(36)	NE (NE, NE)	0.745 (0.484,1.146)
BRIP1	PBO+AAP	4(2)	NE (10.45, NE)		4(0)	NE (NE, NE)		4(1)	NE (10.45, NE)	
	Nira+AAP	9(2)	NE (10.97, NE)	NE (NE, NE)	9(0)	NE (NE, NE)	NE (NE, NE)	9(2)	NE (12.75, NE)	NE (NE, NE)
PALB2	PBO+AAP	13(4)	NE (14.78, NE)		13(2)	NE (19.94, NE)		13(2)	NE (28.16, NE)	
	Nira+AAP	9(6)	18.14 (1.81, NE)	2.410 (0.664,8.744)	9(1)	NE (16.36, NE)	NE (NE, NE)	9(3)	NE (2.50, NE)	3.304 (0.515,21.206)
RAD51B	PBO+AAP	5(0)	NE (NE, NE)		5(0)	NE (NE, NE)		5(0)	NE (NE, NE)	
	Nira+AAP	4(0)	NE (NE, NE)	NE (NE, NE)	4(0)	NE (NE, NE)	NE (NE, NE)	4(0)	NE (NE, NE)	NE (NE, NE)
RAD54L	PBO+AAP	6(2)	NE (10.64, NE)		6(1)	NE (6.24, NE)		6(2)	NE (18.89, NE)	
	Nira+AAP	12(4)	NE (11.01, NE)	0.499 (0.074,3.349)	12(4)	41.40 (15.01, NE)	0.675 (0.069,6.586)	12(3)	NE (16.89, NE)	0.311 (0.044,2.221)
CHEK2	PBO+AAP	76(32)	33.15 (29.47, NE)		76(18)	43.14 (43.14, NE)		76(21)	NE (NE, NE)	
	Nira+AAP	72(24)	NE (32.92, NE)	0.653 (0.383,1.113)	72(9)	NE (NE, NE)	0.467 (0.208,1.049)	72(18)	NE (35.25, NE)	0.846 (0.450,1.590)
CDK12	PBO+AAP	28(10)	NE (18.20, NE)		28(12)	NE (14.55, NE)		28(15)	34.40 (25.63, 43.73)	
	Nira+AAP	28(13)	30.00 (18.60, NE)	1.014 (0.431,2.386)	28(9)	NE (26.48, NE)	0.675 (0.281,1.623)	28(9)	41.63 (28.12, NE)	0.568 (0.247,1.309)
FANCA	PBO+AAP	15(5)	NE (10.87, NE)		15(3)	NE (15.57, NE)		15(4)	NE (28.75, NE)	
	Nira+AAP	15(4)	NE (22.80, NE)	0.756 (0.202,2.823)	15(2)	NE (26.51, NE)	0.713 (0.119,4.273)	15(3)	NE (22.80, NE)	0.915 (0.203,4.124)

Key: AAP = abiraterone acetate plus prednisone, PBO = placebo.
Key: rPFS=radiographic progression-free survival; TSP=time to symptomatic progression; ORR=objective response rate; OS=overall survival; CI=confidence interval; HR=hazard ratio; RR=relative risk; BRCA1=Breast Cancer gene 1; BRCA2=Breast Cancer gene 2; BRIP1=BRCA1 Interacting Protein C-terminal Helicase 1 gene; CDK12=Cyclin-Dependent Kinase 12; CHEK2=Checkpoint Kinase 2 gene; FANCA=Fanconi Anemia Complementation Group A gene; PALB2=Partner and Localizer of BRCA2 gene; RAD51B=RAD51 paralog B; RAD54L=RAD54-Like;
Note: Hazard ratio is from stratified proportional hazards model by stratification factors: volume of disease (high versus low). Hazard ratio <1 favors Nira + AAP treatment.

CHEK2-related sensitivity analyses

Table 61: CHEK2 related sensitivity analysis key efficacy endpoints; full analysis set

		rPFS			TSP			OS			ORR	
Gene	Treatment group	N (events)	Median (95% CI)	HR(95% CI)	N (events)	Median (95% CI)	HR(95% CI)	N (events)	Median (95% CI)	HR(95% CI)	N* (responder)	RR(95% CI)
All HRR	PBO+AAP	348(151)	29.54 (25.82, NE)		348(104)	NE (43.14, NE)		348(108)	NE (41.26, NE)		110(81)	
	Nira+AAP	348(113)	NE (41.20, NE)	0.646 (0.506,0.825)	348(57)	NE (NE, NE)	0.518 (0.375,0.715)	348(85)	NE (NE, NE)	0.792 (0.596,1.053)	106(76)	0.974 (0.827,1.147)
All HRR excluding: CHEK2+ by cfDNA and CHEK2- by tissue	PBO+AAP	321(145)	29.27 (25.76, NE)		321(101)	NE (43.14, NE)		321(103)	NE (41.26, NE)		103(77)	
	Nira+AAP	331(109)	NE (41.20, NE)	0.627 (0.489,0.804)	331(57)	NE (NE, NE)	0.519 (0.375,0.719)	331(82)	NE (41.63, NE)	0.784 (0.587,1.048)	99(71)	0.959 (0.812,1.134)
All HRR excluding: CHEK2+ by cfDNA only	PBO+AAP	316(144)	28.16 (25.63, NE)		316(101)	NE (43.14, NE)		316(102)	NE (39.59, NE)		103(77)	
	Nira+AAP	323(105)	NE (41.20, NE)	0.610 (0.474,0.784)	323(56)	NE (NE, NE)	0.512 (0.370,0.710)	323(79)	NE (NE, NE)	0.767 (0.572,1.029)	99(71)	0.959 (0.812,1.134)
Non-BRCA	PBO+AAP	152(58)	40.21 (29.47, NE)		152(38)	NE (43.14, NE)		152(47)	43.73 (37.19, NE)		38(28)	
	Nira+AAP	157(56)	NE (30.00, NE)	0.871 (0.603,1.258)	157(26)	NE (41.40, NE)	0.641 (0.389,1.056)	157(41)	NE (41.63, NE)	0.864 (0.568,1.313)	43(28)	0.884 (0.661,1.181)
Non-BRCA excluding: CHEK2+ by cfDNA and CHEK2- by tissue	PBO+AAP	125(52)	40.21 (25.82, NE)		125(35)	NE (43.14, NE)		125(42)	43.73 (37.19, NE)		31(24)	
	Nira+AAP	140(52)	NE (30.00, NE)	0.837 (0.570,1.230)	140(26)	NE (41.40, NE)	0.654 (0.393,1.086)	140(38)	NE (41.63, NE)	0.845 (0.545,1.311)	36(23)	0.825 (0.605,1.126)
Non-BRCA excluding: CHEK2+ by cfDNA only	PBO+AAP	120(51)	40.21 (21.98, NE)		120(35)	NE (43.14, NE)		120(41)	43.73 (37.19, NE)		31(24)	
	Nira+AAP	132(48)	NE (30.00, NE)	0.791 (0.533,1.174)	132(25)	NE (41.40, NE)	0.634 (0.379,1.059)	132(35)	NE (41.63, NE)	0.807 (0.514,1.268)	36(23)	0.825 (0.605,1.126)
CHEK2+	PBO+AAP	76(32)	33.15 (29.47, NE)		76(18)	43.14 (43.14, NE)		76(21)	NE (NE, NE)		19(13)	
	Nira+AAP	72(24)	NE (32.92, NE)		72(9)	NE (NE, NE)	0.491 (0.221,1.094)	72(18)	NE (35.25, NE)		17(13)	
CHEK2+ excluding: CHEK2+ by cfDNA and CHEK2- by tissue	PBO+AAP	49(26)	29.47 (14.69, NE)		49(15)	43.14 (30.59, NE)		49(16)	NE (34.46, NE)		12(9)	
	Nira+AAP	55(20)	NE (25.82, NE)		55(9)	NE (NE, NE)	0.505 (0.221,1.155)	55(15)	NE (35.25, NE)		10(8)	
CHEK2+ excluding: CHEK2+ by cfDNA only	PBO+AAP	44(25)	29.47 (14.65, NE)		44(15)	43.14 (28.09, NE)		44(15)	NE (34.46, NE)		12(9)	
	Nira+AAP	47(16)	NE (32.92, NE)		47(8)	NE (NE, NE)	0.458 (0.194,1.080)	47(12)	NE (35.25, NE)		10(8)	

Key: AAP = abiraterone acetate plus prednisone, PBO = placebo.
Key: rPFS=radiographic progression-free survival; TSP=time to symptomatic progression; ORR=objective response rate; OS=overall survival; CI=confidence interval; HR=hazard ratio; RR=relative risk.
* N is the number of subjects with measurable disease at baseline.
CHEK2+ : subjects with a single CHEK2 alterations identified by tissue or cfDNA.
CHEK2+ by cfDNA only: Subjects with a single CHEK2 alteration identified by a liquid biopsy and with either negative HRR gene alteration by paired tissue testing or no available paired tissue testing.
CHEK2+ by cfDNA only and CHEK2- by tissue : Subjects with a single CHEK2 alteration identified by a liquid biopsy and negative for HRR gene alterations by paired tissue testing.
Note: Hazard ratio is from nonstratified proportional hazards model. Non estimable HRs are due to few or no events.

By gene grouping

Table 62: Key efficacy endpoints by gene alteration groupings - stratified analysis; full analysis set

		rPFS			TSP			OS		
Gene[a]	Treatment group	N (events)	Median (95% CI)	HR(95% CI)[b]	N (events)	Median (95% CI)	HR(95% CI)[b]	N (events)	Median (95% CI)	HR(95% CI)[b]
All HRR	PBO+AAP	348(151)	29.54 (25.82, NE)		348(104)	NE (43.14, NE)		348(108)	NE (41.26, NE)	
	Nira+AAP	348(113)	NE (41.20, NE)	0.625 (0.490,0.799)	348(57)	NE (NE, NE)	0.503 (0.364,0.695)	348(85)	NE (NE, NE)	0.785 (0.591,1.044)
BRCA	PBO+AAP	196(93)	25.99 (22.11, 41.17)		196(66)	NE (39.72, NE)		196(61)	NE (36.17, NE)	
	Nira+AAP	191(57)	NE (41.20, NE)	0.515 (0.370,0.717)	191(31)	NE (NE, NE)	0.444 (0.290,0.681)	191(44)	NE (NE, NE)	0.750 (0.509,1.106)
BRCA2	PBO+AAP	163(83)	25.63 (18.37, 27.73)		163(59)	NE (39.72, NE)		163(55)	NE (35.58, NE)	
	Nira+AAP	163(48)	NE (41.20, NE)	0.456 (0.319,0.652)	163(27)	NE (NE, NE)	0.417 (0.264,0.658)	163(36)	NE (NE, NE)	0.658 (0.432,1.002)
BRCA1 excluding BRCA2	PBO+AAP	33(10)	41.17 (25.99, NE)		33(7)	NE (37.13, NE)		33(6)	NE (39.59, NE)	
	Nira+AAP	28(9)	NE (21.26, NE)	1.127 (0.447,2.843)	28(4)	NE (NE, NE)	0.695 (0.203,2.383)	28(8)	NE (26.15, NE)	1.799 (0.586,5.523)
Non-BRCA	PBO+AAP	152(58)	40.21 (29.47, NE)		152(38)	NE (43.14, NE)		152(47)	43.73 (37.19, NE)	
	Nira+AAP	157(56)	NE (30.00, NE)	0.815 (0.563,1.178)	157(26)	NE (41.40, NE)	0.593 (0.360,0.978)	157(41)	NE (41.63, NE)	0.829 (0.545,1.261)
HRR Effectors	PBO+AAP	226(102)	27.56 (25.59, NE)		226(69)	NE (NE, NE)		226(67)	NE (41.26, NE)	
	Nira+AAP	230(71)	NE (41.20, NE)	0.571 (0.421,0.774)	230(37)	NE (41.40, NE)	0.495 (0.332,0.738)	230(54)	NE (NE, NE)	0.810 (0.566,1.159)
Non-BRCA HRR Effectors	PBO+AAP	30(9)	NE (28.16, NE)		30(3)	NE (NE, NE)		30(6)	NE (NE, NE)	
	Nira+AAP	39(14)	NE (18.14, NE)	1.066 (0.460,2.474)	39(6)	41.40 (41.40, NE)	1.338 (0.334,5.361)	39(10)	NE (NE, NE)	1.306 (0.474,3.598)
Non-HRR Effectors	PBO+AAP	122(49)	40.21 (29.47, NE)		122(35)	NE (43.14, NE)		122(41)	43.73 (34.40, NE)	
	Nira+AAP	118(42)	36.80 (30.00, NE)	0.746 (0.493,1.129)	118(20)	NE (NE, NE)	0.514 (0.296,0.892)	118(31)	NE (41.63, NE)	0.749 (0.469,1.195)

Key: AAP = abiraterone acetate plus prednisone, PBO = placebo.
Key: rPFS=radiographic progression-free survival; TSP=time to symptomatic progression; OS=overall survival; CI=confidence interval; HR=hazard ratio.
[a] BRCA: Subjects with single or co-occurring BRCA1 or BRCA2; BRCA2: subjects with single or co-occurring BRCA2; BRCA1 excluding BRCA2: includes subjects with single or co-occurring BRCA1 excluding co-occurring BRCA2; HRR Effectors: subjects with single or co-occurring BRCA1, BRCA2, BRIP1, PALB2, RAD51B, RAD54L; Non-BRCA HRR Effectors: subjects with single or co-occurring BRIP1, PALB2, RAD51B, RAD54L alterations excluding those with BRCA co-occurring; Non-HRR Effectors: subjects with single or co-occurring CDK12, CHEK2, FANCA alterations excluding HRR Effectors.
[b] Hazard ratio is from stratified proportional hazards model by stratification factors: volume of disease (high versus low) and only for All HRR, the gene status (BRCA2 versus all other pathogenic alterations) is also used. Non estimable HRs are due to few or no events.

- Non-BRCA

Radiographic progression-free survival (rPFS)

Table 63: Summary of radiographic progression-free survival by investigator review – stratified analysis; Non-BRCA full analysis set

	Placebo + AAP	Nira + AAP
Analysis set: Full	152	157
Event	58 (38.2%)	56 (35.7%)
Censored	94 (61.8%)	101 (64.3%)
Time to event (months)		
25th percentile (95% CI)	14.65 (11.07, 18.33)	17.71 (14.09, 23.23)
Median (95% CI)	40.21 (29.47, NE)	NE (30.00, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 44.5+)	(0.0+, 45.2+)
6-month event-free rate (95% CI)	0.947 (0.896, 0.973)	0.980 (0.939, 0.993)
12-month event-free rate (95% CI)	0.784 (0.707, 0.843)	0.836 (0.765, 0.887)
18-month event-free rate (95% CI)	0.702 (0.619, 0.771)	0.744 (0.665, 0.808)
24-month event-free rate (95% CI)	0.639 (0.552, 0.713)	0.672 (0.586, 0.744)
30-month event-free rate (95% CI)	0.571 (0.473, 0.656)	0.594 (0.496, 0.679)
36-month event-free rate (95% CI)	0.534 (0.430, 0.627)	0.536 (0.427, 0.633)
p-value [a]		0.2749
Hazard ratio (95% CI) [b]		0.815 (0.563,1.178)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Time to symptomatic progression (TSP)

Table *64. Summary of time to symptomatic progression - stratified analysis; Non-BRCA full analysis set*

	Placebo + AAP	Nira + AAP
Analysis set: Full	152	157
Event	38 (25.0%)	26 (16.6%)
Censored	114 (75.0%)	131 (83.4%)
Time to event (months)		
25th percentile (95% CI)	26.87 (15.57, NE)	41.40 (26.48, NE)
Median (95% CI)	NE (43.14, NE)	NE (41.40, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.5+, 47.5+)	(0.9+, 46.3+)
6-month event-free rate (95% CI)	0.980 (0.939, 0.993)	0.993 (0.954, 0.999)
12-month event-free rate (95% CI)	0.883 (0.818, 0.925)	0.966 (0.919, 0.986)
18-month event-free rate (95% CI)	0.811 (0.737, 0.867)	0.913 (0.853, 0.950)
24-month event-free rate (95% CI)	0.765 (0.685, 0.827)	0.865 (0.793, 0.913)
30-month event-free rate (95% CI)	0.729 (0.641, 0.798)	0.791 (0.700, 0.857)
36-month event-free rate (95% CI)	0.714 (0.623, 0.787)	0.771 (0.672, 0.844)
p-value [a]		0.0385
Hazard ratio (95% CI) [b]		0.593 (0.360,0.978)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

Overall survival (OS)

Table 65. Summary of Overall Survival (IA2) – Stratified Analysis; Non-BRCA Full Analysis Set

	Placebo + AAP	Nira + AAP
Analysis set: Full	152	157
Event	60 (39.5%)	56 (35.7%)
Censored	92 (60.5%)	101 (64.3%)
Time to event (months)		
25th percentile (95% CI)	26.28 (21.26, 34.07)	28.12 (21.06, 36.47)
Median (95% CI)	48.36 (41.33, NE)	53.03 (42.58, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (53.03, NE)
Range	(0.5, 51.8+)	(0.9+, 55.3+)
6-month event-free rate (95% CI)	0.967 (0.923, 0.986)	0.987 (0.948, 0.997)
12-month event-free rate (95% CI)	0.914 (0.857, 0.949)	0.954 (0.905, 0.978)
18-month event-free rate (95% CI)	0.855 (0.789, 0.902)	0.847 (0.779, 0.895)
24-month event-free rate (95% CI)	0.796 (0.722, 0.852)	0.793 (0.719, 0.850)
30-month event-free rate (95% CI)	0.701 (0.621, 0.768)	0.739 (0.660, 0.802)
36-month event-free rate (95% CI)	0.647 (0.561, 0.720)	0.681 (0.598, 0.751)
42-month event-free rate (95% CI)	0.583 (0.488, 0.666)	0.611 (0.517, 0.692)
48-month event-free rate (95% CI)	0.536 (0.435, 0.627)	0.556 (0.450, 0.650)
p-value [a]		0.3762
Hazard ratio (95% CI) [b]		0.847 (0.587,1.223)

Key: AAP = abiraterone acetate plus prednisone.
[a] p-value is from a log-rank test stratified by stratification factors: volume of disease (high versus low).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Nira + AAP treatment.
Note: + = censored observation, NE = not estimable.

[tefos01nobrca.rtf] [PROD/jnj-67652000/pcr3002/dbr ia2/re ia2/tefos01.sas] 05NOV2025, 09:43

Table *66. Summary of other efficacy endpoints (IA1); Non-BRCA subgroup*

Analysis set: FAS	Placebo + AAP 152	Nira + AAP 157
Time to Subsequent Therapy		
Events	49 (32.2%)	39 (24.8%)
Median (95% CI) time to event (months)	NE (34.76, NE)	NE (41.49, NE)
Hazard ratio (95% CI); p value	0.685 (0.449,1.044); p=0.0767	
Objective Response Rate		
Responders	28 (73.7%)	28 (65.1%)
Complete Response (CR)	8 (21.1%)	9 (20.9%)
Partial Response (PR)	20 (52.6%)	19 (44.2%)
Non-responders	10 (26.3%)	15 (34.9%)
Relative response rate (95% CI); p value	0.884 (0.661,1.181); p=0.405	
Duration of Response		
Events	15 (53.6%)	11 (39.3%)
Median (95% CI) time to event (months)	14.75 (9.23, 28.35)	27.63 (13.50, NE)
Hazard ratio (95% CI); p value	0.523 (0.237,1.153); p=0.1026	
Time to PSA Progression		
Events	64 (42.1%)	50 (31.8%)
Median (95% CI) time to event (months)	33.05 (20.30, NE)	NE (33.41, NE)
Hazard ratio (95% CI); p value	0.626 (0.431,0.907); p=0.0125	
PSA Response Rate		
Subjects with PSA Response	141 (92.8%)	140 (89.2%)
Confirmed	132 (86.8%)	136 (86.6%)
Unconfirmed	9 (5.9%)	4 (2.5%)
Relative response rate (95% CI); p value	0.997 (0.914,1.088); p=0.955	
Progression-free Survival on First Subsequent Therapy		
Events	53 (34.9%)	45 (28.7%)
Median (95% CI) time to event (months)	NE (34.20, NE)	NE (36.93, NE)
Hazard ratio (95% CI); p value	0.766 (0.514,1.140); p=0.1874	

Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 67 Summary of Efficacy for trial AMPLITUDE

Title: A Phase 3 randomized, placebo-controlled, double-blind study of niraparib in combination with abiraterone acetate and prednisone versus abiraterone acetate and prednisone for the treatment of participants with deleterious germline or somatic homologous recombination repair gene-mutated metastatic castration-sensitive prostate cancer		
Study 67652000PCR3002 NCT number: NCT04497844 EudraCT number: 2020-002209-25		
Phase III, randomized, double-blind, placebo-controlled, multicenter study		
Duration of main phase:		03-Dec-2020 (FPI). Ongoing.
Superiority		
Nira+APP		Niraparib 200 mg and AA 1000 mg plus prednisone 5 mg daily, 348 patients randomized
Pbo+AAP		Placebo and AA 1000 mg plus prednisone 5 mg daily, 348 patients randomized
Primary endpoint	rPFS by investigator	Radiographic progression-free survival is defined as the time interval from the date of randomization to the first date of radiographic progression as assessed by investigator or death due to any cause, whichever occurs first.
Key Secondary endpoint	TSP	Time to symptomatic progression is defined as time from the date of randomization to the date of first of the following:

		• The use of external beam radiation therapy for skeletal or pelvic symptoms. Note: Only radiation planned prior to randomization will not be considered as symptomatic progression • The need for tumor-related orthopedic surgical intervention • Other cancer-related procedures (eg, nephrostomy insertion, bladder catheter insertion, external beam radiation therapy, or surgery for tumor symptoms) • Cancer-related morbid events (ie, fracture [symptomatic and/or pathologic], cord compression, urinary obstructive events) • Initiation of a new systemic anti-cancer therapy because of cancer symptoms.
Key secondary endpoint	OS	Overall survival is defined as time from date of randomization to date of death due to any cause.

DCO: 07-Jan-2025 for the final analysis of rPFS and interim analysis 1 for the key secondary endpoint of TSP.
DCO: 03-Oct-2025 for the interim analysis of OS.

Analysis description	**Primary Analysis – All BRCA population**		
Analysis population and time point description	Intent to treat in the BRCA population.		
Descriptive statistics and estimate variability	Treatment group	Nira+AAP	Pbo+AAP
	Number of subject	191	196
	Median rPFS by investigator (months)	NE	25.99
	95% CI	41.20, NE	22.11, 41.17
	Median TSP (months)	NE	NE
	95% CI	NE, NE	39.72, NE
	Median OS (months)	52.0	47.6
Effect estimate per comparison	Primary endpoint: rPFS	Comparison groups	Nira+AAP vs. pbo+AAP
		Hazard ratio	0.515
		95% CI	0.370, 0.717
		P-value	p<0.0001
	Key secondary Endpoint: TSP	Comparison groups	Nira+AAP vs. pbo+AAP
		Hazard ratio	0.444
		95% CI	0.290, 0.681
		P-value	p=0.0001
	Key secondary Endpoint: OS	Comparison groups	Nira+AAP vs. pbo+AAP
		Hazard ratio	0.80
		95% CI	0.58, 1.11
		P-value	Descriptive
Analysis description	**Primary Analysis – All HRR population**		
Analysis population and time point description	Intent to treat in the All HRR population. The BRCA population and the HRR effector population were also tested. The FAS included all randomized patients.		
Descriptive statistics and estimate variability	Treatment group	Nira+AAP	Pbo+AAP
	Number of subject	348	348

	Median rPFS by investigator (months)	NE	29.54
	95% CI	41.20, NE	25.82, NE
	Median TSP (months)	NE	NE
	95% CI	NE, NE	43.14, NE
	Median OS (months)	52.0	48.4
Effect estimate per comparison	Primary endpoint: rPFS	Comparison groups	Nira+AAP vs. pbo+AAP
		Hazard ratio	0.625
		95% CI	0.490, 0.799
		P-value	p=0.0001
	Key secondary Endpoint: TSP	Comparison groups	Nira+AAP vs. pbo+AAP
		Hazard ratio	0.503
		95% CI	0.364, 0.695
		P-value	p<0.0001
	Key secondary Endpoint: OS	Comparison groups	Nira+AAP vs. pbo+AAP
		Hazard ratio	0.825
		95% CI	0.647, 1.052
		P-value	Descriptive

In vitro biomarker test for patient selection for efficacy

Participants enrolled in this study must have demonstrated at least one deleterious germline or somatic HRR gene alteration.

HRR testing

The following central assays used in the AMPLITUDE study: Foundation Medicine, Inc (FMI) tissue test FoundationOne CDx, FMI FoundationOneLiquidCDx ctDNA test (F1LCDx), and AmoyDx HRD complete tissue and germline assays (China only). Note that Invitae Corp was initially used as a central assay,but stopped supporting clinical trials during the course of the study, and is therefore listed as a local assay below.

Enrolment of 622 out of 696 (89.4%) participants was performed based on four central assays: Invitae (discontinued), AmoyDx (only in China), F1CDx and F1LCDx. The F1CDx and the F1Liquid CDx are the same assays that were used for enrolment and subsequent approval of AKEEGA in mCRPC in the EU. In total, 82.6% (575/696) of participants were enrolled by these assays in the current AMPLITUDE study, being the tissue test (F1CDx) the main one (n=468).

The MAH has submitted a summary of the results of the clinical validation study to establish F1CDx as CDx for Akeega based on the AMPLITUDE study and the technical information for both F1CDx and F1LiquidCDx.

The F1CDx platform employs whole-genome library construction and hybridization-based capture on DNA extracted from FFPE tumour tissue prior to sequencing on the Illumina® Novaseq 6000.

Performance characteristics were established using DNA derived from a wide range of FFPE tissue types. To assess concordance, the detection of alterations by the F1CDx assay was compared to results of an externally validated NGS assay. A total of 230 (120 positive, 110 negative by F1CDx) samples were analysed to determine concordance specific to HRR alterations (including base substitutions, indels, rearrangements and homozygous deletions). For HRR substitutions, PPA was 97.22% and NPA 99.99%. For HRR gene indels, PPA was 92.59% and NPA was 99.99%. For HRR rearrangements, PPA was 90.91% and NPA 99.73%; while for HRR copy number alterations, PPA was 95.24% and NPA 99.78%. Precision was also evaluated for HRR gene panels by assessing and comparing inter-run replicates across multiple study factors. Overall, reproducibility was 94.2 (95% CI: 92.9, 95.4).

Regarding analytical sensitivity, a Limit of Blank of zero was confirmed for HRR gene panel CDx variants. The Limit of Detection estimation for HRR gene panel biomarkers in prostate cancer ranges from 6.33% for base substitutions and 23.9% for HRR (HD).

Clinical validation for the indication to identify BRCA1/2 alterations in prostate cancer patients intended to be treated with niraparib + abiraterone (Akeega) was performed using specimens from patients screened for enrolment in the MAGNITUDE study (the pivotal trial for the original indication of mCRPC).

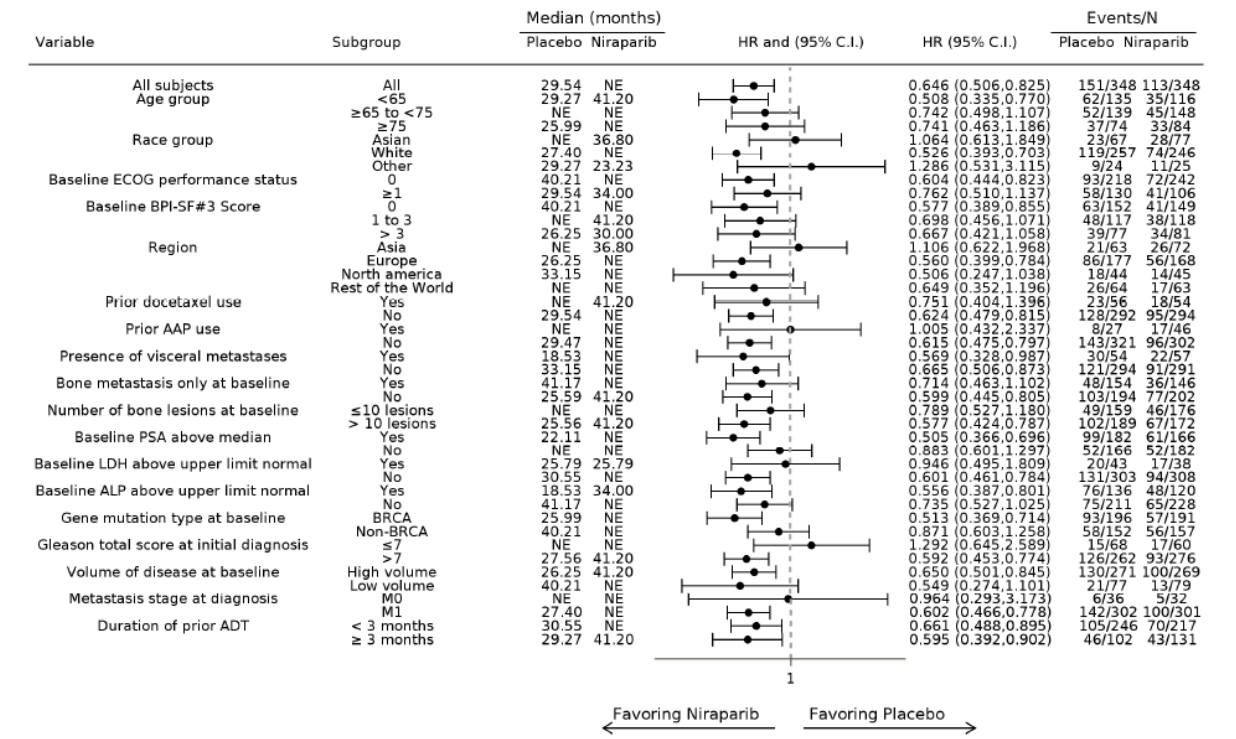
A clinical validation study has been performed based on the HRR-deficient ITT population of the AMPLITUDE study to support the designation of F1CDx as CDx for detection of HRR (including BRCA1/2) gene alterations in candidates for treatment with Akeega.

From the HRR-deficient ITT (n=696), 147 patients had invalid F1CDx testing results (missing rate: 21.1%). For the F1CDx+ All HRR population (n=468), rPFS HR was 0.56 (95% two-sided CI: [0.42, 0.76]). For the F1CDx+ BRCA subgroup (n=273), the estimated HR was s 0.46 (95% two-sided CI: [0.30, 0.69]). Exploratory analyses evaluated the efficacy in F1CDx- subgroups, with HR for the F1CDx- All HRR population being 0.55 (95% two-sided CI: [0.23, 1.31]) and HR 0.66 (95% two-sided CI: [0.45, 0.98]) for the F1CDx- BRCA subgroup.

For F1LCDx, no further details on clinical performance based on the AMPLITUDE study have been provided.

Clinical studies in special populations

Figure 22 Forest Plot of Radiographic Progression-free Survival by Investigator Review for Subgroups Defined by Baseline Characteristics; Full Analysis Set (Study 67652000PCR3002)



2.4.3. Discussion on clinical efficacy

The basis for this submission is the AMPLITUDE study, an ongoing phase 3 study.

With this submission the MAH presented the final analysis (FA) of the primary endpoint and the first interim analysis (IA1) of the two key secondary endpoints (DCO: 07-Jan-2025). Within the assessment phase, the MAH submitted updated exploratory results for the primary and secondary endpoints at IA2 (DCO: 03-Oct-2025).

Design and conduct of clinical studies

The study AMPLITUDE is a randomized, placebo-controlled, double-blind multicentre study in which patients were randomized 1:1 to oral niraparib 200 mg in combination with abiraterone acetate/prednisone 1000 mg/5 mg (nira+AAP) or abiraterone acetate/prednisone (pbo+AAP) 1000 mg/5 mg alone. The dose and posology of niraparib + abiraterone acetate administered in this study is the same as the dose already approved for the mCRPC indication.

Patients were stratified by HRR gene alteration (BRCA2 vs. CDK12 vs. all other pathogenic alterations), prior docetaxel use (yes vs. no), and volume of disease at screening (high vs. low). Although BRCA1 was not included as stratification factor due to its lower prevalence, the percentage of patients included in each arm was balanced (see section "Baseline characteristics"). These stratification factors are considered adequate.

The MAH sought scientific advice from the CHMP in 2020 (EMA/CHMP/SAWP/220901/2020). Overall, the MAH followed the advice received. Inclusion and exclusion criteria are overall considered adequate and reflective of the targeted indication.

In this study there were three pre-specified populations, based on the gene alterations: the BRCA population (formed solely for patients with BRCA1 and BRCA2), the HRR effector population (which included the BRCA population together with patients with the following gene alterations: BRIP1, PALB2, RAD51B and RAD54L) and the All HRR population.

Overall, the primary (rPFS) and secondary endpoints (key secondary endpoints: TSP and OS) are considered adequate. However, it is noted that in the SA (EMA/CHMP/SAWP/220901/2020) the CHMP recommended to consider rPFS and OS as co-primary endpoints since it was considered that OS results (which is the preferred endpoint) could be obtained within a reasonable timeframe, although using rPFS as primary endpoint was also agreed. It is also noted that assessment by BICR would have been preferred over assessment by investigator.

The comparator of the study was placebo + abiraterone/prednisone, which is considered adequate since it allows to assess the contribution of the components of the FDC. Additionally, patients who were not surgically castrated had to be on ADT; therefore, the study indeed compared the combination of ADT + abiraterone/prednisone (which is one of the therapies considered as standard of care in the EU) versus ADT + abiraterone/prednisone + niraparib. Of note, the use of abiraterone + prednisone as comparator was recommended in the SA received by CHMP in 2020 (EMA/CHMP/SAWP/220901/2020). As of today, several therapies exist as standard of care in the EU, but none of them has been positioned over the others.

There were four protocol amendments to the original protocol, dated 10-Jun-2020. The most relevant ones were protocol amendment 3 and protocol amendment 4.

Protocol amendment 4 (28-Aug-2023) was implemented to modify the secondary efficacy endpoint from "symptomatic progression-free survival" to "time to symptomatic progression". The difference between both endpoints is that "symptomatic progression-free survival" included any-cause death as an event, whereas "time to symptomatic progression" did not include it. The MAH's justification for this change is the capture of a solely patient-centred endpoint. Although it is noted that this endpoint is placed in a strategic order in the hierarchical testing procedure (i.e., if this endpoint was not statistically significant no formal analysis of OS could be conducted), this change is not considered critical as any-cause death is already included in the definition of rPFS and OS. Overall, the implemented protocol amendments are not considered concerning, even more considering that the study was double-blinded.

In terms of protocol deviations, there were 44 subjects (6.3%) with major protocol deviations in the study. The most frequently reported major deviation was "received wrong treatment or incorrect dose", with 16 (4.6%) subjects in nira+AAP and 5 (1.4%) subjects in pbo+AAP. The imbalance between both arms is due to the fact that 9 patients in nira+AAP did not receive the correct dose of niraparib following an AE (i.e., niraparib was not reduced or interrupted per protocol or restarted at the wrong dose). Since the percentage of protocol deviations was low, it is not expected that the protocol deviations have affected the results.

Statistical methods

The original sample size accounted for approximately 788 participants, randomized 1:1 to receive nira+AAP or pbo+AAP. It was estimated that approximately 305 rPFS events were required to provide 96% power in detecting a HR of 0.65 (median rPFS of 33 months for the pbo+AAP arm vs. 51 months for the nira+AAP) at a 2-tailed level of significance of 0.05 in the entire study

population and 98% power to detect a HR of 0.5 for rPFS (33 vs. 66 months) in the subgroup of subjects with BRCA gene alterations. With amendment 3 (09-Feb-2023) the sample size was revised due to emerging data from the MAGNITUDE study, reducing the sample size from 788 to 692. Considering that the study was double-blind, the change was implemented before the respective DCO (7 Feb 2025) and the final study power was 91% for the All HRR population, no concern is raised.

The stratified analysis was based on factors as per HRR gene status (BRCA2 vs. CDK12 vs. all other gene alterations), prior docetaxel use (yes vs. no), and volume of disease (high vs. low). However, if any stratum had a sample size of less than 10% of the total sample size, this particular stratum could be combined with other strata for the stratified analysis. Based on this, prior to database lock, it was decided that only volume of disease (high vs. low) and gene group (BRCA2 vs. other) would be used in analyses for the All HRR population, while only volume of disease (high vs. low) would be used in BRCA and HRR effector subgroups analyses. Consequently, the MAH pre-planned a prognostic factor sensitivity analysis using a backward selection method, where the final set of prognostic factors were identified with an exit p-value set of 0.10. Overall, this approach is considered acceptable.

With regard to rPFS censoring rules, the MAH stated that patients lost to follow-up or withdrawn from the study would have been censored, but this was valid only if their outcomes were expected to be similar to those remaining in the trial. Since loss to follow-up / withdrawn from the study might have been associated with treatment discontinuations, this assumption may not hold, making censoring inadequate. A tipping point sensitivity analysis is usually used in such cases to help understand the robustness of the results to departures from these assumptions. However, the number of patients lost to follow-up or withdrawn was of 8 (2.3%) in pbo+AAP and 14 (4%) in nira+AAP, which is unlikely to impact the results.

Concerning multiplicity, a strategy to preserve the overall family-wise type I error rate at the 2-sided 0.05 level was considered, where the multiple comparisons were included in a testing procedure following a group sequential design. These multiple comparisons included the primary endpoint (rPFS) and the two key secondary endpoints (TSP and OS; analysed in that order); and the three studied populations (the BRCA subgroup, the HRR effector subgroup and the All HRR population) also analysed in that order. It should be noted that in the above-mentioned SA the CHMP considered that after the test in the BRCA-mutated patients and in the All HRR population, the next population to be formally tested should have been the Non-BRCA mutated patients (i.e., the complementary to the BRCA population), to confirm that the observed results in the whole population were not driven by the most sensitive group (i.e., the BRCA-mutated patients). Unfortunately, this recommendation was not followed by the MAH.

No interim analysis was planned for the primary endpoint, rPFS. An IA was planned for TSP (IF: around 66.8%), while two IAs were planned for OS (IF IA1: around 43.7%; IF IA2: around 65.6%). This approach is considered acceptable.

Regarding estimands and the handling of intercurrent events (ICE) for the rPFS primary endpoint, a treatment policy strategy was to be employed in case of premature stopping study treatment due to an AE or other reasons than AE or worsening of disease. Overall, the described treatment policy for the ICEs is acceptable.

Regarding the handling of missing data, the SAP stated that no imputation was planned unless specified. A supplementary estimand, such as composite for the treatment related ICEs considering them as treatment failure was requested, which showed that the conclusions were not significantly affected by using this approach. A hypothetical strategy was applied in subjects in whom

subsequent anti-cancer therapy was initiated prior to the documented disease progression or death; and a sensitivity analysis was planned without this type of censoring. Therefore, no concerns are raised in this regard.

Efficacy data and additional analyses

Unless otherwise specified, the population referred to along this discussion is the All HRR population.

Baseline and disease characteristics

No relevant differences were observed between both arms or between the BRCA population and the All HRR population.

Regarding the extent of the disease, almost all patients had bone metastasis (98.3%), of whom 43.2% only had bone metastasis. Metastatic prostate cancer is frequently found in the bone only, therefore this is consistent with the target population. Concerning prior prostate cancer therapy overall, prior prostate cancer therapies were well balanced between both arms.

Regarding concomitant treatment, a rather high percentage of patients received analgesics in both arms, including opioids. However, it is noted that this percentage was lower in the nira+AAP arm than in the pbo+AAP arm (70.7% in pbo+AAP vs. 63.1% in nira+AAP). Use of antihypertensive treatment was higher in the nira+AAP arm, although this was expected considering the known safety profile of niraparib. Around 20% of patients received drugs for treatment of bone disease.

With respect to gene alterations, participants enrolled in the study had to have demonstrated at least 1 deleterious germline or somatic HRR gene alteration. The most frequent gene alteration was BRCA2 (41.4% in pbo+AAP vs. 42.5% in nira+AAP). In total, there were 387 patients (55.6%) with BRCA gene alterations.

Patients were enrolled based on central and/or local testing. Most participants were enrolled based on central testing (N=622), with the remaining participants (N=74) enrolled using local tests. Most participants were enrolled using the FoundationOne® CDx (tissue; N=469). During the study, there were changes to the tests allowed in pre-screening to identify HRR gene mutations: participants were allowed to be tested by liquid biopsy from amendment 3; germline testing was discontinued in September 2022 due to the test vendor no longer supporting clinical trials. The difficulties related to maintaining a limited number of assays during the conduct of the study are acknowledged. Details about analytical and clinical performance of F1CDx testing for HRR in patients intended to receive Nira+APP were submitted upon request and are reflected in this report.

Endpoints

BRCA1/2 population

The primary endpoint, rPFS by investigator, was statistically significant in the BRCA population [HR: 0.51 (95% CI: 0.370, 0.717); p<0.0001]. There were 93 (47.4%) events in pbo+AAP, whereas in nira+AAP there were 57 (29.8%). Median rPFS was not reached in the nira+AAP arm, while it was 25.99 (95% CI: 22.11, 41.17) in the placebo arm. KM curves clearly separate at around month 3. Sensitivity analysis by central review were consistent with these results [HR: 0.514 (95% CI: 0.366, 0.723)], as well as sensitivity analysis of rPFS not censored for subsequent therapy [HR: 0.515 (95% CI: 0.375, 0.706)].

The pre-planned prognostic factor sensitivity analysis using a backward selection method identified the following final set of prognostic factors: PSA, lactate dehydrogenase, worst pain score at baseline, Gleason score and volume of disease. They were included as covariates in a multivariate Cox regression model. This analysis demonstrated a consistent treatment effect with nira+AAP on rPFS (HR=0.507; 95% CI: 0.360, 0.715; p=0.0001).

The secondary endpoint time to symptomatic progression also met statistical significance in the BRCA population, with 31 (16.2%) events in the nira+AAP arm vs. 66 (33.7%) events in the pbo+AAP arm [HR: 0.444 (95% CI: 0.290, 0.681); p=0.0001

The KM curves also separate from month 3.

The secondary endpoint OS did not reach statistical significance at IA1 [HR: 0.750 (95% CI: 0.509, 1.106); p=0.1454, although a trend favouring nira+AAP was observed: there were 44 (23%) deaths in the nira+AAP, while in the pbo+AAP arm there were 61 (31.1%) deaths. mOS was not reached in either arm, and mFU was 30.7 months. The analysis adjusted for prognostic factors and the non-stratified analysis were consistent with the results of the stratified analysis.

At IA2, a predefined OS analysis was performed based on 65 (34%) deaths in the Nira+AAP arm and 80 (40.8%) deaths in the Pbo+AAP treatment arm. Median OS was 52.0 months and 47.6 months in the Nira+AAP and PBO+AAP arms, respectively, although it should be noted that a single event occurred late in follow-up, so these figures might be driven by this. HR point estimate was 0.799 (95% CI: 0.576, 1.109), stratified Log-rank test p=0.1793. Therefore, the OS IA2 results did not reach statistical significance either. The Applicant should submit the final analysis for Study AMPLITUDE once available. **(REC).**

Overall, secondary endpoints support the efficacy results observed for the primary and key secondary endpoints.

Based on the data presented for subgroups of patients, BRCA1 patients (i.e. excluding those with BRCA2 co-existing mutation) showed an unfavourable trend for both rPFS and OS. Specifically, rPFS HR was 1.127 (95% CI: 0.447, 2.843) and OS IA2 HR was 1.545 (95% CI: 0.639, 3.734). These results raise some concern as to whether patients harbouring only BRCA1 mutations derive benefit from the addition of niraparib. However, the number of BRCA1 patients included in this study was significantly low (n=28 in the nira+AAP group and n=33 in the pbo+AAP group) and the analyses are based on a limited number of events, precluding a reliable interpretation of these findings. There were also six additional patients with co-occurring BRCA1 and BRCA2 mutations, for whom similarly unfavourable results were observed. The MAH provided additional discussion about these findings. When breaking down populations into such smaller subgroups, balance of prognostic factors is no longer guaranteed. In this case, it seems that there was an imbalance in Gleason score within the BRCA1 subgroup, leaving higher Gleason score patients mostly in the experimental arm. Although not conclusive, this could have played a role in the observed results. Moreover, while there is some evidence suggesting a differential response to some PARPi by BRCA1 and BRCA2 mutation in CRPC, again it is based on limited data , similarly to what was observed for this study, thereby hampering definitive conclusions. An exclusion of patients with BRCA1 mutations is not considered justified, based on the available information.

HRR effector population

In the HRR effector population both the primary endpoint, rPFS and the key secondary endpoint TSP were statistically significant. The key secondary endpoint OS could not be formally tested since OS in the BRCA population (which was placed before in the hierarchical testing procedure) was not statistically significant at OS IA1. Overall, the results in the HRR effector population are quite

aligned with the results observed in the BRCA population; which is not surprising, considering that most of the patients in the HRR effector population were BRCA-mutated patients. Indeed, from the total number of patients in the HRR effector population (N=456), 387 patients were BRCA-mutated patients, with either single gene or co-occurring gene alterations, and only 69 patients had a gene alteration in BRIP1, PALB2, RAD51B or RAD54L.

All HRR population

The primary endpoint, rPFS, reached statistical significance in the All HRR population, with 151 (43.4%) events in the pbo+AAP arm and 113 (32.5%) events in the nira+AAP arm [HR: 0.625 (95% CI: 0.490, 0.799); p=0.0001]. Median rPFS was not reached in the nira+AAP arm, vs. 29.5 months in the pbo+AAP arm. KM curves separate from month 3. From amendment 3 on (09-Feb-2023), participants with radiographic progression could remain on therapy if still receiving clinical benefit. At IA1, a relevant number of the patients who reported radiographic disease progression received treatment after it. From the 92 (26.4%) patients who progressed on the nira+AAP arm, 82 (23.6%) received further treatment while, in the PBO+AAP arm, there were 139 (39.9%) patients who progressed and, from them, 118 (33.9%) received treatment beyond progression. Nevertheless, the duration of exposure was lower than 2 months for most of the patients, being the median duration of exposure around 1.75 months in both arms. Even if treatment beyond progression was maintained for more than 6 months in some patients, the decision could be multifactorial and could reflect clinical practice for patients who are not deemed candidates for (further) taxane therapy or for whom deferring initiation of a subsequent line of therapy is preferred. In any case, it is unlikely that this treatment has a relevant impact on secondary endpoints.

The secondary endpoint TSP also reached statistical significance in the All HRR population, with 104 (29.9%) events in the pbo+AAP arm vs. 57 (16.4%) events in the nira+AAP [HR: 0.503 (95% CI: 0.364, 0.695); p<0.0001]. The KM curves showed separation from the beginning (around month 3). IF at IA1 was 80.9% (161 events / 199 planned events).

Bone-sparing agents (bisphosphonates or denosumab) were used to treat 23.5% of patients with similar rates between the treatment arms. This information is reflected in section 5.1 of the SmPC where detail for each treatment arm separately is also presented.

OS could not be formally tested in the All HRR population since OS in the BRCA population (which was placed before in the hierarchical testing procedure) did not reach statistical significance at OS IA1. However, a trend favouring nira+AAP was observed, with 108 deaths (31%) in pbo+AAP vs. 85 deaths (24.4%) in nira+AAP [HR: 0.785 (95% CI: 0.591, 1.044); p=0.0951. KM curves separate around month 21, until that month both curves overlapped. Median OS was not reached in either arm. The IF at this OS IA1 was 49.6% (193 events / 389 planned events). In terms of post-treatment therapy, 76% of patients who discontinued study treatment in pbo+AAP arm received subsequent therapy, vs. 59.1% in nira+AAP. The most frequent subsequent prostate cancer therapy received was chemotherapy (44.7% in nira+AAP vs. 52% in pbo+AAP). In the pbo+AAP arm there were 47 patients (24%) who started subsequent therapy with PARPi, in comparison with 10 patients (6.3%) in the nira+AAP arm. Almost all the patients who received a PARPi received olaparib (42 patients in pbo+AAP vs. 10 patients in nira+AAP).

At IA2, with an overall 40.5 months median follow-up and an IF of 67.1% (261/389) in the All HRR population, OS HR point estimate was 0.82 (0.65,1.05), stratified 2-sided Log-rank Test p-value 0.121.

Overall, secondary endpoints support the efficacy results observed for the primary and key secondary endpoints.

Non-BRCA subgroup

A broad All HRR indication was initially requested by the MAH. The MAH provided results in the Non-BRCA subgroup and by gene alteration. As expected, results in the Non-BRCA subgroup were worse than in the BRCA subgroup. In terms of rPFS, no differences were observed between treatment arms with 56 (35.7%) events in nira+AAP and 58 (38.2%) events in pbo+AAP, with a HR point estimate of 0.815 (95% CI: 0.563, 1.178). A clear separation of the KM curves was not observed. In terms of OS, the lower benefit was also confirmed at IA2, with a HR of 0.85 (0.59,1.22), nominal p-value of 0.376. KM curves slightly separate after month 24 in favour of the nira+AAP arm, although they overlap most of time. Therefore, with the data so far available the benefit of adding niraparib to AAP in this subgroup is not clear in terms of OS and a positive B/R cannot be concluded in the Non-BRCA population.

Further, there are uncertainties regarding the type of HRR gene alterations included in the study and whether the selection adequately represent all the HRR gene alterations that can be found in clinical practice. Although the MAH provided justification for the HRR gene panel included in the study, the uncertainties regarding why some alterations were included and why some other were excluded remained.

Based on the data submitted, no clear benefit was observed in either endpoint- rPFS or OS- in the patients with non-BRCA mutations. Uncertainties remain on the clinical benefit across all the included HRR gene mutations, especially considering that certain mutations (e.g., ATM, CDK12) were proactively excluded from the study due to anticipated lack of efficacy in patients harbouring these gene alterations. Further, additional toxicity is observed with the administration of niraparib (refer to Clinical Safety section). Based on all these uncertainties, the indication has been restricted to patients with BRCA1/2 mutated genes.

Subgroup analyses

In the BRCA population no relevant differences in rPFS were observed among the different pre-specified subgroups; Asian patients seem to have worse outcomes than White patients [HR: 1.104; CI 95%: 0.572, 2.133)] and Europe region. Some other subgroup analyses resulted in apparently less beneficial outcomes (i.e., "other" race group, baseline LDH above upper limit normal, Gleason total score ≤7 at initial diagnosis, metastasis stage M0 at diagnosis), however no conclusions can be drawn due to the scarce number of patients and events in each subgroup. In terms of OS subgroup analyses, no conclusions can be drawn due to the immaturity of the data, which entails higher uncertainty (i.e., wider CIs) and impairs a proper data assessment.

The subgroup analyses were **overall** similar to those in the BRCA population.

In the All HRR population the results of the rPFS subgroup analyses were overall similar to those in the BRCA population.

Wording of the indication

The MAH initially requested the following extension of indication:

"Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) and HRR gene alterations (germline and/or somatic)."

However, based on the data submitted, no clear benefit was observed in either endpoint- rPFS or OS- in the patients with non-BRCA mutations. Consequently, the indication was restricted to patients with BRCA1/2 mutated genes.

In addition, patients enrolled in the AMPLITUDE study were required to remain on androgen deprivation therapy (ADT) throughout the entire treatment period; patients had to be either medically or surgically castrated. This requirement was not adequately reflected in the proposed indication.

Although section 4.2 of the SmPC states that "*medical castration with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in patients not surgically castrated,"* this was considered insufficient to fully address the requirement

The indication was updated based on the background above and the final indication is

Akeega is indicated with prednisone or prednisolone in combination with androgen deprivation therapy (ADT) for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) and BRCA 1/2 mutations, (germline and/or somatic).

2.4.4. Conclusions on the clinical efficacy

The primary endpoint of the study AMPLITUDE was met, demonstrating superiority of nira+AAP over pbo+AAP in terms of rPFS in the BRCA population as well as in the All HRR population. TSP, one of the key secondary endpoints, also in favoured of the nira+AAP arm in BRCA positive population. Although statistical significance for OS in the nira+AAP was not reached in any of the studied populations, a positive trend has been observed.

No clear benefit was observed neither in rPFS nor in OS in the non-BRCA mutations patients' population and considering the additive toxicity of the combination in a subset of patients in whom no clinical benefit is observed, the indication has been restricted to patients harbouring BRCA mutations.

2.5. Clinical safety

Introduction

The pivotal data for the clinical safety of the current application are provided from the AMPLITUDE study with data cut-off (DCO) 07-Jan-2025.

Additionally, the safety data from AMPLITUDE has been integrated with safety data from MAGNITUDE Cohort 1 (Study 64091742PCR3001 supporting the initial approval of Akeega) which comprised mCRPC patients with HRR gene alterations.

Integrated safety data include:

- **AMPLITUDE (***Study 67652000PCR3002***) (mCSPC):**
    - All HRR: 695 subjects, **347** subjects received combination therapy with niraparib and abiraterone acetate (AA) as two fixed-dose combination (FDC) tablets (niraparib 100 mg/AA 500 mg per tablet) plus prednisone (or prednisolone) tablet, and 348 subjects received placebo instead of niraparib in the same combination therapy.
- **MAGNITUDE Cohort 1 (mCRPC):**
    - All HRR: 423 subjects, **212** subjects received niraparib + AAP and 211 subjects received placebo + AAP

Therefore, the totality of the safety data, the so called "combined data set mCSPC + mCRPC is as follows:

- All HRR: 1118 subjects, **559** subjects received niraparib + AAP and 559 subjects received placebo + AAP

The dose of nira+AA was the same in AMPLITUDE and MAGNITUDE, with patients receiving niraparib (200 mg) and AA (1000 mg) in both trials. Prednisone dosing was consistent with the labeled indication for each study: 5 mg for mHSPC on AMPLITUDE and 10 mg for mCRPC on MAGNITUDE.

Table 68. Overview of the clinical study data included in the summary of clinical safety (SCS)

Study (status)	Study Design	Study Population	Treatment (daily)	Number of Participants Treated	CCO Date
Metastatic castration-sensitive prostate cancer					
AMPLITUDE 67652000PCR3002 (ongoing)	Phase 3, randomized, placebo-controlled, double-blind, multinational study to evaluate the safety and efficacy of nira+AAP versus AAP alone	Participants with deleterious germline or somatic HRR gene-mutated mHSPC and limited prior treatment (no more than 6 cycles of docetaxel, 45 days of AAP, or 6 months of ADT prior to randomization)	Niraparib (200 mg) and AAP (1,000 mg+5 mg)[1] or PBO+AAP (1,000 mg+ 5 mg)	**Nira+AAP:** 347 (All HRR) includes 191 (BRCA) **PBO+AAP:** 348 (All HRR) includes 196 (BRCA)	07 January 2025 (PA-IA1)
Metastatic castration-resistant prostate cancer					
MAGNITUDE 64091742PCR3001 Cohort 1[2] (completed)	Phase 3, randomized, placebo-controlled, double-blind, multinational study to assess the efficacy and safety of niraparib in combination with AAP versus AAP alone	Participants with mCRPC and HRR gene alterations who previously received no prior treatment for mCRPC except ≤4 months of AAP	Niraparib (200 mg) and AAP (1,000 mg+10 mg) as SAC or PBO+AAP (1,000 mg+10 mg)	**Nira+AAP:** 212 (All HRR) includes 113 (BRCA) **PBO+AAP:** 211 (All HRR) includes 112 (BRCA)	15 May 2023 (FA)

Note: HRR gene alterations for MAGNITUDE included ATM, BRCA1, BRCA2, BR1P1, CDK-12, CHEK2, FANCA, HDAC2, PALB2. HRR gene alterations for AMPLITUDE included BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, and RAD54L.

AA=abiraterone acetate; AAP=AA plus prednisone; ADT=androgen deprivation therapy; ATM=ataxia telangiectasia mutated gene; BRCA1= breast cancer gene 1; BRCA2=breast cancer gene 2; BR1P1=BRCA1 interacting protein C-terminal Helicase 1 gene; CCO=clinical cutoff; CDK-12=cyclin-dependent kinase 12; CHEK2=checkpoint kinase 2 gene; FANCA=Fanconi anemia complementation Group A gene; FA=final analysis; FDC=fixed-dose combination; HDAC2=histone deacetylase 2 gene; HRR=homologous recombination repair; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; P=prednisone; PA-IA1=primary analysis of rPFS and 1st interim analysis of secondary/other efficacy endpoints for AMPLITUDE; PALB2=partner and localizer of BRCA2 gene; PBO=placebo; RAD51B=RAD51 paralog B; RAD54L=RAD54-like; rPFS=radiographic progression-free survival; SAC=single-agent combination; SCS=Summary of Clinical Safety

[1] Low-strength FDC (nira 50 mg/AA 500 mg per tablet) and single-agent niraparib (or placebo) were provided when applicable to allow for dose reduction as for management of TEAEs.

[2] Data from MAGNITUDE Cohort 2 (participants with mCRPC and no HRR gene alterations) and Cohort 3 (single-arm, open-label nira+AAP FDC treatment experience in participants with mCRPC and HRR gene alterations) are not included in the SCS.

The FDC (immediate release film-coated tablet) administered was the regular strength, a 100 mg niraparib/500 mg AA tablet. However, the low-strength FDC (niraparib 50 mg/ AA 500 mg per tablet) and single-agent niraparib (or placebo) were provided to allow for dose reductions as for management of TEAEs when applicable.

The proposed posology is 200 mg/1000 mg (two 100 mg niraparib/500 mg abiraterone acetate tablets) as a single daily dose.

Patient exposure

Exposure

Table 69. Extent of exposure; Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Duration of study treatment (months)[d]								
N	196	191	348	347	211	212	559	559
Mean (SD)	21.4 (11.77)	25.2 (11.07)	21.9 (11.86)	24.5 (11.29)	18.0 (12.49)	20.4 (12.46)	20.4 (12.24)	23.0 (11.90)
Median	21.5	25.7	22.5	25.3	15.2	20.2	18.5	23.8
Range	(1; 47)	(0; 48)	(0; 47)	(0; 48)	(0; 48)	(0; 48)	(0; 48)	(0; 48)
Duration of study treatment (months)[d]								
> 0 months	196 (100.0%)	191 (100.0%)	348 (100.0%)	347 (100.0%)	211 (100.0%)	212 (100.0%)	559 (100.0%)	559 (100.0%)
≥ 6 months	180 (91.8%)	178 (93.2%)	320 (92.0%)	322 (92.8%)	166 (78.7%)	182 (85.8%)	486 (86.9%)	504 (90.2%)
≥ 12 months	143 (73.0%)	160 (83.8%)	258 (74.1%)	288 (83.0%)	130 (61.6%)	146 (68.9%)	388 (69.4%)	434 (77.6%)
≥ 18 months	114 (58.2%)	146 (76.4%)	211 (60.6%)	254 (73.2%)	81 (38.4%)	112 (52.8%)	292 (52.2%)	366 (65.5%)
≥ 24 months	84 (42.9%)	112 (58.6%)	154 (44.3%)	190 (54.8%)	60 (28.4%)	85 (40.1%)	214 (38.3%)	275 (49.2%)
≥ 30 months	47 (24.0%)	66 (34.6%)	91 (26.1%)	115 (33.1%)	45 (21.3%)	53 (25.0%)	136 (24.3%)	168 (30.1%)
≥ 36 months	25 (12.8%)	34 (17.8%)	52 (14.9%)	60 (17.3%)	25 (11.8%)	29 (13.7%)	77 (13.8%)	89 (15.9%)
≥ 42 months	11 (5.6%)	7 (3.7%)	20 (5.7%)	14 (4.0%)	10 (4.7%)	9 (4.2%)	30 (5.4%)	23 (4.1%)
≥ 48 months	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Number of cycles started[e]								
N	196	191	348	347	211	212	559	559
Mean (SD)	22.8 (12.28)	26.7 (11.47)	23.4 (12.40)	26.0 (11.71)	19.4 (13.25)	21.9 (13.21)	21.9 (12.87)	24.5 (12.46)
Median	23.5	25.0	25.0	25.0	17.0	21.0	21.0	25.0
Range	(1; 49)	(1; 49)	(1; 49)	(1; 49)	(1; 52)	(1; 52)	(1; 52)	(1; 52)
Number of cycles started[e]								
≥ 1 cycle	196 (100.0%)	191 (100.0%)	348 (100.0%)	347 (100.0%)	211 (100.0%)	212 (100.0%)	559 (100.0%)	559 (100.0%)
≥ 6 cycles	183 (93.4%)	181 (94.8%)	323 (92.8%)	326 (93.9%)	177 (83.9%)	190 (89.6%)	500 (89.4%)	516 (92.3%)
≥ 12 cycles	152 (77.6%)	166 (86.9%)	277 (79.6%)	300 (86.5%)	146 (69.2%)	157 (74.1%)	423 (75.7%)	457 (81.8%)
≥ 18 cycles	122 (62.2%)	152 (79.6%)	223 (64.1%)	265 (76.4%)	92 (43.6%)	120 (56.6%)	315 (56.4%)	385 (68.9%)
≥ 24 cycles	98 (50.0%)	135 (70.7%)	183 (52.6%)	230 (66.3%)	64 (30.3%)	92 (43.4%)	247 (44.2%)	322 (57.6%)
≥ 30 cycles	48 (24.5%)	69 (36.1%)	95 (27.3%)	122 (35.2%)	52 (24.6%)	64 (30.2%)	147 (26.3%)	186 (33.3%)
≥ 36 cycles	35 (17.9%)	52 (27.2%)	73 (21.0%)	87 (25.1%)	35 (16.6%)	39 (18.4%)	108 (19.3%)	126 (22.5%)
≥ 42 cycles	16 (8.2%)	11 (5.8%)	25 (7.2%)	21 (6.1%)	18 (8.5%)	18 (8.5%)	43 (7.7%)	39 (7.0%)
≥ 48 cycles	5 (2.6%)	2 (1.0%)	8 (2.3%)	5 (1.4%)	8 (3.8%)	7 (3.3%)	16 (2.9%)	12 (2.1%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC).

[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.

[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.

[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.

[d] Treatment duration is defined as the duration from the date of the first dose of study drug to the date of last dose of study drug+1 divided by 30.4375, and is based on study drug administration page of Case Report Form.

[e] Cycles are defined as total number of cycles started based on drug accountability page of Case Report Form.

Dose modifications

Table 70. Dose Modifications of Niraparib or Placebo; Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Dose level reductions due to AE								
No reduction	189 (96.4%)	127 (66.5%)	332 (95.4%)	235 (67.7%)	203 (96.2%)	166 (78.3%)	535 (95.7%)	401 (71.7%)
Any reduction	7 (3.6%)	64 (33.5%)	16 (4.6%)	112 (32.3%)	8 (3.8%)	46 (21.7%)	24 (4.3%)	158 (28.3%)
To 100mg[d]	7 (3.6%)	63 (33.0%)	16 (4.6%)	110 (31.7%)	8 (3.8%)	46 (21.7%)	24 (4.3%)	156 (27.9%)
To 50mg	0	1 (0.5%)	0	2 (0.6%)	0	0	0	2 (0.4%)
Number of dose interruptions due to AE								
No interruption	126 (64.3%)	64 (33.5%)	209 (60.1%)	122 (35.2%)	150 (71.1%)	96 (45.3%)	359 (64.2%)	218 (39.0%)
Any interruption	70 (35.7%)	127 (66.5%)	139 (39.9%)	225 (64.8%)	61 (28.9%)	116 (54.7%)	200 (35.8%)	341 (61.0%)
1	54 (27.6%)	58 (30.4%)	99 (28.4%)	105 (30.3%)	44 (20.9%)	60 (28.3%)	143 (25.6%)	165 (29.5%)
2	12 (6.1%)	45 (23.6%)	24 (6.9%)	72 (20.7%)	11 (5.2%)	32 (15.1%)	35 (6.3%)	104 (18.6%)
3	3 (1.5%)	12 (6.3%)	10 (2.9%)	26 (7.5%)	6 (2.8%)	17 (8.0%)	16 (2.9%)	43 (7.7%)
4	1 (0.5%)	8 (4.2%)	5 (1.4%)	13 (3.7%)	0	6 (2.8%)	5 (0.9%)	19 (3.4%)
5	0	2 (1.0%)	1 (0.3%)	4 (1.2%)	0	1 (0.5%)	1 (0.2%)	5 (0.9%)
≥ 6	0	2 (1.0%)	0	5 (1.4%)	0	0	0	5 (0.9%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE=adverse event.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
[d] AMPLITUDE FDC includes dose reduction to Low strength FDC, Regular strength FDC and Single-agent niraparib.
Note: Dose level reduction and dose interruption are determined from the exposure page of the Case Report Form.
Percent is based on the integrated safety analysis set.
Subjects experiencing more than one dose reduction are counted only once according to the largest change in the dose level.
[tsiex03a.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsiex03a.sas] 23FEB2025, 23:36

Adverse events

Table 71. Overall Safety Profile; Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Subjects with 1 or more:								
AEs	191 (97.4%)	191 (100.0%)	341 (98.0%)	346 (99.7%)	205 (97.2%)	212 (100.0%)	546 (97.7%)	558 (99.8%)
Related AEs[d]	143 (73.0%)	175 (91.6%)	257 (73.9%)	309 (89.0%)	123 (58.3%)	168 (79.2%)	380 (68.0%)	477 (85.3%)
COVID-19 associated AEs	49 (25.0%)	45 (23.6%)	80 (23.0%)	75 (21.6%)	24 (11.4%)	35 (16.5%)	104 (18.6%)	110 (19.7%)
Grade 3 or 4 AEs	112 (57.1%)	145 (75.9%)	205 (58.9%)	261 (75.2%)	108 (51.2%)	157 (74.1%)	313 (56.0%)	418 (74.8%)
Related grade 3 or 4 AEs[d]	58 (29.6%)	109 (57.1%)	105 (30.2%)	193 (55.6%)	34 (16.1%)	96 (45.3%)	139 (24.9%)	289 (51.7%)
COVID-19 associated grade 3 or 4 AEs	4 (2.0%)	3 (1.6%)	5 (1.4%)	4 (1.2%)	6 (2.8%)	18 (8.5%)	11 (2.0%)	22 (3.9%)
Serious AEs	53 (27.0%)	67 (35.1%)	96 (27.6%)	136 (39.2%)	65 (30.8%)	100 (47.2%)	161 (28.8%)	236 (42.2%)
Related serious AEs[d]	4 (2.0%)	20 (10.5%)	11 (3.2%)	44 (12.7%)	8 (3.8%)	29 (13.7%)	19 (3.4%)	73 (13.1%)
COVID-19 associated serious AEs	2 (1.0%)	3 (1.6%)	2 (0.6%)	5 (1.4%)	7 (3.3%)	19 (9.0%)	9 (1.6%)	24 (4.3%)
AEs leading to discontinuation of study agent[f]	22 (11.2%)	24 (12.6%)	36 (10.3%)	51 (14.7%)	17 (8.1%)	39 (18.4%)	53 (9.5%)	90 (16.1%)
AEs leading to death[e]	3 (1.5%)	8 (4.2%)	7 (2.0%)	14 (4.0%)	10 (4.7%)	22 (10.4%)	17 (3.0%)	36 (6.4%)
Related AEs leading to death[d]	0	1 (0.5%)	0	1 (0.3%)	1 (0.5%)	1 (0.5%)	1 (0.2%)	2 (0.4%)
COVID-19 associated AEs leading to death	0	2 (1.0%)	0	2 (0.6%)	2 (0.9%)	10 (4.7%)	2 (0.4%)	12 (2.1%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
[d] An AE is categorized as related if assessed by the investigator as related to any of the study medication.
[e] AEs leading to death are based on AE outcome of Fatal.
[f] An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of Niraparib/Placebo or Abiraterone Acetate/Placebo or Prednisone.
[tsfae01.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsfae01.sas] 23FEB2025, 23:30

Table 72. Overall Summary of TEAEs by Gene Subgroup

TSFAE01_gsubgrp: Overall Summary of Treatment-emergent Adverse Events by Gene Subgroup; Safety Analysis Set (Study 67652000PCR3002)

	All HRR		BRCA		HRR Effector		Non-BRCA	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Safety	348	347	196	191	226	230	152	156
Subjects with 1 or more:								
AEs	341 (98.0%)	346 (99.7%)	191 (97.4%)	191 (100.0%)	221 (97.8%)	230 (100.0%)	150 (98.7%)	155 (99.4%)
Related AEs[a]	257 (73.9%)	309 (89.0%)	143 (73.0%)	175 (91.6%)	165 (73.0%)	211 (91.7%)	114 (75.0%)	134 (85.9%)
Grade 3 or 4 AEs	205 (58.9%)	261 (75.2%)	112 (57.1%)	145 (75.9%)	132 (58.4%)	177 (77.0%)	93 (61.2%)	116 (74.4%)
Related grade 3 or 4 AEs[a]	105 (30.2%)	193 (55.6%)	58 (29.6%)	109 (57.1%)	70 (31.0%)	133 (57.8%)	47 (30.9%)	84 (53.8%)
Serious AEs	96 (27.6%)	136 (39.2%)	53 (27.0%)	67 (35.1%)	62 (27.4%)	86 (37.4%)	43 (28.3%)	69 (44.2%)
Related serious AEs[a]	11 (3.2%)	44 (12.7%)	4 (2.0%)	20 (10.5%)	6 (2.7%)	27 (11.7%)	7 (4.6%)	24 (15.4%)
AEs leading to discontinuation of study agent[c]	36 (10.3%)	51 (14.7%)	22 (11.2%)	24 (12.6%)	23 (10.2%)	29 (12.6%)	14 (9.2%)	27 (17.3%)
AEs leading to death[b]	7 (2.0%)	14 (4.0%)	3 (1.5%)	8 (4.2%)	3 (1.3%)	10 (4.3%)	4 (2.6%)	6 (3.8%)
Related AEs leading to death[a]	0	1 (0.3%)	0	1 (0.5%)	0	1 (0.4%)	0	0

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event.
[a] An AE is categorized as related if assessed by the investigator as related to Niraparib/Placebo or Abiraterone Acetate/Placebo or Prednisone.
[b] AEs leading to death are based on AE outcome of Fatal.
[c] An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of Niraparib/Placebo or Abiraterone Acetate/Placebo or Prednisone.

[tsfae01gsubgrp.rtf] [PROD/jnj-67652000/pcr3002/dbr_csr/re_csr/tsfae01gsubgrp.sas] 27MAR2025, 13:04

Common adverse events

Table 73. Treatment-emergent Adverse Events with Frequency of at Least 10% in Any Group by System Organ Class and Preferred Term; Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Subjects with 1 or more AEs	191 (97.4%)	191 (100.0%)	341 (98.0%)	346 (99.7%)	205 (97.2%)	212 (100.0%)	546 (97.7%)	558 (99.8%)
System organ class Preferred term								
Gastrointestinal disorders	95 (48.5%)	139 (72.8%)	176 (50.6%)	235 (67.7%)	101 (47.9%)	134 (63.2%)	277 (49.6%)	369 (66.0%)
Constipation	33 (16.8%)	77 (40.3%)	57 (16.4%)	122 (35.2%)	35 (16.6%)	72 (34.0%)	92 (16.5%)	194 (34.7%)
Nausea	32 (16.3%)	55 (28.8%)	50 (14.4%)	107 (30.8%)	31 (14.7%)	53 (25.0%)	81 (14.5%)	160 (28.6%)
Vomiting	17 (8.7%)	31 (16.2%)	30 (8.6%)	56 (16.1%)	17 (8.1%)	32 (15.1%)	47 (8.4%)	88 (15.7%)
Diarrhoea	23 (11.7%)	29 (15.2%)	40 (11.5%)	51 (14.7%)	10 (4.7%)	18 (8.5%)	50 (8.9%)	69 (12.3%)
Blood and lymphatic system disorders	77 (39.3%)	121 (63.4%)	128 (36.8%)	220 (63.4%)	67 (31.8%)	134 (63.2%)	195 (34.9%)	354 (63.3%)
Anaemia	50 (25.5%)	103 (53.9%)	83 (23.9%)	179 (51.6%)	48 (22.7%)	111 (52.4%)	131 (23.4%)	290 (51.9%)
Neutropenia	18 (9.2%)	39 (20.4%)	28 (8.0%)	76 (21.9%)	15 (7.1%)	34 (16.0%)	43 (7.7%)	110 (19.7%)
Thrombocytopenia	14 (7.1%)	37 (19.4%)	20 (5.7%)	66 (19.0%)	20 (9.5%)	51 (24.1%)	40 (7.2%)	117 (20.9%)
Leukopenia	8 (4.1%)	31 (16.2%)	18 (5.2%)	58 (16.7%)	5 (2.4%)	23 (10.8%)	23 (4.1%)	81 (14.5%)
Lymphopenia	16 (8.2%)	27 (14.1%)	27 (7.8%)	45 (13.0%)	5 (2.4%)	23 (10.8%)	32 (5.7%)	68 (12.2%)
Vascular disorders	91 (46.4%)	114 (59.7%)	161 (46.3%)	201 (57.9%)	72 (34.1%)	99 (46.7%)	233 (41.7%)	300 (53.7%)
Hypertension	63 (32.1%)	89 (46.6%)	113 (32.5%)	152 (43.8%)	49 (23.2%)	72 (34.0%)	162 (29.0%)	224 (40.1%)
Hot flush	21 (10.7%)	39 (20.4%)	48 (13.8%)	63 (18.2%)	16 (7.6%)	16 (7.5%)	64 (11.4%)	79 (14.1%)
General disorders and administration site conditions	90 (45.9%)	111 (58.1%)	175 (50.3%)	195 (56.2%)	89 (42.2%)	124 (58.5%)	264 (47.2%)	319 (57.1%)
Fatigue	34 (17.3%)	55 (28.8%)	64 (18.4%)	91 (26.2%)	41 (19.4%)	66 (31.1%)	105 (18.8%)	157 (28.1%)
Oedema peripheral	22 (11.2%)	33 (17.3%)	42 (12.1%)	55 (15.9%)	19 (9.0%)	22 (10.4%)	61 (10.9%)	77 (13.8%)
Asthenia	20 (10.2%)	25 (13.1%)	44 (12.6%)	47 (13.5%)	21 (10.0%)	36 (17.0%)	65 (11.6%)	83 (14.8%)
Infections and infestations	91 (46.4%)	107 (56.0%)	174 (50.0%)	188 (54.2%)	79 (37.4%)	103 (48.6%)	253 (45.3%)	291 (52.1%)

COVID-19	42 (21.4%)	40 (20.9%)	71 (20.4%)	65 (18.7%)	17 (8.1%)	27 (12.7%)	88 (15.7%)	92 (16.5%)
Urinary tract infection	21 (10.7%)	14 (7.3%)	37 (10.6%)	39 (11.2%)	18 (8.5%)	22 (10.4%)	55 (9.8%)	61 (10.9%)
Musculoskeletal and connective tissue disorders	125 (63.8%)	99 (51.8%)	220 (63.2%)	184 (53.0%)	119 (56.4%)	114 (53.8%)	339 (60.6%)	298 (53.3%)
Arthralgia	43 (21.9%)	37 (19.4%)	74 (21.3%)	73 (21.0%)	22 (10.4%)	39 (18.4%)	96 (17.2%)	112 (20.0%)
Back pain	46 (23.5%)	38 (19.9%)	77 (22.1%)	68 (19.6%)	52 (24.6%)	36 (17.0%)	129 (23.1%)	104 (18.6%)
Pain in extremity	27 (13.8%)	19 (9.9%)	41 (11.8%)	31 (8.9%)	18 (8.5%)	13 (6.1%)	59 (10.6%)	44 (7.9%)
Bone pain	14 (7.1%)	10 (5.2%)	28 (8.0%)	19 (5.5%)	25 (11.8%)	24 (11.3%)	53 (9.5%)	43 (7.7%)
Metabolism and nutrition disorders	81 (41.3%)	94 (49.2%)	148 (42.5%)	183 (52.7%)	77 (36.5%)	104 (49.1%)	225 (40.3%)	287 (51.3%)
Hypokalaemia	34 (17.3%)	50 (26.2%)	70 (20.1%)	90 (25.9%)	22 (10.4%)	33 (15.6%)	92 (16.5%)	123 (22.0%)
Decreased appetite	8 (4.1%)	25 (13.1%)	18 (5.2%)	51 (14.7%)	17 (8.1%)	33 (15.6%)	35 (6.3%)	84 (15.0%)
Hyperglycaemia	25 (12.8%)	26 (13.6%)	42 (12.1%)	48 (13.8%)	18 (8.5%)	27 (12.7%)	60 (10.7%)	75 (13.4%)
Investigations	77 (39.3%)	75 (39.3%)	139 (39.9%)	147 (42.4%)	70 (33.2%)	82 (38.7%)	209 (37.4%)	229 (41.0%)
Weight decreased	7 (3.6%)	26 (13.6%)	18 (5.2%)	53 (15.3%)	8 (3.8%)	25 (11.8%)	26 (4.7%)	78 (14.0%)
Blood creatinine increased	8 (4.1%)	21 (11.0%)	16 (4.6%)	44 (12.7%)	12 (5.7%)	22 (10.4%)	28 (5.0%)	66 (11.8%)
Aspartate aminotransferase increased	25 (12.8%)	16 (8.4%)	50 (14.4%)	28 (8.1%)	21 (10.0%)	14 (6.6%)	71 (12.7%)	42 (7.5%)
Alanine aminotransferase increased	27 (13.8%)	14 (7.3%)	54 (15.5%)	22 (6.3%)	22 (10.4%)	12 (5.7%)	76 (13.6%)	34 (6.1%)
Blood alkaline phosphatase increased	12 (6.1%)	6 (3.1%)	22 (6.3%)	14 (4.0%)	17 (8.1%)	25 (11.8%)	39 (7.0%)	39 (7.0%)
Weight increased	26 (13.3%)	5 (2.6%)	39 (11.2%)	12 (3.5%)	4 (1.9%)	4 (1.9%)	43 (7.7%)	16 (2.9%)
Nervous system disorders	57 (29.1%)	81 (42.4%)	112 (32.2%)	143 (41.2%)	57 (27.0%)	73 (34.4%)	169 (30.2%)	216 (38.6%)
Dizziness	14 (7.1%)	27 (14.1%)	32 (9.2%)	50 (14.4%)	14 (6.6%)	28 (13.2%)	46 (8.2%)	78 (14.0%)
Headache	14 (7.1%)	25 (13.1%)	34 (9.8%)	47 (13.5%)	20 (9.5%)	20 (9.4%)	54 (9.7%)	67 (12.0%)
Respiratory, thoracic and mediastinal disorders	43 (21.9%)	64 (33.5%)	81 (23.3%)	112 (32.3%)	43 (20.4%)	79 (37.3%)	124 (22.2%)	191 (34.2%)
Dyspnoea	8 (4.1%)	21 (11.0%)	20 (5.7%)	46 (13.3%)	13 (6.2%)	40 (18.9%)	33 (5.9%)	86 (15.4%)
Cough	20 (10.2%)	23 (12.0%)	40 (11.5%)	38 (11.0%)	12 (5.7%)	20 (9.4%)	52 (9.3%)	58 (10.4%)
Psychiatric disorders	35 (17.9%)	50 (26.2%)	65 (18.7%)	91 (26.2%)	24 (11.4%)	38 (17.9%)	89 (15.9%)	129 (23.1%)
Insomnia	15 (7.7%)	28 (14.7%)	27 (7.8%)	49 (14.1%)	9 (4.3%)	24 (11.3%)	36 (6.4%)	73 (13.1%)
Injury, poisoning and procedural complications	33 (16.8%)	50 (26.2%)	73 (21.0%)	83 (23.9%)	52 (24.6%)	44 (20.8%)	125 (22.4%)	127 (22.7%)
Fall	15 (7.7%)	14 (7.3%)	32 (9.2%)	29 (8.4%)	30 (14.2%)	19 (9.0%)	62 (11.1%)	48 (8.6%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 27.1.

[tsfae04.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsfae04.sas] 23FEB2025, 23:12

Grade 3 or 4 adverse events

Table *74. Number of Subjects with Grade 3 or 4 Related Treatment-emergent Adverse Events by SOC and PT. Safety Analysis Set (Study AMPLITUDE)*

TSFAE07ar: Number of Subjects with Grades 3 or 4 Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 67652000PCR3002)

	Placebo + AAP			Nira + AAP		
	Toxicity Grade			Toxicity Grade		
	Total	3	4	Total	3	4
Analysis set: Safety	348			347		
Subjects with 1 or more grade 3/4 related AEs	105 (30.2%)	101 (29.0%)	4 (1.1%)	193 (55.6%)	175 (50.4%)	18 (5.2%)
System organ class Preferred term						
Blood and lymphatic system disorders	12 (3.4%)	12 (3.4%)	0	125 (36.0%)	113 (32.6%)	12 (3.5%)
Anaemia	6 (1.7%)	6 (1.7%)	0	92 (26.5%)	90 (25.9%)	2 (0.6%)
Neutropenia	5 (1.4%)	5 (1.4%)	0	29 (8.4%)	27 (7.8%)	2 (0.6%)
Thrombocytopenia	0	0	0	18 (5.2%)	11 (3.2%)	7 (2.0%)
Leukopenia	0	0	0	13 (3.7%)	13 (3.7%)	0
Lymphopenia	1 (0.3%)	1 (0.3%)	0	13 (3.7%)	12 (3.5%)	1 (0.3%)
Vascular disorders	50 (14.4%)	50 (14.4%)	0	62 (17.9%)	62 (17.9%)	0
Hypertension	50 (14.4%)	50 (14.4%)	0	61 (17.6%)	61 (17.6%)	0
Hypotension	0	0	0	1 (0.3%)	1 (0.3%)	0
Metabolism and nutrition disorders	32 (9.2%)	29 (8.3%)	3 (0.9%)	36 (10.4%)	31 (8.9%)	5 (1.4%)
Hypokalaemia	28 (8.0%)	25 (7.2%)	3 (0.9%)	30 (8.6%)	26 (7.5%)	4 (1.2%)
Hyperglycaemia	2 (0.6%)	2 (0.6%)	0	4 (1.2%)	4 (1.2%)	0
Decreased appetite	0	0	0	2 (0.6%)	2 (0.6%)	0
Dehydration	0	0	0	2 (0.6%)	2 (0.6%)	0
Hyperkalaemia	0	0	0	1 (0.3%)	0	1 (0.3%)
Hypernatraemia	0	0	0	1 (0.3%)	1 (0.3%)	0
Hypocalcaemia	0	0	0	1 (0.3%)	1 (0.3%)	0
Diabetes mellitus	1 (0.3%)	1 (0.3%)	0	0	0	0
Hypertriglyceridaemia	1 (0.3%)	1 (0.3%)	0	0	0	0
General disorders and administration site conditions	3 (0.9%)	3 (0.9%)	0	11 (3.2%)	11 (3.2%)	0
Asthenia	2 (0.6%)	2 (0.6%)	0	5 (1.4%)	5 (1.4%)	0
Fatigue	1 (0.3%)	1 (0.3%)	0	5 (1.4%)	5 (1.4%)	0
General physical health deterioration	0	0	0	1 (0.3%)	1 (0.3%)	0
Investigations	18 (5.2%)	18 (5.2%)	0	10 (2.9%)	9 (2.6%)	1 (0.3%)
Alanine aminotransferase increased	15 (4.3%)	15 (4.3%)	0	4 (1.2%)	4 (1.2%)	0
Aspartate aminotransferase increased	7 (2.0%)	7 (2.0%)	0	3 (0.9%)	3 (0.9%)	0
Blood creatinine increased	0	0	0	2 (0.6%)	1 (0.3%)	1 (0.3%)
Weight decreased	0	0	0	2 (0.6%)	2 (0.6%)	0
Blood pressure increased	0	0	0	1 (0.3%)	1 (0.3%)	0
Weight increased	2 (0.6%)	2 (0.6%)	0	1 (0.3%)	1 (0.3%)	0
Gamma-glutamyltransferase increased	1 (0.3%)	1 (0.3%)	0	0	0	0
Cardiac disorders	4 (1.1%)	3 (0.9%)	1 (0.3%)	5 (1.4%)	5 (1.4%)	0
Cardiac failure	0	0	0	2 (0.6%)	2 (0.6%)	0
Cardiac failure acute	0	0	0	2 (0.6%)	2 (0.6%)	0
Atrial fibrillation	0	0	0	1 (0.3%)	1 (0.3%)	0
Cardiac failure congestive	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0
Acute myocardial infarction	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	0
Angina pectoris	2 (0.6%)	2 (0.6%)	0	0	0	0
Gastrointestinal disorders	1 (0.3%)	1 (0.3%)	0	4 (1.2%)	4 (1.2%)	0
Stomatitis	0	0	0	2 (0.6%)	2 (0.6%)	0
Vomiting	0	0	0	2 (0.6%)	2 (0.6%)	0
Diarrhoea	0	0	0	1 (0.3%)	1 (0.3%)	0
Abdominal pain	1 (0.3%)	1 (0.3%)	0	0	0	0
Infections and infestations	0	0	0	2 (0.6%)	2 (0.6%)	0
Pneumonia	0	0	0	1 (0.3%)	1 (0.3%)	0
Urinary tract infection	0	0	0	1 (0.3%)	1 (0.3%)	0

Renal and urinary disorders	0	0	0	2 (0.6%)	2 (0.6%)	0
Acute kidney injury	0	0	0	2 (0.6%)	2 (0.6%)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	2 (0.6%)	2 (0.6%)	0
Dyspnoea	0	0	0	1 (0.3%)	1 (0.3%)	0
Pulmonary embolism	0	0	0	1 (0.3%)	1 (0.3%)	0
Endocrine disorders	0	0	0	1 (0.3%)	1 (0.3%)	0
Adrenal insufficiency	0	0	0	1 (0.3%)	1 (0.3%)	0
Injury, poisoning and procedural complications	0	0	0	1 (0.3%)	1 (0.3%)	0
Femur fracture	0	0	0	1 (0.3%)	1 (0.3%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (0.3%)	0	1 (0.3%)
Myelodysplastic syndrome	0	0	0	1 (0.3%)	0	1 (0.3%)
Nervous system disorders	4 (1.1%)	4 (1.1%)	0	1 (0.3%)	1 (0.3%)	0
Memory impairment	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0
Apraxia	1 (0.3%)	1 (0.3%)	0	0	0	0
Ischaemic stroke	2 (0.6%)	2 (0.6%)	0	0	0	0
Tremor	1 (0.3%)	1 (0.3%)	0	0	0	0
Psychiatric disorders	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0
Mania	0	0	0	1 (0.3%)	1 (0.3%)	0
Insomnia	1 (0.3%)	1 (0.3%)	0	0	0	0

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event.
Note: An AE is assessed by the investigator as related to study agent. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity grade for a specific adverse event, the subject is only counted in the total column for that adverse event.
Adverse events are coded using MedDRA Version 27.1.

Serious adverse event/deaths/other significant events

Table 75. Number of Subjects with Treatment-Emergent Serious Adverse Events with Frequency of at Least 1% in Any Treatment Group by System Organ Class and Preferred Term; Safety Analysis Set (Study AMPLITUDE)

	Placebo + AAP	Nira + AAP
Analysis set: Safety	348	347
Subjects with 1 or more SAEs	96 (27.6%)	136 (39.2%)
System organ class Preferred term		
Infections and infestations	29 (8.3%)	47 (13.5%)
Pneumonia	10 (2.9%)	12 (3.5%)
Urinary tract infection	6 (1.7%)	9 (2.6%)
Sepsis	3 (0.9%)	5 (1.4%)
Blood and lymphatic system disorders	5 (1.4%)	25 (7.2%)
Anaemia	4 (1.1%)	20 (5.8%)
Cardiac disorders	15 (4.3%)	18 (5.2%)
Cardiac failure	2 (0.6%)	4 (1.2%)
Renal and urinary disorders	18 (5.2%)	18 (5.2%)
Acute kidney injury	4 (1.1%)	6 (1.7%)
Haematuria	5 (1.4%)	4 (1.2%)
Injury, poisoning and procedural complications	10 (2.9%)	16 (4.6%)
Fall	1 (0.3%)	4 (1.2%)
Metabolism and nutrition disorders	3 (0.9%)	16 (4.6%)
Hypokalaemia	2 (0.6%)	8 (2.3%)
Nervous system disorders	13 (3.7%)	10 (2.9%)
Spinal cord compression	4 (1.1%)	0
Musculoskeletal and connective tissue disorders	14 (4.0%)	8 (2.3%)
Back pain	3 (0.9%)	4 (1.2%)
Pathological fracture	4 (1.1%)	0

Key: AAP = abiraterone acetate plus prednisone, SAE = serious adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 27.1.

Deaths

Table 76. Summary of Deaths; Safety Analysis Set (Study AMPLITUDE)

	Placebo + AAP	Nira + AAP
Analysis set: Safety	348	347
All deaths	108 (31.0%)	84 (24.2%)
Progressive disease	75 (21.6%)	55 (15.9%)
Adverse event	8 (2.3%)	16 (4.6%)
Covid-19 related[c]	0	2 (0.6%)
Other	25 (7.2%)	13 (3.7%)
Covid-19 related	0	0
Subjects died		
On-Study treatment[a]	14 (4.0%)	21 (6.1%)
Progressive disease	6 (1.7%)	7 (2.0%)
Adverse event	8 (2.3%)	14 (4.0%)
Covid-19 related[c]	0	1 (0.3%)
Follow-up[b]	94 (27.0%)	63 (18.2%)
Progressive disease	69 (19.8%)	48 (13.8%)
Adverse event	0	2 (0.6%)
Covid-19 related[c]	0	1 (0.3%)
Other	25 (7.2%)	13 (3.7%)
Covid-19 related	0	0

Key: AAP = abiraterone acetate plus prednisone.
Percent is based on the Safety population.
[a] On-study treatment death is defined as the death that occurs within 30 days of the last dose of study drug.
[b] Follow-up death is defined as the death occurs more than 30 days after the last dose of study drug.
[c] Covid-19 AEs leading to death.

Only 1 (0.3%) patient in the study experienced a TEAE leading to death that was considered treatment-related by the investigator (sudden death); the participant was in the nira+AAP arm and had multiple risk factors (ie, cardiac medical history including prior myocardial infarction). All other patients had underlying risk factors contributing to the TEAE leading to death.

Table *77. Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; Integrated Safety*

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Subjects with 1 or more AEs leading to death	3 (1.5%)	8 (4.2%)	7 (2.0%)	14 (4.0%)	10 (4.7%)	22 (10.4%)	17 (3.0%)	36 (6.4%)
System organ class Preferred term								
Infections and infestations	0	4 (2.1%)	1 (0.3%)	5 (1.4%)	3 (1.4%)	13 (6.1%)	4 (0.7%)	18 (3.2%)
COVID-19 pneumonia	0	2 (1.0%)	0	2 (0.6%)	0	4 (1.9%)	0	6 (1.1%)
Pneumocystis jirovecii pneumonia	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Pneumonia	0	1 (0.5%)	0	1 (0.3%)	0	1 (0.5%)	0	2 (0.4%)
Sepsis	0	0	0	1 (0.3%)	0	1 (0.5%)	0	2 (0.4%)
COVID-19	0	0	0	0	0	6 (2.8%)	0	6 (1.1%)
Pulmonary sepsis	0	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Septic shock	0	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.2%)	1 (0.2%)
Suspected COVID-19	0	0	0	0	2 (0.9%)	0	2 (0.4%)	0
Cardiac disorders	1 (0.5%)	1 (0.5%)	3 (0.9%)	4 (1.2%)	4 (1.9%)	2 (0.9%)	7 (1.3%)	6 (1.1%)
Cardiac arrest	1 (0.5%)	0	2 (0.6%)	2 (0.6%)	0	0	2 (0.4%)	2 (0.4%)
Cardio-respiratory arrest	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Cardiogenic shock	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Acute myocardial infarction	0	0	1 (0.3%)	0	2 (0.9%)	1 (0.5%)	3 (0.5%)	1 (0.2%)
Cor pulmonale	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Myocardial infarction	0	0	0	0	2 (0.9%)	0	2 (0.4%)	0
General disorders and administration site conditions	1 (0.5%)	3 (1.6%)	1 (0.3%)	4 (1.2%)	0	3 (1.4%)	1 (0.2%)	7 (1.3%)
Sudden death	1 (0.5%)	3 (1.6%)	1 (0.3%)	3 (0.9%)	0	1 (0.5%)	1 (0.2%)	4 (0.7%)
Multiple organ dysfunction syndrome	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Adverse drug reaction	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Death	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.5%)	0	1 (0.3%)	1 (0.3%)	0	0	1 (0.2%)	1 (0.2%)
Subdural haematoma	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Head injury	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Hepatobiliary disorders	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Hepatic failure	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Nervous system disorders	0	0	1 (0.3%)	0	1 (0.5%)	0	2 (0.4%)	0
Cerebral arteriosclerosis	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Cerebral ischaemia	0	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Psychiatric disorders	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Completed suicide	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.2%)	1 (0.2%)
Dyspnoea	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Pulmonary embolism	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Vascular disorders	0	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.2%)	1 (0.2%)
Circulatory collapse	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Embolism	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event.

[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.

[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.

[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.

Note: Subjects are counted only once for any given event.

Adverse events are coded using MedDRA Version 27.1.

Adverse Events of Special Interest (AESI)

The AESI terms selected for nira+AAP were based upon the known adverse event profiles of the individual components.

Table *78. Number of Subjects with TEAEs by Special Interest Category and Preferred Term; Safety Analysis Set (Study AMPLITUDE)*

	Placebo + AAP	Nira + AAP
Analysis set: Safety	348	347
Subjects with 1 or more AEs of special interest	261 (75.0%)	306 (88.2%)
Special interest category Preferred term		
Anemia	83 (23.9%)	179 (51.6%)
Anaemia	83 (23.9%)	179 (51.6%)
Anaemia macrocytic	0	1 (0.3%)
Red blood cell count decreased	0	1 (0.3%)
Hypertension	113 (32.5%)	155 (44.7%)
Hypertension	113 (32.5%)	152 (43.8%)
Essential hypertension	0	3 (0.9%)
Orthostatic hypertension	0	1 (0.3%)
Hypokalemia	70 (20.1%)	92 (26.5%)
Hypokalaemia	70 (20.1%)	90 (25.9%)
Hypomagnesaemia	3 (0.9%)	5 (1.4%)
Neutropenia	28 (8.0%)	76 (21.9%)
Neutropenia	28 (8.0%)	76 (21.9%)
Fluid Retention/Oedema	58 (16.7%)	70 (20.2%)
Oedema peripheral	42 (12.1%)	55 (15.9%)
Peripheral swelling	9 (2.6%)	8 (2.3%)
Joint swelling	6 (1.7%)	4 (1.2%)
Pleural effusion	4 (1.1%)	4 (1.2%)
Ascites	0	2 (0.6%)
Localised oedema	1 (0.3%)	2 (0.6%)
Oedema	0	2 (0.6%)
Pericardial effusion	1 (0.3%)	2 (0.6%)
Bone swelling	0	1 (0.3%)
Injection site swelling	0	1 (0.3%)
Swelling	2 (0.6%)	1 (0.3%)
Generalised oedema	1 (0.3%)	0
Lymphoedema	2 (0.6%)	0
Testicular swelling	1 (0.3%)	0
Arrhythmia	28 (8.0%)	68 (19.6%)
Sinus tachycardia	2 (0.6%)	21 (6.1%)
Atrial fibrillation	6 (1.7%)	17 (4.9%)
Palpitations	7 (2.0%)	7 (2.0%)
Syncope	6 (1.7%)	7 (2.0%)
Heart rate increased	0	3 (0.9%)
Sudden death	1 (0.3%)	3 (0.9%)
Supraventricular tachycardia	0	3 (0.9%)
Tachycardia	0	3 (0.9%)
Atrial flutter	1 (0.3%)	2 (0.6%)
Cardiac arrest	3 (0.9%)	2 (0.6%)
Supraventricular extrasystoles	0	2 (0.6%)
Ventricular tachycardia	0	2 (0.6%)
Arrhythmia supraventricular	0	1 (0.3%)
Cardio-respiratory arrest	0	1 (0.3%)
Electrocardiogram P wave abnormal	0	1 (0.3%)
Electrocardiogram abnormal	0	1 (0.3%)
Loss of consciousness	0	1 (0.3%)
Ventricular arrhythmia	2 (0.6%)	1 (0.3%)
Ventricular extrasystoles	1 (0.3%)	1 (0.3%)
Bradycardia	1 (0.3%)	0
Thrombocytopenia	20 (5.7%)	66 (19.0%)
Thrombocytopenia	20 (5.7%)	66 (19.0%)
Hepatotoxicity	71 (20.4%)	46 (13.3%)
Aspartate aminotransferase increased	50 (14.4%)	28 (8.1%)
Alanine aminotransferase increased	54 (15.5%)	22 (6.3%)
Hyperbilirubinaemia	11 (3.2%)	16 (4.6%)

	Placebo + AAP	Nira + AAP
Ascites	0	2 (0.6%)
Gamma-glutamyltransferase increased	6 (1.7%)	2 (0.6%)
Cholestasis	0	1 (0.3%)
Hepatic cirrhosis	0	1 (0.3%)
Hepatomegaly	0	1 (0.3%)
Liver disorder	1 (0.3%)	1 (0.3%)
Portal hypertension	0	1 (0.3%)
Spontaneous bacterial peritonitis	0	1 (0.3%)
Varices oesophageal	0	1 (0.3%)
Hepatic cytolysis	1 (0.3%)	0
Hepatic steatosis	2 (0.6%)	0
Hepatotoxicity	1 (0.3%)	0
Cardiac Failure	6 (1.7%)	20 (5.8%)
Cardiac failure	3 (0.9%)	10 (2.9%)
Cardiac failure congestive	3 (0.9%)	5 (1.4%)
Pulmonary oedema	0	3 (0.9%)
Cardiac failure acute	0	2 (0.6%)
Cardiac failure chronic	0	1 (0.3%)
Cardiogenic shock	0	1 (0.3%)
Heart failure with preserved ejection fraction	0	1 (0.3%)
Right ventricular failure	0	1 (0.3%)
Ischaemic Heart Disease	18 (5.2%)	19 (5.5%)
Angina pectoris	7 (2.0%)	8 (2.3%)
Blood creatine phosphokinase increased	1 (0.3%)	4 (1.2%)
Acute coronary syndrome	0	2 (0.6%)
Coronary artery disease	2 (0.6%)	2 (0.6%)
Myocardial infarction	2 (0.6%)	2 (0.6%)
Angina unstable	1 (0.3%)	1 (0.3%)
Electrocardiogram T wave inversion	1 (0.3%)	1 (0.3%)
Acute myocardial infarction	3 (0.9%)	0
Arteriosclerosis coronary artery	1 (0.3%)	0
Coronary artery stenosis	2 (0.6%)	0
Electrocardiogram T wave abnormal	1 (0.3%)	0
Myocardial ischaemia	2 (0.6%)	0
Troponin I increased	1 (0.3%)	0
Troponin T increased	1 (0.3%)	0
Troponin increased	1 (0.3%)	0
Osteoporosis Including Osteoporosis-Related Fractures	10 (2.9%)	14 (4.0%)
Osteoporosis	2 (0.6%)	8 (2.3%)
Osteopenia	10 (2.9%)	6 (1.7%)
Cerebrovascular Disorders	14 (4.0%)	12 (3.5%)
Carotid arteriosclerosis	0	3 (0.9%)
Ischaemic stroke	3 (0.9%)	2 (0.6%)
Aphasia	2 (0.6%)	1 (0.3%)
Cerebral artery occlusion	0	1 (0.3%)
Cerebral infarction	0	1 (0.3%)
Dysarthria	3 (0.9%)	1 (0.3%)
Haemorrhagic stroke	0	1 (0.3%)
Hemiparesis	1 (0.3%)	1 (0.3%)
Subdural haematoma	0	1 (0.3%)
Subdural haemorrhage	0	1 (0.3%)
Vascular encephalopathy	0	1 (0.3%)
Vertebrobasilar insufficiency	0	1 (0.3%)
Basal ganglia infarction	1 (0.3%)	0
Cerebral ischaemia	1 (0.3%)	0
Cerebral venous sinus thrombosis	1 (0.3%)	0
Diplegia	1 (0.3%)	0
Monoparesis	1 (0.3%)	0
Monoplegia	1 (0.3%)	0
Paraparesis	1 (0.3%)	0
Subarachnoid haemorrhage	1 (0.3%)	0
MDS/AML	0	1 (0.3%)
Myelodysplastic syndrome	0	1 (0.3%)
Rhabdomyolysis/Myopathy	0	1 (0.3%)
Myopathy	0	1 (0.3%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 27.1.

- **Anaemia**

The median time to onset of the first event of anaemia was 65.0 days in the nira+AAP arm and 85.0 days in the PBO+AAP arm and generally occurred within the first 2-3 dose cycles of therapy in the nira+APP arm.

TEAEs of anaemia were managed with dose modifications and supportive care. The median time to the first dose interruption of study treatment due to anaemia in the nira+AAP arm was 85.0 days (range: 15 to 1028). Blood transfusions for the TEAEs of anaemia (anaemia related red blood cell transfusion) were administered to 25.1% of patients in the nira+AAP arm and 3.7% of patients in the PBO+AAP arm, with 14.7% and 2.3% of patients requiring more than 1 transfusion in the nira+AAP and PBO+AAP arms, respectively. Anaemia initially occurred during the first 2-3 dose cycles of therapy, supporting the instruction for regular monitoring of hematology laboratory parameters.

Table 79. Characteristics of the AESI of Anaemia (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	50 (25.5%)	103 (53.9%)	83 (23.9%)	179 (51.6%)	48 (22.7%)	111 (52.4%)	131 (23.4%)	290 (51.9%)
Exposure-Adjusted Incidence Rate[d]	16.75	48.01	15.00	44.06	16.16	48.43	15.41	45.64
Grade 3 Incidence	5 (2.6%)	55 (28.8%)	16 (4.6%)	99 (28.5%)	18 (8.5%)	62 (29.2%)	34 (6.1%)	161 (28.8%)
Grade 4 Incidence	0	1 (0.5%)	0	2 (0.6%)	0	3 (1.4%)	0	5 (0.9%)
Grade 5 Incidence	0	0	0	0	0	0	0	0
Serious	0	9 (4.7%)	4 (1.1%)	20 (5.8%)	3 (1.4%)	14 (6.6%)	7 (1.3%)	34 (6.1%)
Treatment Discontinuation	1 (0.5%)	4 (2.1%)	2 (0.6%)	8 (2.3%)	1 (0.5%)	6 (2.8%)	3 (0.5%)	14 (2.5%)
Dose Interruption	3 (1.5%)	56 (29.3%)	8 (2.3%)	95 (27.4%)	8 (3.8%)	51 (24.1%)	16 (2.9%)	146 (26.1%)
Dose Reduction	0	29 (15.2%)	1 (0.3%)	47 (13.5%)	1 (0.5%)	29 (13.7%)	2 (0.4%)	76 (13.6%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AESI=adverse event of special interest.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
[d] Exposure-Adjusted Incidence Rate for safety endpoints are calculated as: 100 * the number of subjects with a specific adverse event / the number of patient-years at risk. Patient-years at risk is the total exposure-time among the subjects in the treatment group and at risk of an initial occurrence of the adverse event. For a subject with one or multiple adverse events of the same term, the exposure-time is the time interval from the date of the first study treatment dose administration to the date of the occurrence of the first adverse event. For a subject without the specific adverse event, the exposure-time is the treatment emergent follow-up period of that patient. For EAIR, the treatment emergent follow-up period is defined as the time interval between the date of the first study treatment dose administration and date of last dose +30 days.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used for Grade incidences.
Adverse events are coded using MedDRA Version 27.1.
[tsfaesi01.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsfaesi01.sas] 23FEB2025, 23:37

- **Thrombocytopenia**

The median time to the onset of the first event of thrombocytopenia was 46.5 days in the nira+AAP arm and 260.0 days in the PBO+AAP arm. In the nira+AAP arm, thrombocytopenia initially occurred during the first 1-2 dose cycles of therapy. The increased median time to onset noted in the PBO+AAP arm (260.0 days) as compared to the previously conducted MAGNITUDE study (38.0 days) is possibly related to the different disease states, with more advanced disease and likely bone marrow involvement in MAGNITUDE's mCRPC population.

The median time to the first dose interruption of study treatment due to thrombocytopenia in the nira+AAP arm was 70.0 days (range: 15 to 906). The median time to the first dose-level reduction of niraparib due to thrombocytopenia in the nira+AAP arm was 58.0 days (range: 55 to 71). Platelet transfusions were administered for TEAEs of thrombocytopenia to 1.7% of patients in the nira+AAP arm and 0.6% of patients in the PBO+AAP. Most adverse events of thrombocytopenia were managed with dose modification (mainly drug interruption). Overall, 66 (19.0%) patients in

the nira+AAP arm and 49 (14.3%) patients in the PBO+AAP arm reported a bleeding event. Of these, 8 (2.3%) patients in the nira+AAP arm and no participant in the PBO+AAP arm had an event of thrombocytopenia with a concurrent bleeding event (within 7 days). Bleeding events were generally mild, included epistaxis, urinary tract or rectal bleeding, and were managed with supportive care when indicated. One participant reported an inguinal hematoma after a balloon valvuloplasty, and an additional participant with thrombocytopenia attributed to progressive disease sustained a subdural hematoma after a fall.

Table 80. Characteristics of the AESI of Thrombocytopenia (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	14 (7.1%)	37 (19.4%)	20 (5.7%)	66 (19.0%)	20 (9.5%)	51 (24.1%)	40 (7.2%)	117 (20.9%)
Exposure-Adjusted Incidence Rate[d]	4.17	10.77	3.21	10.59	6.36	16.02	4.26	12.43
Grade 3 Incidence	0	3 (1.6%)	0	15 (4.3%)	5 (2.4%)	9 (4.2%)	5 (0.9%)	24 (4.3%)
Grade 4 Incidence	0	6 (3.1%)	1 (0.3%)	9 (2.6%)	0	9 (4.2%)	1 (0.2%)	18 (3.2%)
Grade 5 Incidence	0	0	0	0	0	0	0	0
Serious	0	0	0	3 (0.9%)	0	5 (2.4%)	0	8 (1.4%)
Treatment Discontinuation	0	0	0	2 (0.6%)	0	1 (0.5%)	0	3 (0.5%)
Dose Interruption	0	15 (7.9%)	1 (0.3%)	29 (8.4%)	4 (1.9%)	24 (11.3%)	5 (0.9%)	53 (9.5%)
Dose Reduction	0	1 (0.5%)	0	3 (0.9%)	2 (0.9%)	6 (2.8%)	2 (0.4%)	9 (1.6%)

- **Neutropenia**

The median time to onset of the first event of neutropenia was 58.0 days in the nira+AAP arm and 38.0 days in the PBO+AAP arm and occurred initially during the first 2-3 dose cycles of therapy.

Most adverse events of neutropenia were managed with dose modification (mainly interruption). Supportive care with granulocyte colony stimulating factors was administered to 8 (2.3%) patients in the nira+AAP arm and to 1 (0.3%) participant in the PBO+AAP arm. The median time to the first dose interruption of study treatment due to neutropenia in the nira+AAP arm was 65.5 days (range: 4 to 756). The median time to the first dose-level reduction of niraparib due to neutropenia in the nira+AAP arm was 40.0 days (range: 36 to 146). Two (0.6%) patients in the nira+AAP arm and 1 (0.3%) participant in the PBO+AAP arm discontinued study treatment due to neutropenia.

Any infection event was reported in 54.2% of patients in the nira+AAP arm and 50.0% of patients in the PBO+AAP arm. The incidence of patients who had an event of neutropenia with a concurrent event of infection (ie, TEAE of neutropenia that occurred within 7 days of infection) was 11 (3.2%) in the nira+AAP arm and 3 (0.9%) in the PBO+AAP arm. Infections temporally associated with neutropenia were generally mild and treated with supportive care and antibiotics. Three events of neutropenia in the nira+AAP arm and 1 event in the PBO+AAP arm were temporally associated with SAEs of infection. Among patients receiving nira+AAP, 1 participant had Grade 4 pneumonia that was attributed to underlying progressive disease. One participant had neutropenia reported in the context of a Clostridium difficile infection. One participant with a medical history of Grade 1 urinary retention and TEAEs of recurrent urosepsis had a Grade 3 episode of urinary tract infection preceded by neutropenia. There were no Grade 3 or higher TEAEs of febrile neutropenia or neutropenic sepsis reported in the AMPLITUDE All HRR population.

Table 81. Characteristics of the AESI of Neutropenia (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	18 (9.2%)	39 (20.4%)	28 (8.0%)	76 (21.9%)	15 (7.1%)	34 (16.0%)	43 (7.7%)	110 (19.7%)
Exposure-Adjusted Incidence Rate[d]	5.61	11.64	4.71	13.01	4.70	10.23	4.71	12.01
Grade 3 Incidence	3 (1.5%)	14 (7.3%)	6 (1.7%)	28 (8.1%)	4 (1.9%)	11 (5.2%)	10 (1.8%)	39 (7.0%)
Grade 4 Incidence	1 (0.5%)	0	1 (0.3%)	5 (1.4%)	1 (0.5%)	3 (1.4%)	2 (0.4%)	8 (1.4%)
Grade 5 Incidence	0	0	0	0	0	0	0	0
Serious	0	0	0	2 (0.6%)	1 (0.5%)	3 (1.4%)	1 (0.2%)	5 (0.9%)
Treatment Discontinuation	0	0	1 (0.3%)	2 (0.6%)	0	0	1 (0.2%)	2 (0.4%)
Dose Interruption	3 (1.5%)	14 (7.3%)	7 (2.0%)	36 (10.4%)	2 (0.9%)	14 (6.6%)	9 (1.6%)	50 (8.9%)
Dose Reduction	1 (0.5%)	2 (1.0%)	1 (0.3%)	4 (1.2%)	1 (0.5%)	3 (1.4%)	2 (0.4%)	7 (1.3%)

- **Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)**

For the AESI of MDS, 1 (0.3%) subject reported an event in the nira+AAP arm of AMPLITUDE. This patient had normal blood counts at study entry, a CHEK2 alteration, and reported multiple AEs related to acute onset of low blood counts late into treatment (Day 633). In both the AMPLITUDE and MAGNITUDE studies, MDS/AML, including cases with fatal outcome, have been reported in patients with prostate cancer treated with 200 mg niraparib and 1 000 mg abiraterone acetate plus prednisone or prednisolone

- **Hypertension**

The median time to onset of the first event of hypertension was 71.0 days in the nira+AAP arm and 83.0 days in the PBO+AAP arm. Hypertension initially occurred within the first 2-3 cycles of therapy.

Hypertension was noted to be a common comorbid medical condition; 181 (52.2%) patients in the nira+AAP arm and 188 (54.0%) patients in the PBO+AAP arm had a prior medical history of hypertension, and there was a high concomitant use of anti-hypertensive treatments at study entry and during study treatment.

In the nira+AAP arm, one (50.0%) of the 2 patients with SAEs of hypertension had a pre-existing medical history of hypertension. There were no reports of hypertensive crisis or PRES.

Most events of hypertension were managed with dose modifications and supportive care, including anti-hypertensive medications.

Table 82. Characteristics of the AESI of Hypertension (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	63 (32.1%)	90 (47.1%)	113 (32.5%)	155 (44.7%)	49 (23.2%)	72 (34.0%)	162 (29.0%)	227 (40.6%)
Exposure-Adjusted Incidence Rate[d]	24.43	38.10	24.06	35.05	17.53	28.96	21.63	32.86
Grade 3 Incidence	37 (18.9%)	57 (29.8%)	64 (18.4%)	93 (26.8%)	27 (12.8%)	35 (16.5%)	91 (16.3%)	128 (22.9%)
Grade 4 Incidence	0	0	0	0	0	0	0	0
Grade 5 Incidence	0	0	0	0	0	0	0	0
Serious	0	0	0	2 (0.6%)	0	0	0	2 (0.4%)
Treatment Discontinuation	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Dose Interruption	8 (4.1%)	19 (9.9%)	18 (5.2%)	30 (8.6%)	3 (1.4%)	4 (1.9%)	21 (3.8%)	34 (6.1%)
Dose Reduction	3 (1.5%)	2 (1.0%)	3 (0.9%)	3 (0.9%)	0	1 (0.5%)	3 (0.5%)	4 (0.7%)

Events of Mineralocorticoid Excess (Hypokalemia, Fluid Retention/Edema)

Hypokalemia

The median time to onset of the first event of hypokalemia was 142.0 days in the nira+AAP arm and 195.5 days in the PBO+AAP arm.

TEAEs of hypokalemia were manageable with dose modifications, potassium supplementation and rarely, administration of prednisone doses exceeding 5 mg.

Table *83. Characteristics of the AESI of Hypokalemia (grouped term), Integrated Safety*

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	34 (17.3%)	50 (26.2%)	70 (20.1%)	92 (26.5%)	22 (10.4%)	34 (16.0%)	92 (16.5%)	126 (22.5%)
Exposure-Adjusted Incidence Rate[d]	11.06	14.98	12.67	15.70	7.04	10.36	10.64	13.78
Grade 3 Incidence	16 (8.2%)	20 (10.5%)	33 (9.5%)	34 (9.8%)	7 (3.3%)	10 (4.7%)	40 (7.2%)	44 (7.9%)
Grade 4 Incidence	1 (0.5%)	0	5 (1.4%)	6 (1.7%)	0	2 (0.9%)	5 (0.9%)	8 (1.4%)
Grade 5 Incidence	0	0	0	0	0	0	0	0
Serious	1 (0.5%)	2 (1.0%)	2 (0.6%)	8 (2.3%)	1 (0.5%)	4 (1.9%)	3 (0.5%)	12 (2.1%)
Treatment Discontinuation	1 (0.5%)	0	3 (0.9%)	0	0	0	3 (0.5%)	0
Dose Interruption	14 (7.1%)	13 (6.8%)	26 (7.5%)	28 (8.1%)	1 (0.5%)	11 (5.2%)	27 (4.8%)	39 (7.0%)
Dose Reduction	0	0	2 (0.6%)	2 (0.6%)	0	1 (0.5%)	2 (0.4%)	3 (0.5%)

Fluid Retention/Oedema

The median time to onset of the first event of fluid retention/edema was 168.0 days in the nira+AAP arm and 195.5 days in the PBO+AAP arm.

SAEs were reported in 1 participant (0.3%) in the nira+AAP arm (PT: pericardial effusion) and in no patients in the PBO+AAP arm. In MAGNITUDE Cohort 1 one subject had a SAE (PT: pleural effusion).

Most events of fluid retention/edema were managed with supportive care. Few TEAEs of fluid retention and edema led to interruptions or reductions, and none led to discontinuation of study treatment.

Table 84. Characteristics of the AESI of Fluid retention/oedema (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	33 (16.8%)	41 (21.5%)	58 (16.7%)	70 (20.2%)	30 (14.2%)	36 (17.0%)	88 (15.7%)	106 (19.0%)
Exposure-Adjusted Incidence Rate[d]	10.43	11.82	10.14	11.18	9.96	10.86	10.08	11.07
Grade 3 Incidence	0	1 (0.5%)	0	2 (0.6%)	0	2 (0.9%)	0	4 (0.7%)
Grade 4 Incidence	0	0	0	0	0	0	0	0
Grade 5 Incidence	0	0	0	0	0	0	0	0
Serious	0	0	0	1 (0.3%)	0	1 (0.5%)	0	2 (0.4%)
Treatment Discontinuation	0	0	0	0	0	0	0	0
Dose Interruption	2 (1.0%)	1 (0.5%)	3 (0.9%)	6 (1.7%)	1 (0.5%)	4 (1.9%)	4 (0.7%)	10 (1.8%)
Dose Reduction	0	1 (0.5%)	0	2 (0.6%)	1 (0.5%)	0	1 (0.2%)	2 (0.4%)

Hepatotoxicity

The median time to onset of the first hepatotoxicity event was 49.0 days in the nira+AAP arm and 56.0 days in the PBO+AAP arm. No participant in the AMPLITUDE study met criteria for drug induced liver injury according to Hy's law.

TEAEs of hepatotoxicity in the PBO+AAP arm occurred more frequently in the AMPLITUDE study compared with MAGNITUDE Cohort 1, where events were more common in the nira+AAP arm. This is likely due to the pre-existing risk factors for hepatotoxicity such as prior hepatitis in the PBO+AAP arm in the AMPLITUDE study. In MAGNITUDE Cohort 1, there was one Grade 4 (PT: hepatitis acute) and one Grade 5 (PT: hepatic failure in a participant with pre-existing alcoholic

cirrhosis) hepatotoxicity event in the nira+AAP arm; no Grade 4 or Grade 5 hepatotoxicity events were reported in the PBO+AAP arm.

Table 85. Characteristics of the AESI of Hepatotoxicity (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	34 (17.3%)	25 (13.1%)	71 (20.4%)	46 (13.3%)	27 (12.8%)	30 (14.2%)	98 (17.5%)	76 (13.6%)
Exposure-Adjusted Incidence Rate[d]	11.46	6.97	13.57	7.16	9.09	9.05	11.95	7.80
Grade 3 Incidence	9 (4.6%)	4 (2.1%)	19 (5.5%)	8 (2.3%)	10 (4.7%)	3 (1.4%)	29 (5.2%)	11 (2.0%)
Grade 4 Incidence	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Grade 5 Incidence	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Serious	0	0	0	1 (0.3%)	1 (0.5%)	3 (1.4%)	1 (0.2%)	4 (0.7%)
Treatment Discontinuation	4 (2.0%)	0	6 (1.7%)	1 (0.3%)	2 (0.9%)	2 (0.9%)	8 (1.4%)	3 (0.5%)
Dose Interruption	10 (5.1%)	3 (1.6%)	20 (5.7%)	7 (2.0%)	8 (3.8%)	4 (1.9%)	28 (5.0%)	11 (2.0%)
Dose Reduction	5 (2.6%)	2 (1.0%)	8 (2.3%)	2 (0.6%)	6 (2.8%)	2 (0.9%)	14 (2.5%)	4 (0.7%)

Major Adverse Cardiovascular Events, MACE (Ischemic Heart Disease, Cardiac Failure, Arrhythmias, Cerebrovascular Disorders)

Ischemic Heart Disease

The median time to onset of the first ischemic heart disease event was 93.0 days in the nira+AAP arm and 352.0 days in the PBO+AAP arm.

Grade 4 events included events of blood creatine phosphokinase increased, acute coronary syndrome, and myocardial infarction. One Grade 5 event of acute myocardial infarction was reported in the PBO+AAP arm.

At the time of the CCO, TEAEs of ischemic heart disease were resolved in 68.4% of patients in the nira+AAP arm and 61.1% of patients in the PBO+AAP arm.

Table 86. Characteristics of the AESI of Ischaemic heart disease (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	8 (4.1%)	11 (5.8%)	18 (5.2%)	19 (5.5%)	10 (4.7%)	11 (5.2%)	28 (5.0%)	30 (5.4%)
Exposure-Adjusted Incidence Rate[d]	2.32	2.83	2.86	2.74	3.09	2.99	2.94	2.83
Grade 3 Incidence	5 (2.6%)	3 (1.6%)	8 (2.3%)	3 (0.9%)	4 (1.9%)	6 (2.8%)	12 (2.1%)	9 (1.6%)
Grade 4 Incidence	0	1 (0.5%)	2 (0.6%)	3 (0.9%)	0	1 (0.5%)	2 (0.4%)	4 (0.7%)
Grade 5 Incidence	0	0	1 (0.3%)	0	4 (1.9%)	1 (0.5%)	5 (0.9%)	1 (0.2%)
Serious	4 (2.0%)	2 (1.0%)	9 (2.6%)	4 (1.2%)	8 (3.8%)	8 (3.8%)	17 (3.0%)	12 (2.1%)
Treatment Discontinuation	1 (0.5%)	0	3 (0.9%)	0	5 (2.4%)	1 (0.5%)	8 (1.4%)	1 (0.2%)
Dose Interruption	3 (1.5%)	2 (1.0%)	5 (1.4%)	5 (1.4%)	0	4 (1.9%)	5 (0.9%)	9 (1.6%)
Dose Reduction	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)

Cardiac Failure

The median time to onset of the first cardiac failure event was 359.5 days in the nira+AAP arm and 219.5 days in the PBO+AAP arm.

All patients had preexisting risk factors for cardiac failure except 1 participant in the nira+AAP arm who developed a SAE of Grade 3 cardiac failure. Grade 5 events of cardiac failure were reported in one of patients in the nira+AAP arm (cardiogenic shock in the context of a ruptured pre-existing abdominal aortic aneurysm). At the time of the CCO, TEAEs of cardiac failure were resolved in 50.0% of patients in each treatment arm.

Table 87. Characteristics of the AESI of Cardiac failure (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	4 (2.0%)	8 (4.2%)	6 (1.7%)	20 (5.8%)	4 (1.9%)	6 (2.8%)	10 (1.8%)	26 (4.7%)
Exposure-Adjusted Incidence Rate[d]	1.15	2.03	0.94	2.86	1.24	1.61	1.04	2.43
Grade 3 Incidence	2 (1.0%)	4 (2.1%)	4 (1.1%)	8 (2.3%)	1 (0.5%)	2 (0.9%)	5 (0.9%)	10 (1.8%)
Grade 4 Incidence	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Grade 5 Incidence	0	0	0	1 (0.3%)	0	1 (0.5%)	0	2 (0.4%)
Serious	2 (1.0%)	4 (2.1%)	3 (0.9%)	10 (2.9%)	1 (0.5%)	3 (1.4%)	4 (0.7%)	13 (2.3%)
Treatment Discontinuation	0	0	1 (0.3%)	2 (0.6%)	0	1 (0.5%)	1 (0.2%)	3 (0.5%)
Dose Interruption	2 (1.0%)	4 (2.1%)	3 (0.9%)	9 (2.6%)	0	4 (1.9%)	3 (0.5%)	13 (2.3%)
Dose Reduction	0	2 (1.0%)	0	2 (0.6%)	0	1 (0.5%)	0	3 (0.5%)

Arrhythmias

The median time to onset of the first event of arrhythmia was 167.0 days in the nira+AAP arm and 233.5 days in the PBO+AAP arm.

TEAEs of arrhythmia were driven largely by tachyarrhythmias and atrial arrhythmias. There were 8 (2.3%) patients in the nira+AAP arm and 1 (0.3%) participant in the PBO+AAP arm who reported anaemia concurrent with tachyarrhythmia.

The higher number of arrhythmia events in the nira+AAP arm compared with the PBO+AAP arm was largely driven by events of sinus tachycardia (6.1% in the nira+AAP arm and 0.6% in the PBO+AAP arm) and atrial fibrillation (4.9% in the nira+AAP arm and 1.7% in the PBO+AAP arm); in both arms, most of these events were Grade 1 or 2 in severity. Other arrhythmia events reported in ≥1% of patients in either treatment arm included palpitations (reported in 2.0% of patients in both treatment arms) and syncope (reported in 2.0% of patients in the nira+AAP arm and 1.7% patients in the PBO arm); none of these events were considered serious by the investigator.

The incidence of potentially life-threatening ventricular arrhythmias was similar across treatment arms. Ventricular tachycardia was reported in 2 patients in the nira+AAP arm (Grade 2 and Grade 3), and in no participant in the PBO+AAP arm. One participant in the nira+AAP arm and 2 patients in the PBO+AAP arm experienced ventricular arrhythmia; all events were low grade.

Grade 3 events of any arrhythmia included PTs of atrial fibrillation, syncope and ventricular tachycardia in the nira+APP arm, while in the PBO+AAP arm all were syncope. Grade 4 events of arrhythmia included atrial fibrillation and cardiac arrest in the nira+APP arm, and cardiac arrest (in the context of a myocardial infarction in a subject with a history of cardiac disorders) in the PBO+AAP arm. Grade 5 events of arrhythmia reported in the nira+AAP arm were 3 events of sudden death, 2 events of cardiac arrest, and 1 event of cardiorespiratory arrest, while in the PBO+AAP arm were 1 event of sudden death, 2 events cardiac arrest. All subjects had preexisting risk factors such as cardiac disease, cardiac valvular disease, prior cardiac events (myocardial infarction) or diabetes.

At the time of the CCO, TEAEs of arrhythmia were resolved in 73.5% of patients in the nira+AAP arm and 78.6% of patients in the PBO+AAP arm.

Table 88. Characteristics of the AESI of Arrhythmia (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	14 (7.1%)	39 (20.4%)	28 (8.0%)	68 (19.6%)	16 (7.6%)	28 (13.2%)	44 (7.9%)	96 (17.2%)
Exposure-Adjusted Incidence Rate[d]	4.08	11.29	4.53	10.89	5.06	8.48	4.71	10.06
Grade 3 Incidence	3 (1.5%)	7 (3.7%)	6 (1.7%)	12 (3.5%)	4 (1.9%)	5 (2.4%)	10 (1.8%)	17 (3.0%)
Grade 4 Incidence	0	0	2 (0.6%)	1 (0.3%)	0	1 (0.5%)	2 (0.4%)	2 (0.4%)
Grade 5 Incidence	2 (1.0%)	4 (2.1%)	3 (0.9%)	6 (1.7%)	0	1 (0.5%)	3 (0.5%)	7 (1.3%)
Serious	2 (1.0%)	6 (3.1%)	5 (1.4%)	9 (2.6%)	2 (0.9%)	4 (1.9%)	7 (1.3%)	13 (2.3%)
Treatment Discontinuation	2 (1.0%)	4 (2.1%)	2 (0.6%)	5 (1.4%)	0	2 (0.9%)	2 (0.4%)	7 (1.3%)
Dose Interruption	1 (0.5%)	2 (1.0%)	3 (0.9%)	8 (2.3%)	3 (1.4%)	5 (2.4%)	6 (1.1%)	13 (2.3%)
Dose Reduction	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0

Cerebrovascular Disorders

Grade 5 cerebrovascular events reported in 1 participant in each treatment arm were subdural hematoma in the nira+APP and cerebral ischaemia in PBO+APP.

Table 89. Characteristics of the AESI of Cerebrovascular disorders (grouped term), Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Incidence (All Grades)	3 (1.5%)	4 (2.1%)	14 (4.0%)	12 (3.5%)	5 (2.4%)	7 (3.3%)	19 (3.4%)	19 (3.4%)
Exposure-Adjusted Incidence Rate[d]	0.86	1.01	2.21	1.70	1.53	1.91	1.98	1.77
Grade 3 Incidence	2 (1.0%)	1 (0.5%)	6 (1.7%)	4 (1.2%)	1 (0.5%)	2 (0.9%)	7 (1.3%)	6 (1.1%)
Grade 4 Incidence	0	0	1 (0.3%)	1 (0.3%)	0	0	1 (0.2%)	1 (0.2%)
Grade 5 Incidence	0	0	1 (0.3%)	1 (0.3%)	1 (0.5%)	0	2 (0.4%)	1 (0.2%)
Serious	2 (1.0%)	1 (0.5%)	8 (2.3%)	6 (1.7%)	4 (1.9%)	2 (0.9%)	12 (2.1%)	8 (1.4%)
Treatment Discontinuation	1 (0.5%)	0	2 (0.6%)	2 (0.6%)	1 (0.5%)	0	3 (0.5%)	2 (0.4%)
Dose Interruption	0	2 (1.0%)	3 (0.9%)	7 (2.0%)	2 (0.9%)	2 (0.9%)	5 (0.9%)	9 (1.6%)
Dose Reduction	0	0	0	0	0	0	0	0

Other AESI Events (Osteoporosis; Rhabdomyolysis/myopathy)

Osteoporosis-related fractures were reported in 14 (4.0%) patients in the nira+AAP arm and in 10 (2.9%) patients in the PBO+AAP arm. Osteoporosis (PT only) occurred in 8 (2.3%) of patients in the nira+AAP arm and 2 (0.6%) of patients in the PBO+AAP arm; there were no Grade 3 or higher events and none of the events reported were serious. None of the TEAEs of osteoporosis led to discontinuation of study treatment.

Rhabdomyolysis/myopathy was reported in 1 (0.3%) participant in the nira+AAP arm and in no participant in the PBO+AAP arm; the event was Grade 1 in severity and non-serious. No events of rhabdomyolysis/myopathy resulted in dose interruption, dose-level reduction, or study treatment discontinuation. One event was reported in the PBO+AAP arm of MAGNITUDE Cohort 1. None of the events of myopathy were Grade 3 or higher and none were SAEs. No events of rhabdomyolysis were reported in either study.

The AESIs of allergic alveolitis, CYP2D drug interactions and food effect, and PRES were not reported in AMPLITUDE or MAGNITUDE Cohort 1.

- Second Primary Cancer

Table 90. Treatment-emergent Primary Cancers (excluding events of prostate cancer and non-melanoma skin cancers) Event by Preferred Term; Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Subjects with 1 or more TEAEs of primary cancer	4 (2.0%)	7 (3.7%)	7 (2.0%)	14 (4.0%)	3 (1.4%)	8 (3.8%)	10 (1.8%)	22 (3.9%)
Preferred term								
Colon cancer	0	2 (1.0%)	0	2 (0.6%)	0	0	0	2 (0.4%)
Transitional cell carcinoma	1 (0.5%)	0	1 (0.3%)	2 (0.6%)	0	0	1 (0.2%)	2 (0.4%)
Adenocarcinoma gastric	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
B-cell lymphoma	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Bladder neoplasm	1 (0.5%)	0	1 (0.3%)	1 (0.3%)	0	0	1 (0.2%)	1 (0.2%)
Cholangiocarcinoma	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Chronic lymphocytic leukaemia	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Gastrointestinal carcinoma	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Malignant melanoma	0	1 (0.5%)	1 (0.3%)	1 (0.3%)	0	0	1 (0.2%)	1 (0.2%)
Malignant melanoma stage III	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Metastatic gastric cancer	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Myelodysplastic syndrome	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Renal cell carcinoma	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Acute myeloid leukaemia	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Adenocarcinoma of colon	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Adenocarcinoma pancreas	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Bladder cancer	0	0	0	0	1 (0.5%)	2 (0.9%)	1 (0.2%)	2 (0.4%)
Colorectal adenocarcinoma	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Gastric cancer	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Gastrointestinal submucosal tumour	0	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Hepatocellular carcinoma	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Lung adenocarcinoma stage I	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Lung neoplasm malignant	0	0	0	0	2 (0.9%)	1 (0.5%)	2 (0.4%)	1 (0.2%)
Neuroendocrine tumour of the lung	0	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Ocular neoplasm	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Penile cancer	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Rectal cancer	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)

Adverse drug reactions

The primary data source used for determination of ADR terms was AMPLITUDE, which provided blinded, randomized, and controlled data in the target population. In addition, the totality of data from the integrated safety population includes data from the AMPLITUDE mHSPC, All HRR patient population plus the MAGNITUDE Cohort 1 mCRPC All HRR patient population. Previously established ADRs for AKEEGA (niraparib plus AA FDC) in combination with prednisone or prednisolone formed the base list of ADRs as well as the known safety profile of the individual components (niraparib and AA).

Any TEAEs with ≥1% absolute incidence in the nira+AAP arm as compared with the PBO+AAP arm were selected for further analysis to determine if they should be classified as ADRs.

The ADR list for niraparib/AA FDC tablets (Table 91) includes events from the previously established list for MAGNITUDE as well as newly added PTs based on the AMPLITUDE study (gastritis, lethargy, hot flush hyperbilirubinaemia, hepatitis, pruritus, urethral haemorrhage and MDS). Gastritis was reported as a TEAE at a higher frequency in the nira+AAP arm as compared with the PBO+AAP arm in AMPLITUDE [11 (3.2%) vs 4 (1.1%)]. The magnitude of the difference between the treatment arms was similar to that observed with other existing ADRs in the Gastrointestinal Disorders SOC (dyspepsia, abdominal distention). Gastrointestinal toxicities are frequently observed with nira+AAP treatment; gastritis may be another manifestation, and therefore, has been included as an ADR for nira+AAP.

Lethargy was reported as a TEAE at a higher frequency in the nira+AAP arm as compared with the PBO+AAP arm in AMPLITUDE [9 (2.6%) vs 2 (0.6%)]. Fatigue is an existing ADR for nira+AAP. Lethargy is a related medical concept, which has therefore been included as an ADR for nira+AAP.

Hot flush was reported as a TEAE seen at a higher frequency in the nira+AAP arm as compared with the PBO+AAP arm in AMPLITUDE [63 (18.2%) vs 48 (13.8%)]. The difference persisted when looking across the Combined population in the nira+AAP arm vs PBO+AAP arms (14.1% vs 11.4%). The etiology of hot flush is multifactorial, with androgen deprivation also known to play a role. The PT of hot flush has been added as an ADR for nira+AAP.

The following additional terms were added to already existing groupings of PTs, as they were observed at a higher frequency in nira+AAP and represented a medical concept addressed by an existing ADR:

- Cardiac failure acute was added to the grouping of PTs for cardiac failure.
- Laryngopharyngitis, viral upper respiratory tract infection, and respiratory tract infection viral were added to the grouping of PTs for respiratory tract infections.
- Gastroenteritis viral was added to the grouping of PTs for gastrointestinal infection.
- Taste disorder was added to the grouping of PTs for dysgeusia.
- Musculoskeletal discomfort was added to the grouping of PTs for musculoskeletal pain.

Table 91. Adverse Drug Reactions Associated with Niraparib/AAP by System Organ Class and Preferred Term Category for AMPLITUDE and MAGNITUDE Cohort 1, Integrated Safety

Adverse Drug Reactions Associated with Niraparib/AAP by System Organ Class and Preferred Term Category for AMPLITUDE and MAGNITUDE Cohort 1;Integrated Safety

		Frequency of All CTCAE Grades (N=559)		Frequency of CTCAE Grade 3-4 (N=559)	
System Organ Class (SOC)	Preferred Terms	Frequency n (%)	Frequency Category	Frequency n (%)	Frequency Category
Blood and lymphatic system disorders	Anaemia	290 (51.9%)	Very common	166 (29.7%)	Very common
	Thrombocytopenia	117 (20.9%)	Very common	42 (7.5%)	Common
	Neutropenia	110 (19.7%)	Very common	47 (8.4%)	Common
	Leukopenia	81 (14.5%)	Very common	20 (3.6%)	Common
	Lymphopenia	68 (12.2%)	Very common	29 (5.2%)	Common
Cardiac disorders	Tachycardia (Sinus tachycardia, Atrial tachycardia)	37 (6.6%)	Common	1 (0.2%)	Uncommon
	Arrhythmia (Atrial fibrillation, Extrasystoles, Supraventricular extrasystoles, Ventricular extrasystoles, Sinus arrhythmia)	33 (5.9%)	Common	9 (1.6%)	Common
	Cardiac failure (Cardiac failure acute, Cardiac failure congestive, Cor pulmonale, Left ventricular dysfunction)	20 (3.6%)	Common	10 (1.8%)	Common
	Angina pectoris (Coronary artery disease, Acute coronary syndrome)	16 (2.9%)	Common	4 (0.7%)	Uncommon
	Palpitations	13 (2.3%)	Common	0	Not observed

Adverse Drug Reactions Associated with Niraparib/AAP by System Organ Class and Preferred Term Category for AMPLITUDE and MAGNITUDE Cohort 1;Integrated Safety

		Frequency of All CTCAE Grades (N=559)		Frequency of CTCAE Grade 3-4 (N=559)	
System Organ Class (SOC)	Preferred Terms	Frequency n (%)	Frequency Category	Frequency n (%)	Frequency Category
	Myocardial infarction (Myocardial ischaemia)	5 (0.9%)	Uncommon	5 (0.9%)	Uncommon
Gastrointestinal disorders	Constipation	194 (34.7%)	Very common	1 (0.2%)	Uncommon
	Nausea	160 (28.6%)	Very common	1 (0.2%)	Uncommon
	Vomiting	88 (15.7%)	Very common	6 (1.1%)	Common
	Abdominal pain (Abdominal pain upper, Abdominal pain lower)	75 (13.4%)	Very common	4 (0.7%)	Uncommon
	Diarrhoea	69 (12.3%)	Very common	5 (0.9%)	Uncommon
	Dyspepsia	42 (7.5%)	Common	0	Not observed
	Dry mouth	28 (5.0%)	Common	0	Not observed
	Abdominal distension	25 (4.5%)	Common	0	Not observed
	Gastritis	14 (2.5%)	Common	0	Not observed
	Stomatitis	13 (2.3%)	Common	3 (0.5%)	Uncommon
General disorders and administration site conditions	Fatigue (Asthenia)	222 (39.7%)	Very common	27 (4.8%)	Common
	Oedema (Oedema peripheral, Swelling, Face oedema, Peripheral swelling, Swelling face)	101 (18.1%)	Very common	1 (0.2%)	Uncommon
	Non-cardiac chest pain	18 (3.2%)	Common	1 (0.2%)	Uncommon
	Chest pain	5 (0.9%)	Uncommon	0	Not observed

Adverse Drug Reactions Associated with Niraparib/AAP by System Organ Class and Preferred Term Category for AMPLITUDE and MAGNITUDE Cohort 1;Integrated Safety

		Frequency of All CTCAE Grades (N=559)		Frequency of CTCAE Grade 3-4 (N=559)	
System Organ Class (SOC)	Preferred Terms	Frequency n (%)	Frequency Category	Frequency n (%)	Frequency Category
	Mucosal inflammation	1 (0.2%)	Uncommon	0	Not observed
Hepatobiliary disorders	Hyperbilirubinaemia	23 (4.1%)	Common	0	Not observed
	Hepatitis (Hepatic function abnormal, Hepatitis acute, Fulminant hepatitis, Hepatic cytolysis, Hepatotoxicity)	4 (0.7%)	Uncommon	1 (0.2%)	Uncommon
	Hepatic failure	2 (0.4%)	Uncommon	1 (0.2%)	Uncommon
Immune system disorders	Hypersensitivity	1 (0.2%)	Uncommon	0	Not observed
Infections and infestations	Respiratory tract infections (Upper respiratory tract infection, Lower respiratory tract infection, Laryngitis, Rhinitis, Bronchitis, Nasopharyngitis, Respiratory tract infection viral, laryngopharyngitis, Viral upper respiratory tract infection)	99 (17.7%)	Very common	4 (0.7%)	Uncommon
	Urinary tract infection (Cystitis)	66 (11.8%)	Very common	26 (4.7%)	Common
	Pneumonia	36 (6.4%)	Common	26 (4.7%)	Common
	Gastrointestinal infection (Gastroenteritis, Gastroeneteritis viral, Fungal oesophagitis, Oesophageal candidiasis, Oropharyngeal candidiasis)	13 (2.3%)	Common	1 (0.2%)	Uncommon
	Sepsis (Urosepsis)	13 (2.3%)	Common	12 (2.1%)	Common
	Skin infection (Streptococcal infection)	4 (0.7%)	Uncommon	0	Not observed
	Conjunctivitis	3 (0.5%)	Uncommon	0	Not observed

Adverse Drug Reactions Associated with Niraparib/AAP by System Organ Class and Preferred Term Category for AMPLITUDE and MAGNITUDE Cohort 1;Integrated Safety

		Frequency of All CTCAE Grades (N=559)		Frequency of CTCAE Grade 3-4 (N=559)	
System Organ Class (SOC)	Preferred Terms	Frequency n (%)	Frequency Category	Frequency n (%)	Frequency Category
Injury, poisoning and procedural complications	Fractures (Osteoporosis, Rib fracture, Femoral neck fracture, Femur fracture, Ankle fracture, Humerus fracture, Fibula fracture, Lower limb fracture, Sternal fracture, Stress fracture, Upper limb fracture, Acetabulum fracture, Radius fracture, Thoracic vertebral fracture, Tibia fracture)	38 (6.8%)	Common	9 (1.6%)	Common
Investigations	Weight decreased	78 (14.0%)	Very common	7 (1.3%)	Common
	Blood creatinine increased	66 (11.8%)	Very common	6 (1.1%)	Common
	Aspartate aminotransferase increased	42 (7.5%)	Common	6 (1.1%)	Common
	Blood alkaline phosphatase increased	39 (7.0%)	Common	15 (2.7%)	Common
	Alanine aminotransferase increased	34 (6.1%)	Common	6 (1.1%)	Common
	Electrocardiogram QT prolonged	4 (0.7%)	Uncommon	1 (0.2%)	Uncommon
	Gamma-glutamyltransferase increased	4 (0.7%)	Uncommon	1 (0.2%)	Uncommon
Metabolism and nutrition disorders	Hypokalaemia	123 (22.0%)	Very common	52 (9.3%)	Common
	Decreased appetite	84 (15.0%)	Very common	4 (0.7%)	Uncommon
	Hyperglycaemia	75 (13.4%)	Very common	14 (2.5%)	Common
	Lipid metabolism disorders (Hyperlipidaemia, Hypercholesterolaemia, Hypertriglyceridaemia, Dyslipidaemia)	29 (5.2%)	Common	3 (0.5%)	Uncommon

Adverse Drug Reactions Associated with Niraparib/AAP by System Organ Class and Preferred Term Category for AMPLITUDE and MAGNITUDE Cohort 1;Integrated Safety

		Frequency of All CTCAE Grades (N=559)		Frequency of CTCAE Grade 3-4 (N=559)	
System Organ Class (SOC)	Preferred Terms	Frequency n (%)	Frequency Category	Frequency n (%)	Frequency Category
Musculoskeletal and connective tissue disorders	Musculoskeletal pain (Arthralgia, Back pain, Myalgia, Musculoskeletal discomfort)	200 (35.8%)	Very common	22 (3.9%)	Common
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Myelodysplastic syndrome/acute myeloid leukaemia	1 (0.2%)	Uncommon	1 (0.2%)	Uncommon
Nervous system disorders	Dizziness	78 (14.0%)	Very common	2 (0.4%)	Uncommon
	Headache	67 (12.0%)	Very common	2 (0.4%)	Uncommon
	Dysgeusia (Taste disorder)	21 (3.8%)	Common	0	Not observed
	Lethargy	12 (2.1%)	Common	1 (0.2%)	Uncommon
	Cognitive disorder	6 (1.1%)	Common	0	Not observed
Psychiatric disorders	Insomnia	73 (13.1%)	Very common	1 (0.2%)	Uncommon
	Depression	20 (3.6%)	Common	0	Not observed
	Anxiety	19 (3.4%)	Common	0	Not observed
	Confusional state	6 (1.1%)	Common	1 (0.2%)	Uncommon
Renal and urinary disorders	Haematuria	39 (7.0%)	Common	7 (1.3%)	Common
	Acute kidney injury	11 (2.0%)	Common	10 (1.8%)	Common
	Urethral haemorrhage	1 (0.2%)	Uncommon	0	Not observed
Respiratory, thoracic and mediastinal disorders	Dyspnoea (Dyspnoea exertional)	93 (16.6%)	Very common	9 (1.6%)	Common

Adverse Drug Reactions Associated with Niraparib/AAP by System Organ Class and Preferred Term Category for AMPLITUDE and MAGNITUDE Cohort 1;Integrated Safety

		Frequency of All CTCAE Grades (N=559)		Frequency of CTCAE Grade 3-4 (N=559)	
System Organ Class (SOC)	Preferred Terms	Frequency n (%)	Frequency Category	Frequency n (%)	Frequency Category
	Cough	58 (10.4%)	Very common	0	Not observed
	Pulmonary embolism	16 (2.9%)	Common	10 (1.8%)	Common
	Epistaxis	12 (2.1%)	Common	0	Not observed
	Pneumonitis	5 (0.9%)	Uncommon	0	Not observed
Skin and subcutaneous tissue disorders	Rash (Erythema, Dermatitis, Rash maculo-papular, Rash pruritic)	21 (3.8%)	Common	1 (0.2%)	Uncommon
	Pruritus	16 (2.9%)	Common	0	Not observed
	Photosensitivity reaction	11 (2.0%)	Common	0	Not observed
Vascular disorders	Hypertension (Systolic hypertension)	224 (40.1%)	Very common	127 (22.7%)	Very common
	Hot flush	79 (14.1%)	Very common	0	Not observed

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC).
Frequency category: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).
Adverse events are coded using MedDRA Version 27.1.

Laboratory findings

Haematology

Haematology laboratory abnormalities that occurred during treatment were mostly Grade 1 or 2. Consistent with the known safety profile of AKEEGA in patients with mCRPC, there were higher incidences of Grade 3 hematologic toxicities in the nira+AAP arm.

Table 92. Summary of Subjects with Anaemia Baseline Laboratory Value Grade ⩾1 and Treatment-Emergent Adverse Event of Anaemia; Integrated Safety

TSFAESI01a: Summary of Subjects with Anemia Baseline Laboratory Value Grade ≥1 and Treatment-Emergent Adverse Event of Anemia; Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Subjects with Anemia baseline laboratory value grade ≥1[d]	68 (34.7%)	79 (41.4%)	108 (31.0%)	140 (40.3%)	77 (36.5%)	84 (39.6%)	185 (33.1%)	224 (40.1%)
Subjects who reported TEAE of Anemia any grade[e]	24 (35.3%)	49 (62.0%)	37 (34.3%)	77 (55.0%)	29 (37.7%)	52 (61.9%)	66 (35.7%)	129 (57.6%)
Grade 3	2 (2.9%)	26 (32.9%)	10 (9.3%)	43 (30.7%)	15 (19.5%)	38 (45.2%)	25 (13.5%)	81 (36.2%)
Grade 4	0	1 (1.3%)	0	2 (1.4%)	0	2 (2.4%)	0	4 (1.8%)
Grade 5	0	0	0	0	0	0	0	0
Any SAE	0	6 (7.6%)	3 (2.8%)	10 (7.1%)	2 (2.6%)	8 (9.5%)	5 (2.7%)	18 (8.0%)
Subjects with Grade 3 Anemia[f]	5 (2.6%)	55 (28.8%)	16 (4.6%)	99 (28.5%)	18 (8.5%)	62 (29.2%)	34 (6.1%)	161 (28.8%)
Subjects with Anemia baseline laboratory value grade ≥1[g]	2 (40.0%)	26 (47.3%)	10 (62.5%)	43 (43.4%)	15 (83.3%)	38 (61.3%)	25 (73.5%)	81 (50.3%)
Subjects with Grade 4 Anemia[f]	0	1 (0.5%)	0	2 (0.6%)	0	3 (1.4%)	0	5 (0.9%)
Subjects with Anemia baseline laboratory value grade ≥1[g]	0	1 (100.0%)	0	2 (100.0%)	0	2 (66.7%)	0	4 (80.0%)
Subjects with Grade 5 Anemia[f]	0	0	0	0	0	0	0	0
Subjects with Anemia baseline laboratory value grade ≥1[g]	0	0	0	0	0	0	0	0
Subjects with any serious Anemia[f]	0	9 (4.7%)	4 (1.1%)	20 (5.8%)	3 (1.4%)	14 (6.6%)	7 (1.3%)	34 (6.1%)
Subjects with Anemia baseline laboratory value grade ≥1[g]	0	6 (66.7%)	3 (75.0%)	10 (50.0%)	2 (66.7%)	8 (57.1%)	5 (71.4%)	18 (52.9%)

Key: AAP = abiraterone acetate(AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC).
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
[d,f] Percentages are calculated with the number of subjects in each treatment group as denominator.
[e] Percentages are calculated with the number of subjects with Anemia baseline laboratory value Grade ≥1 as denominator.
[g] Percentages are calculated with the number of subjects from the corresponding Anemia Grade.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used for Grade incidences.
Adverse events are coded using MedDRA Version 27.1.

[tsfaesi01a.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsfaesi01a.sas] 10APR2025, 15:49

Table 93. Summary of Chemistry and Haematology Worst US NCI-CTCAE Toxicity Grade During Treatment; Integrated Safety

TSFLAB01_PART2OF4: Safety	Summary of Chemistry and Hematology Worst US NCI-CTCAE Toxicity Grade During Treatment; Integrated											
	AMPLITUDE (mCSPC[a])											
	ALL HRR											
	Placebo + AAP (Toxicity Grade)						Nira + AAP (Toxicity Grade)					
	Total	0	1	2	3	4	Total	0	1	2	3	4
Analysis set: Safety	348						347					
Chemistry												
Alanine Aminotransferase Increased	346	246 (71.1%)	71 (20.5%)	12 (3.5%)	16 (4.6%)	1 (0.3%)	344	276 (80.2%)	59 (17.2%)	1 (0.3%)	6 (1.7%)	2 (0.6%)
Alkaline Phosphatase Increased	346	262 (75.7%)	65 (18.8%)	13 (3.8%)	6 (1.7%)	0	344	235 (68.3%)	97 (28.2%)	9 (2.6%)	3 (0.9%)	0
Aspartate Aminotransferase Increased	346	227 (65.6%)	89 (25.7%)	21 (6.1%)	9 (2.6%)	0	344	243 (70.6%)	93 (27.0%)	2 (0.6%)	4 (1.2%)	2 (0.6%)
Blood Bilirubin Increased	346	293 (84.7%)	39 (11.3%)	14 (4.0%)	0	0	344	269 (78.2%)	58 (16.9%)	17 (4.9%)	0	0
Creatinine Increased	346	262 (75.7%)	45 (13.0%)	30 (8.7%)	8 (2.3%)	1 (0.3%)	343	226 (65.9%)	52 (15.2%)	59 (17.2%)	5 (1.5%)	1 (0.3%)
Hyperkalemia	347	285 (82.1%)	35 (10.1%)	16 (4.6%)	6 (1.7%)	5 (1.4%)	347	273 (78.7%)	42 (12.1%)	20 (5.8%)	6 (1.7%)	6 (1.7%)
Hypoalbuminemia	346	298 (86.1%)	25 (7.2%)	22 (6.4%)	1 (0.3%)	0	343	306 (89.2%)	23 (6.7%)	13 (3.8%)	1 (0.3%)	0
Hypoglycemia	346	312 (90.2%)	29 (8.4%)	5 (1.4%)	0	0	344	306 (89.0%)	28 (8.1%)	3 (0.9%)	4 (1.2%)	3 (0.9%)
Hypokalemia	347	230 (66.3%)	0	73 (21.0%)	38 (11.0%)	6 (1.7%)	347	204 (58.8%)	0	99 (28.5%)	38 (11.0%)	6 (1.7%)
Hematology												
Anemia	348	72 (20.7%)	225 (64.7%)	37 (10.6%)	14 (4.0%)	0	347	21 (6.1%)	167 (48.1%)	57 (16.4%)	102 (29.4%)	0
Hemoglobin Increased	348	345 (99.1%)	3 (0.9%)	0	0	0	347	343 (98.8%)	3 (0.9%)	0	1 (0.3%)	0
Leukocytosis	347	347 (100.0%)	0	0	0	0	347	347 (100.0%)	0	0	0	0
Lymphocyte Count Decreased	347	204 (58.8%)	19 (5.5%)	83 (23.9%)	35 (10.1%)	6 (1.7%)	347	131 (37.8%)	25 (7.2%)	120 (34.6%)	65 (18.7%)	6 (1.7%)
Lymphocyte Count Increased	347	340 (98.0%)	0	7 (2.0%)	0	0	347	332 (95.7%)	0	15 (4.3%)	0	0
Neutrophil Count Decreased	348	273 (78.4%)	40 (11.5%)	24 (6.9%)	8 (2.3%)	3 (0.9%)	347	169 (48.7%)	78 (22.5%)	62 (17.9%)	33 (9.5%)	5 (1.4%)
Platelet Count Decreased	348	268 (77.0%)	70 (20.1%)	6 (1.7%)	1 (0.3%)	3 (0.9%)	347	197 (56.8%)	109 (31.4%)	17 (4.9%)	15 (4.3%)	9 (2.6%)
White Blood Cell Decreased	347	229 (66.0%)	84 (24.2%)	28 (8.1%)	4 (1.2%)	2 (0.6%)	347	130 (37.5%)	115 (33.1%)	82 (23.6%)	18 (5.2%)	2 (0.6%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event, , NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events.

[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.

[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.

[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.

Note: N is the number of subjects with at least 1 postbaseline assessment for the specific lab test within the time period.

Table 94. Chemistry/Hematology: Shift from Baseline to Worst US NCI-CTCA (Version 5.0) Toxicity Grade During Treatment; Integrated Safety

TSFLAB02_PART1OF4: Chemistry/Hematology: Shift from Baseline to Worst US NCI-CTCAE (Version 5.0) Toxicity Grade During Treatment; Integrated Safety

	AMPLITUDE (mCSPC[a])											
	BRCA											
	Placebo + AAP (Worst US NCI-CTCAE Toxicity Grade During Treatment)						Niraparib + AAP (Worst US NCI-CTCAE Toxicity Grade During Treatment)					
	Total	0	1	2	3	4	Total	0	1	2	3	4
Analysis set: Safety	196						191					
Category												
Parameter												
Baseline Toxicity Grade												
CHEMISTRY												
Alanine aminotransferase increased												
Total	195	143 (73.3%)	39 (20.0%)	4 (2.1%)	8 (4.1%)	1 (0.5%)	188	152 (80.9%)	31 (16.5%)	1 (0.5%)	3 (1.6%)	1 (0.5%)
0	178	131 (73.6%)	37 (20.8%)	3 (1.7%)	7 (3.9%)	0	168	133 (79.2%)	30 (17.9%)	1 (0.6%)	3 (1.8%)	1 (0.6%)
1	17	12 (70.6%)	2 (11.8%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	18	17 (94.4%)	1 (5.6%)	0	0	0
2	0	0	0	0	0	0	2	2 (100.0%)	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
Alkaline phosphatase increased												
Total	195	143 (73.3%)	40 (20.5%)	7 (3.6%)	5 (2.6%)	0	188	130 (69.1%)	53 (28.2%)	4 (2.1%)	1 (0.5%)	0
0	119	75 (63.0%)	37 (31.1%)	3 (2.5%)	4 (3.4%)	0	110	59 (53.6%)	48 (43.6%)	2 (1.8%)	1 (0.9%)	0
1	48	41 (85.4%)	2 (4.2%)	4 (8.3%)	1 (2.1%)	0	40	37 (92.5%)	2 (5.0%)	1 (2.5%)	0	0
2	17	16 (94.1%)	1 (5.9%)	0	0	0	19	15 (78.9%)	3 (15.8%)	1 (5.3%)	0	0
3	11	11 (100.0%)	0	0	0	0	17	17 (100.0%)	0	0	0	0
4	0	0	0	0	0	0	2	2 (100.0%)	0	0	0	0
Aspartate aminotransferase increased												
Total	195	130 (66.7%)	51 (26.2%)	10 (5.1%)	4 (2.1%)	0	188	140 (74.5%)	44 (23.4%)	2 (1.1%)	1 (0.5%)	1 (0.5%)
0	181	121 (66.9%)	47 (26.0%)	10 (5.5%)	3 (1.7%)	0	171	125 (73.1%)	43 (25.1%)	2 (1.2%)	1 (0.6%)	0
1	14	9 (64.3%)	4 (28.6%)	0	1 (7.1%)	0	16	14 (87.5%)	1 (6.3%)	0	0	1 (6.3%)
2	0	0	0	0	0	0	1	1 (100.0%)	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
Blood bilirubin increased												
Total	195	173 (88.7%)	18 (9.2%)	4 (2.1%)	0	0	188	146 (77.7%)	34 (18.1%)	8 (4.3%)	0	0
0	192	173 (90.1%)	15 (7.8%)	4 (2.1%)	0	0	186	146 (78.5%)	32 (17.2%)	8 (4.3%)	0	0
1	3	0	3 (100.0%)	0	0	0	1	0	1 (100.0%)	0	0	0
2	0	0	0	0	0	0	1	0	1 (100.0%)	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
Creatinine increased												
Total	195	150 (76.9%)	26 (13.3%)	14 (7.2%)	5 (2.6%)	0	188	131 (69.7%)	28 (14.9%)	27 (14.4%)	2 (1.1%)	0
0	177	146 (82.5%)	14 (7.9%)	12 (6.8%)	5 (2.8%)	0	184	131 (71.2%)	25 (13.6%)	26 (14.1%)	2 (1.1%)	0
1	16	4 (25.0%)	10 (62.5%)	2 (12.5%)	0	0	4	0	3 (75.0%)	1 (25.0%)	0	0
2	2	0	2 (100.0%)	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
Hyperkalemia												
Total	196	164 (83.7%)	22 (11.2%)	4 (2.0%)	4 (2.0%)	2 (1.0%)	191	157 (82.2%)	18 (9.4%)	11 (5.8%)	4 (2.1%)	1 (0.5%)
0	185	157 (84.9%)	19 (10.3%)	3 (1.6%)	4 (2.2%)	2 (1.1%)	187	155 (82.9%)	18 (9.6%)	9 (4.8%)	4 (2.1%)	1 (0.5%)
1	10	7 (70.0%)	3 (30.0%)	0	0	0	3	2 (66.7%)	0	1 (33.3%)	0	0
2	0	0	0	0	0	0	1	0	0	1 (100.0%)	0	0
3	1	0	0	1 (100.0%)	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
Hypoalbuminemia												
Total	195	167 (85.6%)	18 (9.2%)	9 (4.6%)	1 (0.5%)	0	188	169 (89.9%)	13 (6.9%)	5 (2.7%)	1 (0.5%)	0
0	195	167 (85.6%)	18 (9.2%)	9 (4.6%)	1 (0.5%)	0	186	168 (90.3%)	12 (6.5%)	5 (2.7%)	1 (0.5%)	0

Chemistry

Table *95*. Summary of Laboratory Abnormalities that worsened from baseline; Integrated Safety

TSFLAB05: Summary of Laboratory Abnormalities That Worsened from Baseline; Integrated Safety

	AMPLITUDE (mCSPC[a])					
	Placebo + AAP			Nira + AAP		
		Worst US NCI-CTCAE Toxicity Grade During Treatment			Worst US NCI-CTCAE Toxicity Grade During Treatment	
	N	All Grades	Grade 3 or 4	N	All Grades	Grade 3 or 4
Analysis set: Integrated Safety	348			347		
Chemistry						
Hypokalemia	347	117 (33.7%)	44 (12.7%)	347	142 (40.9%)	44 (12.7%)
Creatinine Increased	346	67 (19.4%)	9 (2.6%)	343	111 (32.4%)	6 (1.7%)
Alkaline Phosphatase Increased	346	76 (22.0%)	6 (1.7%)	344	103 (29.9%)	3 (0.9%)
Aspartate Aminotransferase Increased	346	114 (32.9%)	9 (2.6%)	344	100 (29.1%)	6 (1.7%)
Blood Bilirubin Increased	346	49 (14.2%)	0	344	73 (21.2%)	0
Hyperkalemia	347	55 (15.9%)	11 (3.2%)	347	71 (20.5%)	12 (3.5%)
Alanine Aminotransferase Increased	346	98 (28.3%)	17 (4.9%)	344	67 (19.5%)	8 (2.3%)
Hypoglycemia	346	33 (9.5%)	0	344	37 (10.8%)	7 (2.0%)
Hypoalbuminemia	346	48 (13.9%)	1 (0.3%)	343	36 (10.5%)	1 (0.3%)
Hematology						
Anemia	348	195 (56.0%)	14 (4.0%)	347	260 (74.9%)	101 (29.1%)
Lymphocyte Count Decreased	347	133 (38.3%)	39 (11.2%)	347	208 (59.9%)	69 (19.9%)
White Blood Cell Decreased	347	101 (29.1%)	6 (1.7%)	347	206 (59.4%)	20 (5.8%)
Neutrophil Count Decreased	348	70 (20.1%)	11 (3.2%)	347	171 (49.3%)	37 (10.7%)
Platelet Count Decreased	348	77 (22.1%)	4 (1.1%)	347	144 (41.5%)	24 (6.9%)
Lymphocyte Count Increased	347	7 (2.0%)	0	347	13 (3.7%)	0
Hemoglobin Increased	348	3 (0.9%)	0	347	4 (1.2%)	1 (0.3%)

Key: AAP = abiraterone acetate (AA) plus prednisone, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events.

[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.

Note: N is the number of subjects with at least 1 postbaseline assessment for the specific lab test within the time period.

[tsflab05.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsflab05.sas] 04APR2025, 13:09

Hepatic function

Table *96*. Shift in Hepatic Laboratory Tests from Baseline to Worst X*ULN Category During Treatment; Integrated

TSFLAB04_PART2OF4: Safety	Shift in Hepatic Laboratory Tests from Baseline to Worst X*ULN Category During Treatment; Integrated											
	AMPLITUDE (mCSPC[a])											
	ALL HRR											
	Placebo + AAP (Worst X*ULN Category During Treatment)						Nira + AAP (Worst X*ULN Category During Treatment)					
	N	Category 0*	Category 1	Category 2	Category 3	Category 4	N	Category 0*	Category 1	Category 2	Category 3	Category 4
Analysis set: Integrated Safety	348						347					
Alkaline Phosphatase Increased												
Baseline												
Category 0	209	144 (68.9%)	58 (27.8%)	3 (1.4%)	4 (1.9%)	0	226	127 (56.2%)	92 (40.7%)	4 (1.8%)	3 (1.3%)	0
Category 1	87	7 (8.0%)	58 (66.7%)	15 (17.2%)	7 (8.0%)	0	66	2 (3.0%)	48 (72.7%)	14 (21.2%)	2 (3.0%)	0
Category 2	28	0	9 (32.1%)	16 (57.1%)	3 (10.7%)	0	28	0	3 (10.7%)	16 (57.1%)	9 (32.1%)	0
Category 3	19	0	0	4 (21.1%)	15 (78.9%)	0	21	0	0	0	20 (95.2%)	1 (4.8%)
Category 4	2	0	0	0	1 (50.0%)	1 (50.0%)	3	0	0	0	2 (66.7%)	1 (33.3%)
Alanine Aminotransferase Increased												
Baseline												
Category 0	316	222 (70.3%)	69 (21.8%)	11 (3.5%)	14 (4.4%)	0	315	248 (78.7%)	58 (18.4%)	1 (0.3%)	6 (1.9%)	2 (0.6%)
Category 1	30	12 (40.0%)	14 (46.7%)	0	4 (13.3%)	0	27	11 (40.7%)	15 (55.6%)	1 (3.7%)	0	0
Category 2	0	0	0	0	0	0	2	0	2 (100.0%)	0	0	0
Category 3	0	0	0	0	0	0	0	0	0	0	0	0
Category 4	0	0	0	0	0	0	0	0	0	0	0	0
Aspartate Aminotransferase Increased												
Baseline												
Category 0	323	211 (65.3%)	84 (26.0%)	21 (6.5%)	7 (2.2%)	0	323	224 (69.3%)	92 (28.5%)	2 (0.6%)	4 (1.2%)	1 (0.3%)
Category 1	23	6 (26.1%)	13 (56.5%)	2 (8.7%)	1 (4.3%)	1 (4.3%)	20	6 (30.0%)	13 (65.0%)	0	0	1 (5.0%)
Category 2	0	0	0	0	0	0	1	0	1 (100.0%)	0	0	0
Category 3	0	0	0	0	0	0	0	0	0	0	0	0
Category 4	0	0	0	0	0	0	0	0	0	0	0	0
Blood Bilirubin Increased												
Baseline												
Category 0	341	293 (85.9%)	36 (10.6%)	12 (3.5%)	0	0	341	269 (78.9%)	56 (16.4%)	16 (4.7%)	0	0
Category 1	4	0	1 (25.0%)	3 (75.0%)	0	0	2	0	0	2 (100.0%)	0	0
Category 2	1	0	0	0	1 (100.0%)	0	1	0	0	1 (100.0%)	0	0
Category 3	0	0	0	0	0	0	0	0	0	0	0	0
Category 4	0	0	0	0	0	0	0	0	0	0	0	0

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event, , NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
* Category 0 is derived for lab values ≤ULN.
Note: Baseline is defined as the last laboratory value collected on or prior to the date of the first dose of study drug.
Note: X*ULN categories are defined as follows per CTCAE cut-offs based on ULN (not following the full definitions of grade from CTCAE v5.0):
Alanine aminotransferase increased and Aspartate aminotransferase increased: Category 0: <=ULN; Category 1: >ULN -3.0 x ULN; Category 2: >3.0 -5.0 x ULN; Category 3: >5.0 -20.0 x ULN; Category 4: >20.0 x ULN
Blood bilirubin increased:Category 1: >ULN -1.5 x ULN; Category 2: >1.5 -3.0 x ULN; Category 3: >3.0 -10.0 x ULN; Category 4: >10.0 x ULN Alkaline Phosphatase increased: Category 1: >ULN -2.5 x ULN; Category 2: >2.5 -5.0 x ULN; Category 3: >5.0 -20.0 x ULN; Category 4: >20.0 x ULN

[tsflab04part2of4.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsflab04.sas] 23FEB2025, 23:15

Hy's Law/eDISH Assessment

In the AMPLITUDE study, one participant in the nira+AAP arm met eDISH criteria on Day 520 preceding a diagnosis of Grade 1 biliary obstruction on Day 560 and Grade 3 cholangiocarcinoma on Day 672.

No subjects met the laboratory criteria for Hy's Law.

Vital signs and Physical Examination Findings

In the AMPLITUDE study, markedly abnormal treatment emergent increases in diastolic blood pressure (defined as >100 mg Hg with >10 mmHg increase from baseline) were recorded in 49 (14.1%) of patients in the nira+AAP arm and 32 (9.2%) of patients in the PBO+AAP arm. Markedly abnormal increases in systolic blood pressure (defined as >160 mmHg with >20 mmHg increase from baseline) were recorded in 76 (21.9%) of patients in the nira+AAP arm and 66 (19.0%) of patients in the PBO+AAP arm. Data from the BRCA subgroup are consistent with the All HRR population.

Table 97. Number and Percentage of Subjects with Markedly Abnormal Blood Pressure during Treatment; Safety Analysis Set (Study67652000PCR3002)

TSFVIT05: Number and Percentage of Subjects With Markedly Abnormal Blood Pressure during Treatment; Safety Analysis Set (Study67652000PCR3002)

	Placebo + AAP	Nira + AAP
Analysis set: Safety	348	347
Systolic Blood Pressure (mmHg)		
N (no. subjects with baseline and any postbaseline measurement)	347 (99.7%)	347 (100.0%)
<90 mmHg and with >20 mmHg decrease from baseline	8 (2.3%)	6 (1.7%)
>160 mmHg and with >20 mmHg increase from baseline	66 (19.0%)	76 (21.9%)
Diastolic Blood Pressure (mmHg)		
N (no. subjects with baseline and any postbaseline measurement)	347 (99.7%)	347 (100.0%)
<50 mmHg and with >10 mmHg decrease from baseline	6 (1.7%)	8 (2.3%)
>100 mmHg and with >10 mmHg increase from baseline	32 (9.2%)	49 (14.1%)

Key: AAP = abiraterone acetate plus prednisone.
Note: Markedly abnormal vital signs are defined in the Statistical Analysis Plan. N is the number of subjects with at least 1 postbaseline value for the specified vital sign parameter.

[tsfvit05.rtf] [PROD/jnj-67652000/pcr3002/dbr_csr/re_csr/tsfvit05.sas] 19FEB2025, 13:43

Safety in special populations

Age

Table 98. Overall Safety Profile by Age; Integrated Safety

	AMPLITUDE (mCSPC[a])											
	BRCA						ALL HRR					
	Placebo + AAP			Nira + AAP			Placebo + AAP			Nira + AAP		
	<65	≥ 65- <75	≥ 75	<65	≥ 65- <75	≥ 75	<65	≥ 65- <75	≥ 75	<65	≥ 65- <75	≥ 75
Analysis set: Integrated Safety	82	81	33	74	69	48	135	139	74	116	147	84
Subjects with 1 or more:												
AEs	79 (96.3%)	79 (97.5%)	33 (100.0%)	74 (100.0%)	69 (100.0%)	48 (100.0%)	132 (97.8%)	135 (97.1%)	74 (100.0%)	115 (99.1%)	147 (100.0%)	84 (100.0%)
Related AEs[d]	60 (73.2%)	59 (72.8%)	24 (72.7%)	64 (86.5%)	65 (94.2%)	46 (95.8%)	99 (73.3%)	101 (72.7%)	57 (77.0%)	94 (81.0%)	135 (91.8%)	80 (95.2%)
COVID-19 associated AEs	26 (31.7%)	18 (22.2%)	5 (15.2%)	11 (14.9%)	20 (29.0%)	14 (29.2%)	38 (28.1%)	32 (23.0%)	10 (13.5%)	18 (15.5%)	35 (23.8%)	22 (26.2%)
Grade 3 or 4 AEs	41 (50.0%)	51 (63.0%)	20 (60.6%)	48 (64.9%)	59 (85.5%)	38 (79.2%)	75 (55.6%)	83 (59.7%)	47 (63.5%)	73 (62.9%)	119 (81.0%)	69 (82.1%)
Related grade 3 or 4 AEs[d]	20 (24.4%)	27 (33.3%)	11 (33.3%)	34 (45.9%)	43 (62.3%)	32 (66.7%)	41 (30.4%)	41 (29.5%)	23 (31.1%)	49 (42.2%)	89 (60.5%)	55 (65.5%)
COVID-19 associated grade 3 or 4 AEs	1 (1.2%)	3 (3.7%)	0	0	2 (2.9%)	1 (2.1%)	1 (0.7%)	4 (2.9%)	0	0	3 (2.0%)	1 (1.2%)
Serious AEs	20 (24.4%)	26 (32.1%)	7 (21.2%)	18 (24.3%)	25 (36.2%)	24 (50.0%)	34 (25.2%)	41 (29.5%)	21 (28.4%)	30 (25.9%)	61 (41.5%)	45 (53.6%)
Related serious AEs[d]	1 (1.2%)	3 (3.7%)	0	5 (6.8%)	10 (14.5%)	5 (10.4%)	3 (2.2%)	4 (2.9%)	4 (5.4%)	8 (6.9%)	25 (17.0%)	11 (13.1%)
COVID-19 associated serious AEs	0	2 (2.5%)	0	0	1 (1.4%)	2 (4.2%)	0	2 (1.4%)	0	0	3 (2.0%)	2 (2.4%)
AEs leading to discontinuation of study agent[f]	7 (8.5%)	7 (8.6%)	8 (24.2%)	5 (6.8%)	8 (11.6%)	11 (22.9%)	10 (7.4%)	10 (7.2%)	16 (21.6%)	8 (6.9%)	18 (12.2%)	25 (29.8%)
AEs leading to death[e]	1 (1.2%)	1 (1.2%)	1 (3.0%)	1 (1.4%)	1 (1.4%)	6 (12.5%)	2 (1.5%)	3 (2.2%)	2 (2.7%)	1 (0.9%)	2 (1.4%)	11 (13.1%)
Related AEs leading to death[d]	0	0	0	1 (1.4%)	0	0	0	0	0	1 (0.9%)	0	0
COVID-19 associated AEs leading to death	0	0	0	0	0	2 (4.2%)	0	0	0	0	0	2 (2.4%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
[d] An AE is categorized as related if assessed by the investigator as related to any of the study medication.
[e] AEs leading to death are based on AE outcome of Fatal.
[f] An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of Niraparib/Placebo or Abiraterone Acetate/Placebo or Prednisone.

[tsfae01agepart1of2.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsfae01age.sas] 23FEB2025, 23:32

	MAGNITUDE Cohort 1 (mCRPC[b])						Combined[c] (mCSPC[a] + mCRPC[b])					
	ALL HRR						ALL HRR					
	Placebo + AAP			Nira + AAP			Placebo + AAP			Nira + AAP		
	<65	≥ 65- <75	≥ 75	<65	≥ 65- <75	≥ 75	<65	≥ 65- <75	≥ 75	<65	≥ 65- <75	≥ 75
Analysis set: Integrated Safety	62	100	49	61	88	63	197	239	123	177	235	147
Subjects with 1 or more:												
AEs	60 (96.8%)	96 (96.0%)	49 (100.0%)	61 (100.0%)	88 (100.0%)	63 (100.0%)	192 (97.5%)	231 (96.7%)	123 (100.0%)	176 (99.4%)	235 (100.0%)	147 (100.0%)
Related AEs[d]	38 (61.3%)	55 (55.0%)	30 (61.2%)	54 (88.5%)	62 (70.5%)	52 (82.5%)	137 (69.5%)	156 (65.3%)	87 (70.7%)	148 (83.6%)	197 (83.8%)	132 (89.8%)
COVID-19 associated AEs	7 (11.3%)	10 (10.0%)	7 (14.3%)	8 (13.1%)	17 (19.3%)	10 (15.9%)	45 (22.8%)	42 (17.6%)	17 (13.8%)	26 (14.7%)	52 (22.1%)	32 (21.8%)
Grade 3 or 4 AEs	31 (50.0%)	52 (52.0%)	25 (51.0%)	41 (67.2%)	65 (73.9%)	51 (81.0%)	106 (53.8%)	135 (56.5%)	72 (58.5%)	114 (64.4%)	184 (78.3%)	120 (81.6%)
Related grade 3 or 4 AEs[d]	8 (12.9%)	18 (18.0%)	8 (16.3%)	26 (42.6%)	38 (43.2%)	32 (50.8%)	49 (24.9%)	59 (24.7%)	31 (25.2%)	75 (42.4%)	127 (54.0%)	87 (59.2%)
COVID-19 associated grade 3 or 4 AEs	2 (3.2%)	1 (1.0%)	3 (6.1%)	3 (4.9%)	10 (11.4%)	5 (7.9%)	3 (1.5%)	5 (2.1%)	3 (2.4%)	3 (1.7%)	13 (5.5%)	6 (4.1%)
Serious AEs	9 (14.5%)	31 (31.0%)	25 (51.0%)	21 (34.4%)	41 (46.6%)	38 (60.3%)	43 (21.8%)	72 (30.1%)	46 (37.4%)	51 (28.8%)	102 (43.4%)	83 (56.5%)
Related serious AEs[d]	0	5 (5.0%)	3 (6.1%)	6 (9.8%)	9 (10.2%)	14 (22.2%)	3 (1.5%)	9 (3.8%)	7 (5.7%)	14 (7.9%)	34 (14.5%)	25 (17.0%)
COVID-19 associated serious AEs	3 (4.8%)	1 (1.0%)	3 (6.1%)	3 (4.9%)	10 (11.4%)	6 (9.5%)	3 (1.5%)	3 (1.3%)	3 (2.4%)	3 (1.7%)	13 (5.5%)	8 (5.4%)
AEs leading to discontinuation of study agent[f]	1 (1.6%)	8 (8.0%)	8 (16.3%)	6 (9.8%)	14 (15.9%)	19 (30.2%)	11 (5.6%)	18 (7.5%)	24 (19.5%)	14 (7.9%)	32 (13.6%)	44 (29.9%)
AEs leading to death[e]	2 (3.2%)	3 (3.0%)	5 (10.2%)	0	13 (14.8%)	9 (14.3%)	4 (2.0%)	6 (2.5%)	7 (5.7%)	1 (0.6%)	15 (6.4%)	20 (13.6%)
Related AEs leading to death[d]	0	1 (1.0%)	0	0	0	1 (1.6%)	0	1 (0.4%)	0	1 (0.6%)	0	1 (0.7%)
COVID-19 associated AEs leading to death	1 (1.6%)	0	1 (2.0%)	0	8 (9.1%)	2 (3.2%)	1 (0.5%)	0	1 (0.8%)	0	8 (3.4%)	4 (2.7%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
[d] An AE is categorized as related if assessed by the investigator as related to any of the study medication.
[e] AEs leading to death are based on AE outcome of Fatal.
[f] An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of Niraparib/Placebo or Abiraterone Acetate/Placebo or Prednisone.

[tsfae01agepart2of2.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsfae01age.sas] 23FEB2025, 23:32

Race

Table 99. Overall Safety Profile by Race; Integrated Safety

	AMPLITUDE (mCSPC[a])											
	BRCA						ALL HRR					
	Placebo + AAP			Nira + AAP			Placebo + AAP			Nira + AAP		
	Asian	White	Other	Asian	White	Other	Asian	White	Other	Asian	White	Other
Analysis set: Integrated Safety	43	144	9	49	125	17	67	257	24	77	245	25
Subjects with 1 or more:												
AEs	42 (97.7%)	140 (97.2%)	9 (100.0%)	49 (100.0%)	125 (100.0%)	17 (100.0%)	66 (98.5%)	251 (97.7%)	24 (100.0%)	77 (100.0%)	244 (99.6%)	25 (100.0%)
Related AEs[d]	28 (65.1%)	107 (74.3%)	8 (88.9%)	47 (95.9%)	112 (89.6%)	16 (94.1%)	49 (73.1%)	189 (73.5%)	19 (79.2%)	70 (90.9%)	215 (87.8%)	24 (96.0%)
COVID-19 associated AEs	20 (46.5%)	27 (18.8%)	2 (22.2%)	14 (28.6%)	27 (21.6%)	4 (23.5%)	26 (38.8%)	51 (19.8%)	3 (12.5%)	22 (28.6%)	47 (19.2%)	6 (24.0%)
Grade 3 or 4 AEs	18 (41.9%)	86 (59.7%)	8 (88.9%)	42 (85.7%)	87 (69.6%)	16 (94.1%)	32 (47.8%)	156 (60.7%)	17 (70.8%)	61 (79.2%)	178 (72.7%)	22 (88.0%)
Related grade 3 or 4 AEs[d]	8 (18.6%)	45 (31.3%)	5 (55.6%)	35 (71.4%)	61 (48.8%)	13 (76.5%)	17 (25.4%)	78 (30.4%)	10 (41.7%)	52 (67.5%)	123 (50.2%)	18 (72.0%)
COVID-19 associated grade 3 or 4 AEs	2 (4.7%)	1 (0.7%)	1 (11.1%)	2 (4.1%)	1 (0.8%)	0	2 (3.0%)	2 (0.8%)	1 (4.2%)	2 (2.6%)	2 (0.8%)	0
Serious AEs	10 (23.3%)	40 (27.8%)	3 (33.3%)	22 (44.9%)	37 (29.6%)	8 (47.1%)	15 (22.4%)	73 (28.4%)	8 (33.3%)	31 (40.3%)	94 (38.4%)	11 (44.0%)
Related serious AEs[d]	0	4 (2.8%)	0	4 (8.2%)	11 (8.8%)	5 (29.4%)	0	9 (3.5%)	2 (8.3%)	7 (9.1%)	30 (12.2%)	7 (28.0%)
COVID-19 associated serious AEs	1 (2.3%)	0	1 (11.1%)	1 (2.0%)	2 (1.6%)	0	1 (1.5%)	0	1 (4.2%)	1 (1.3%)	3 (1.2%)	1 (4.0%)
AEs leading to discontinuation of study agent[f]	4 (9.3%)	17 (11.8%)	1 (11.1%)	7 (14.3%)	16 (12.8%)	1 (5.9%)	6 (9.0%)	29 (11.3%)	1 (4.2%)	10 (13.0%)	37 (15.1%)	4 (16.0%)
AEs leading to death[e]	0	3 (2.1%)	0	4 (8.2%)	4 (3.2%)	0	0	6 (2.3%)	1 (4.2%)	5 (6.5%)	9 (3.7%)	0
Related AEs leading to death[d]	0	0	0	0	1 (0.8%)	0	0	0	0	0	1 (0.4%)	0
COVID-19 associated AEs leading to death	0	0	0	1 (2.0%)	1 (0.8%)	0	0	0	0	1 (1.3%)	1 (0.4%)	0

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
[d] An AE is categorized as related if assessed by the investigator as related to any of the study medication.
[e] AEs leading to death are based on AE outcome of Fatal.
[f] An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of Niraparib/Placebo or Abiraterone Acetate/Placebo or Prednisone.

[tsfae01racepart1of2.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsfae01race.sas] 23FEB2025, 23:29

	MAGNITUDE Cohort 1 (mCRPC[b])						Combined[c] (mCSPC[a] + mCRPC[b])					
	ALL HRR						ALL HRR					
	Placebo + AAP			Nira + AAP			Placebo + AAP			Nira + AAP		
	Asian	White	Other	Asian	White	Other	Asian	White	Other	Asian	White	Other
Analysis set: Integrated Safety	41	153	17	29	160	23	108	410	41	106	405	48
Subjects with 1 or more:												
AEs	40 (97.6%)	148 (96.7%)	17 (100.0%)	29 (100.0%)	160 (100.0%)	23 (100.0%)	106 (98.1%)	399 (97.3%)	41 (100.0%)	106 (100.0%)	404 (99.8%)	48 (100.0%)
Related AEs[d]	23 (56.1%)	86 (56.2%)	14 (82.4%)	22 (75.9%)	129 (80.6%)	17 (73.9%)	72 (66.7%)	275 (67.1%)	33 (80.5%)	92 (86.8%)	344 (84.9%)	41 (85.4%)
COVID-19 associated AEs	4 (9.8%)	19 (12.4%)	1 (5.9%)	2 (6.9%)	29 (18.1%)	4 (17.4%)	30 (27.8%)	70 (17.1%)	4 (9.8%)	24 (22.6%)	76 (18.8%)	10 (20.8%)
Grade 3 or 4 AEs	15 (36.6%)	86 (56.2%)	7 (41.2%)	22 (75.9%)	116 (72.5%)	19 (82.6%)	47 (43.5%)	242 (59.0%)	24 (58.5%)	83 (78.3%)	294 (72.6%)	41 (85.4%)
Related grade 3 or 4 AEs[d]	5 (12.2%)	28 (18.3%)	1 (5.9%)	16 (55.2%)	68 (42.5%)	12 (52.2%)	22 (20.4%)	106 (25.9%)	11 (26.8%)	68 (64.2%)	191 (47.2%)	30 (62.5%)
COVID-19 associated grade 3 or 4 AEs	0	5 (3.3%)	1 (5.9%)	0	16 (10.0%)	2 (8.7%)	2 (1.9%)	7 (1.7%)	2 (4.9%)	2 (1.9%)	18 (4.4%)	2 (4.2%)
Serious AEs	13 (31.7%)	48 (31.4%)	4 (23.5%)	17 (58.6%)	73 (45.6%)	10 (43.5%)	28 (25.9%)	121 (29.5%)	12 (29.3%)	48 (45.3%)	167 (41.2%)	21 (43.8%)
Related serious AEs[d]	0	7 (4.6%)	1 (5.9%)	5 (17.2%)	21 (13.1%)	3 (13.0%)	0	16 (3.9%)	3 (7.3%)	12 (11.3%)	51 (12.6%)	10 (20.8%)
COVID-19 associated serious AEs	0	7 (4.6%)	0	0	17 (10.6%)	2 (8.7%)	1 (0.9%)	7 (1.7%)	1 (2.4%)	1 (0.9%)	20 (4.9%)	3 (6.3%)
AEs leading to discontinuation of study agent[f]	3 (7.3%)	12 (7.8%)	2 (11.8%)	7 (24.1%)	26 (16.3%)	6 (26.1%)	9 (8.3%)	41 (10.0%)	3 (7.3%)	17 (16.0%)	63 (15.6%)	10 (20.8%)
AEs leading to death[e]	1 (2.4%)	9 (5.9%)	0	2 (6.9%)	17 (10.6%)	3 (13.0%)	1 (0.9%)	15 (3.7%)	1 (2.4%)	7 (6.6%)	26 (6.4%)	3 (6.3%)
Related AEs leading to death[d]	0	1 (0.7%)	0	0	1 (0.6%)	0	0	1 (0.2%)	0	0	2 (0.5%)	0
COVID-19 associated AEs leading to death	0	2 (1.3%)	0	0	9 (5.6%)	1 (4.3%)	0	2 (0.5%)	0	1 (0.9%)	10 (2.5%)	1 (2.1%)

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event.

[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.

[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.

[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.

[d] An AE is categorized as related if assessed by the investigator as related to any of the study medication.

[e] AEs leading to death are based on AE outcome of Fatal.

[f] An AE is counted as leading to discontinuation of study racent if it leads to withdrawal of Niraparib/Placebo or Abiraterone Acetate/Placebo or Prednisone.

[tsfae01racepart2of2.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsfae01race.sas] 23FEB2025, 23:29

Geographical Region

Table 100. Overall Safety Profile by Geographical Region; Integrated Safety

	AMPLITUDE (mCSPC[a]) ALL HRR									
	Placebo + AAP					Nira + AAP				
	North America	South America	Europe	Asia	Rest of the World	North America	South America	Europe	Asia	Rest of the World
Analysis set: Integrated Safety	44	48	177	63	16	45	43	168	72	19
Subjects with 1 or more:										
AEs	44 (100.0%)	48 (100.0%)	171 (96.6%)	62 (98.4%)	16 (100.0%)	45 (100.0%)	43 (100.0%)	167 (99.4%)	72 (100.0%)	19 (100.0%)
Related AEs[d]	40 (90.9%)	38 (79.2%)	119 (67.2%)	46 (73.0%)	14 (87.5%)	44 (97.8%)	41 (95.3%)	142 (84.5%)	65 (90.3%)	17 (89.5%)
COVID-19 associated AEs	10 (22.7%)	9 (18.8%)	30 (16.9%)	25 (39.7%)	6 (37.5%)	13 (28.9%)	5 (11.6%)	31 (18.5%)	21 (29.2%)	5 (26.3%)
Grade 3 or 4 AEs	34 (77.3%)	30 (62.5%)	101 (57.1%)	29 (46.0%)	11 (68.8%)	36 (80.0%)	35 (81.4%)	120 (71.4%)	58 (80.6%)	12 (63.2%)
Related grade 3 or 4 AEs[d]	12 (27.3%)	17 (35.4%)	52 (29.4%)	17 (27.0%)	7 (43.8%)	29 (64.4%)	25 (58.1%)	83 (49.4%)	49 (68.1%)	7 (36.8%)
COVID-19 associated grade 3 or 4 AEs	2 (4.5%)	1 (2.1%)	0	2 (3.2%)	0	0	0	2 (1.2%)	2 (2.8%)	0
Serious AEs	15 (34.1%)	16 (33.3%)	45 (25.4%)	13 (20.6%)	7 (43.8%)	16 (35.6%)	19 (44.2%)	62 (36.9%)	30 (41.7%)	9 (47.4%)
Related serious AEs[d]	1 (2.3%)	2 (4.2%)	7 (4.0%)	0	1 (6.3%)	6 (13.3%)	8 (18.6%)	21 (12.5%)	7 (9.7%)	2 (10.5%)
COVID-19 associated serious AEs	0	1 (2.1%)	0	1 (1.6%)	0	1 (2.2%)	1 (2.3%)	2 (1.2%)	1 (1.4%)	0
AEs leading to discontinuation of study agent[f]	7 (15.9%)	3 (6.3%)	21 (11.9%)	5 (7.9%)	0	7 (15.6%)	10 (23.3%)	23 (13.7%)	10 (13.9%)	1 (5.3%)
AEs leading to death[e]	0	3 (6.3%)	4 (2.3%)	0	0	2 (4.4%)	2 (4.7%)	4 (2.4%)	5 (6.9%)	1 (5.3%)
Related AEs leading to death[d]	0	0	0	0	0	1 (2.2%)	0	0	0	0
COVID-19 associated AEs leading to death	0	0	0	0	0	1 (2.2%)	0	0	1 (1.4%)	0
	Combined[c] (mCSPC[a] + mCRPC[b]) ALL HRR									
	Placebo + AAP					Nira + AAP				
	North America	South America	Europe	Asia	Rest of the World	North America	South America	Europe	Asia	Rest of the World
Analysis set: Integrated Safety	62	69	297	103	28	62	68	296	99	34
Subjects with 1 or more:										
AEs	62 (100.0%)	68 (98.6%)	287 (96.6%)	101 (98.1%)	28 (100.0%)	62 (100.0%)	68 (100.0%)	295 (99.7%)	99 (100.0%)	34 (100.0%)
Related AEs[d]	56 (90.3%)	50 (72.5%)	181 (60.9%)	68 (66.0%)	25 (89.3%)	61 (98.4%)	59 (86.8%)	240 (81.1%)	85 (85.9%)	32 (94.1%)
COVID-19 associated AEs	12 (19.4%)	11 (15.9%)	43 (14.5%)	29 (28.2%)	9 (32.1%)	15 (24.2%)	9 (13.2%)	55 (18.6%)	23 (23.2%)	8 (23.5%)
Grade 3 or 4 AEs	46 (74.2%)	43 (62.3%)	163 (54.9%)	44 (42.7%)	17 (60.7%)	48 (77.4%)	55 (80.9%)	215 (72.6%)	78 (78.8%)	22 (64.7%)
Related grade 3 or 4 AEs[d]	17 (27.4%)	23 (33.3%)	69 (23.2%)	22 (21.4%)	8 (28.6%)	40 (64.5%)	36 (52.9%)	139 (47.0%)	63 (63.6%)	11 (32.4%)
COVID-19 associated grade 3 or 4 AEs	3 (4.8%)	2 (2.9%)	4 (1.3%)	2 (1.9%)	0	0	3 (4.4%)	17 (5.7%)	2 (2.0%)	0
Serious AEs	19 (30.6%)	24 (34.8%)	81 (27.3%)	26 (25.2%)	11 (39.3%)	22 (35.5%)	30 (44.1%)	123 (41.6%)	45 (45.5%)	16 (47.1%)
Related serious AEs[d]	1 (1.6%)	5 (7.2%)	12 (4.0%)	0	1 (3.6%)	9 (14.5%)	12 (17.6%)	36 (12.2%)	12 (12.1%)	4 (11.8%)
COVID-19 associated serious AEs	1 (1.6%)	2 (2.9%)	5 (1.7%)	1 (1.0%)	0	1 (1.6%)	4 (5.9%)	18 (6.1%)	1 (1.0%)	0
AEs leading to discontinuation of study agent[f]	7 (11.3%)	5 (7.2%)	33 (11.1%)	8 (7.8%)	0	11 (17.7%)	13 (19.1%)	47 (15.9%)	17 (17.2%)	2 (5.9%)
AEs leading to death[e]	0	5 (7.2%)	11 (3.7%)	1 (1.0%)	0	4 (6.5%)	4 (5.9%)	20 (6.8%)	7 (7.1%)	1 (2.9%)
Related AEs leading to death[d]	0	1 (1.4%)	0	0	0	2 (3.2%)	0	0	0	0
COVID-19 associated AEs leading to death	0	0	2 (0.7%)	0	0	1 (1.6%)	1 (1.5%)	9 (3.0%)	1 (1.0%)	0

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
[d] An AE is categorized as related if assessed by the investigator as related to any of the study medication.
[e] AEs leading to death are based on AE outcome of Fatal.
[f] An AE is counted as leading to discontinuation of study regnt if it leads to withdrawal of Niraparib/Placebo or Abiraterone Acetate/Placebo or Prednisone.

Safety related to drug-drug interactions and other interactions

There have been no relevant changes to data previously supplied for the mCRPC. For the mCRPC, no clinical trial evaluating drug interactions was performed using nira+AAP. Interactions that had been identified in studies with the individual components of nira+AAP (niraparib or abiraterone acetate) determine the interactions that may occur with nira+AAP. This was considered acceptable.

Discontinuation due to adverse events

Overall, 14.7% of subjects in the nira+AAP group and 10.3% of subjects in the PBO+AAP group discontinued at least 1 study drug (niraparib/placebo, AA, or prednisone) due to a TEAE. The most common (≥2% patients in either treatment arm) cause of discontinuation of study treatment was anaemia, reported in 2.3% patients in the nira+AAP arm and 0.6% of patients in the PBO+AAP

arm. All other TEAEs leading to discontinuation of study treatment occurred with <2% frequency in either treatment arm.

Table 101. Number of Subjects with TEAEs Leading to Treatment Discontinuation by SOC and PT; Integrated Safety

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Analysis set: Integrated Safety	196	191	348	347	211	212	559	559
Subjects with 1 or more AEs leading to discontinuation	22 (11.2%)	24 (12.6%)	36 (10.3%)	51 (14.7%)	17 (8.1%)	39 (18.4%)	53 (9.5%)	90 (16.1%)
System organ class Preferred term								
Blood and lymphatic system disorders	1 (0.5%)	5 (2.6%)	3 (0.9%)	12 (3.5%)	1 (0.5%)	7 (3.3%)	4 (0.7%)	19 (3.4%)
Anaemia	1 (0.5%)	4 (2.1%)	2 (0.6%)	8 (2.3%)	1 (0.5%)	6 (2.8%)	3 (0.5%)	14 (2.5%)
Neutropenia	0	0	1 (0.3%)	2 (0.6%)	0	0	1 (0.2%)	2 (0.4%)
Thrombocytopenia	0	0	0	2 (0.6%)	0	1 (0.5%)	0	3 (0.5%)
Haemolytic anaemia	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
General disorders and administration site conditions	3 (1.5%)	7 (3.7%)	5 (1.4%)	10 (2.9%)	1 (0.5%)	6 (2.8%)	6 (1.1%)	16 (2.9%)
Asthenia	1 (0.5%)	2 (1.0%)	3 (0.9%)	4 (1.2%)	0	3 (1.4%)	3 (0.5%)	7 (1.3%)
Sudden death	1 (0.5%)	3 (1.6%)	1 (0.3%)	3 (0.9%)	0	1 (0.5%)	1 (0.2%)	4 (0.7%)
General physical health deterioration	0	1 (0.5%)	0	2 (0.6%)	1 (0.5%)	0	1 (0.2%)	2 (0.4%)
Fatigue	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)	0	1 (0.5%)	1 (0.2%)	2 (0.4%)
Death	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Nervous system disorders	6 (3.1%)	3 (1.6%)	8 (2.3%)	8 (2.3%)	1 (0.5%)	2 (0.9%)	9 (1.6%)	10 (1.8%)
Dizziness	0	1 (0.5%)	0	2 (0.6%)	0	0	0	2 (0.4%)
Dysgeusia	0	1 (0.5%)	0	2 (0.6%)	0	0	0	2 (0.4%)
Hypoglycaemic encephalopathy	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Ischaemic stroke	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Lethargy	0	0	0	1 (0.3%)	0	1 (0.5%)	0	2 (0.4%)
Memory impairment	1 (0.5%)	1 (0.5%)	2 (0.6%)	1 (0.3%)	0	0	2 (0.4%)	1 (0.2%)
Cerebral arteriosclerosis	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Cerebral ischaemia	0	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Cerebral venous sinus thrombosis	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Cognitive disorder	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)

	AMPLITUDE (mCSPC[a])				MAGNITUDE Cohort 1 (mCRPC[b])		Combined[c] (mCSPC[a] + mCRPC[b])	
	BRCA		All HRR		All HRR		All HRR	
	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP	Placebo + AAP	Nira + AAP
Spinal cord compression	3 (1.5%)	0	3 (0.9%)	0	0	0	3 (0.5%)	0
Tremor	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Infections and infestations	1 (0.5%)	5 (2.6%)	3 (0.9%)	6 (1.7%)	2 (0.9%)	14 (6.6%)	5 (0.9%)	20 (3.6%)
COVID-19 pneumonia	0	2 (1.0%)	0	2 (0.6%)	0	4 (1.9%)	0	6 (1.1%)
Cystitis	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Pneumocystis jirovecii pneumonia	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Pneumonia	0	1 (0.5%)	0	1 (0.3%)	0	1 (0.5%)	0	2 (0.4%)
Sepsis	0	0	0	1 (0.3%)	0	1 (0.5%)	0	2 (0.4%)
COVID-19	0	0	0	0	0	5 (2.4%)	0	5 (0.9%)
Herpes dermatitis	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Lower respiratory tract infection	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Necrotising fasciitis	0	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Pulmonary sepsis	0	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Respiratory tract infection	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Septic shock	0	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.2%)	1 (0.2%)
Suspected COVID-19	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Urinary tract infection	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	3 (1.5%)	4 (2.1%)	4 (1.1%)	6 (1.7%)	2 (0.9%)	1 (0.5%)	6 (1.1%)	7 (1.3%)
Muscular weakness	0	1 (0.5%)	0	2 (0.6%)	0	0	0	2 (0.4%)
Back pain	2 (1.0%)	1 (0.5%)	2 (0.6%)	1 (0.3%)	1 (0.5%)	0	3 (0.5%)	1 (0.2%)
Bone pain	1 (0.5%)	1 (0.5%)	2 (0.6%)	1 (0.3%)	0	0	2 (0.4%)	1 (0.2%)
Pathological fracture	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Sacral pain	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Arthralgia	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Musculoskeletal chest pain	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Gastrointestinal disorders	4 (2.0%)	1 (0.5%)	4 (1.1%)	5 (1.4%)	0	6 (2.8%)	4 (0.7%)	11 (2.0%)
Nausea	1 (0.5%)	0	1 (0.3%)	2 (0.6%)	0	2 (0.9%)	1 (0.2%)	4 (0.7%)
Chronic gastritis	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Diarrhoea	0	0	0	1 (0.3%)	0	1 (0.5%)	0	2 (0.4%)
Vomiting	0	0	0	1 (0.3%)	0	4 (1.9%)	0	5 (0.9%)
Abdominal distension	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Abdominal pain	1 (0.5%)	0	1 (0.3%)	0	0	1 (0.5%)	1 (0.2%)	1 (0.2%)
Gastrointestinal haemorrhage	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Small intestinal obstruction	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Toothache	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Cardiac disorders	2 (1.0%)	1 (0.5%)	4 (1.1%)	4 (1.2%)	5 (2.4%)	3 (1.4%)	9 (1.6%)	7 (1.3%)
Cardiac arrest	1 (0.5%)	0	1 (0.3%)	1 (0.3%)	0	0	1 (0.2%)	1 (0.2%)
Cardiac failure	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Cardio-respiratory arrest	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Cardiogenic shock	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Acute coronary syndrome	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Acute myocardial infarction	0	0	1 (0.3%)	0	2 (0.9%)	0	3 (0.5%)	0
Aortic valve stenosis	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Atrial fibrillation	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Cardiac failure congestive	0	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Cor pulmonale	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Coronary artery disease	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Ischaemic cardiomyopathy	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Myocardial infarction	1 (0.5%)	0	2 (0.6%)	0	1 (0.5%)	0	3 (0.5%)	0
Injury, poisoning and procedural complications	1 (0.5%)	1 (0.5%)	1 (0.3%)	4 (1.2%)	0	1 (0.5%)	1 (0.2%)	5 (0.9%)
Fall	1 (0.5%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.5%)	1 (0.2%)	2 (0.4%)
Femur fracture	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Subdural haematoma	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Thermal burn	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Head injury	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5%)	1 (0.5%)	1 (0.3%)	4 (1.2%)	2 (0.9%)	2 (0.9%)	3 (0.5%)	6 (1.1%)
B-cell lymphoma	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Gastrointestinal carcinoma	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Metastatic gastric cancer	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Myelodysplastic syndrome	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Acute myeloid leukaemia	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0

Bladder cancer	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Gastric cancer	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Lung neoplasm malignant	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Rectal cancer	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Metabolism and nutrition disorders	2 (1.0%)	0	4 (1.1%)	3 (0.9%)	0	0	4 (0.7%)	3 (0.5%)
Decreased appetite	1 (0.5%)	0	1 (0.3%)	2 (0.6%)	0	0	1 (0.2%)	2 (0.4%)
Dehydration	0	0	0	2 (0.6%)	0	0	0	2 (0.4%)
Hypokalaemia	1 (0.5%)	0	3 (0.9%)	0	0	0	3 (0.5%)	0
Investigations	5 (2.6%)	0	7 (2.0%)	1 (0.3%)	3 (1.4%)	0	10 (1.8%)	1 (0.2%)
Alanine aminotransferase increased	4 (2.0%)	0	5 (1.4%)	1 (0.3%)	2 (0.9%)	0	7 (1.3%)	1 (0.2%)
Aspartate aminotransferase increased	3 (1.5%)	0	4 (1.1%)	1 (0.3%)	2 (0.9%)	0	6 (1.1%)	1 (0.2%)
Eastern Cooperative Oncology Group performance status worsened	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Weight decreased	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Psychiatric disorders	0	1 (0.5%)	0	1 (0.3%)	0	2 (0.9%)	0	3 (0.5%)
Psychotic disorder	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Suicide attempt	0	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)
Anxiety	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Completed suicide	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Skin and subcutaneous tissue disorders	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Skin hyperpigmentation	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Vascular disorders	1 (0.5%)	0	1 (0.3%)	1 (0.3%)	1 (0.5%)	2 (0.9%)	2 (0.4%)	3 (0.5%)
Hypertension	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
Aortic dissection	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Circulatory collapse	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Embolism	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Hot flush	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Hepatobiliary disorders	0	0	0	0	1 (0.5%)	2 (0.9%)	1 (0.2%)	2 (0.4%)
Hepatic failure	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Hepatitis acute	0	0	0	0	0	1 (0.5%)	0	1 (0.2%)
Hyperbilirubinaemia	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Renal and urinary disorders	1 (0.5%)	0	2 (0.6%)	0	1 (0.5%)	0	3 (0.5%)	0
Chronic kidney disease	1 (0.5%)	0	2 (0.6%)	0	0	0	2 (0.4%)	0
Urinary retention	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0
Reproductive system and breast disorders	2 (1.0%)	0	2 (0.6%)	0	0	1 (0.5%)	2 (0.4%)	1 (0.2%)
Pelvic pain	2 (1.0%)	0	2 (0.6%)	0	0	1 (0.5%)	2 (0.4%)	1 (0.2%)
Perineal pain	1 (0.5%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (0.5%)	2 (0.9%)	1 (0.2%)	2 (0.4%)
Dyspnoea	0	0	0	0	0	2 (0.9%)	0	2 (0.4%)
Pulmonary embolism	0	0	0	0	1 (0.5%)	0	1 (0.2%)	0

Key: AAP = abiraterone acetate (AA) plus prednisone, BRCA = breast cancer gene, HRR = homologous recombination repair, mCRPC = metastatic castration-resistant prostate cancer, mCSPC = metastatic castration-sensitive prostate cancer, nira = niraparib, Nira+AAP = nira 200 mg and AA 1000 mg + prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), Placebo+AAP = AA 1000 mg plus prednisone daily 5 mg (mCSPC) / 10 mg (mCRPC), AE = adverse event.
[a] AMPLITUDE subjects (HRR positive) who received Nira+AAP or Placebo+AAP.
[b] MAGNITUDE Cohort 1 subjects (HRR Positive) who received Nira+AAP or Placebo+AAP.
[c] The Combined group includes the subjects from AMPLITUDE and from MAGNITUDE Cohort 1 who received Nira+AAP or Placebo+AAP.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Note: Table includes treatment emergent adverse events leading to treatment discontinuation of niraparib/placebo or abiraterone acetate/placebo or prednisone.
Adverse events are coded using MedDRA Version 27.1.

[tsfae06.rtf] [PROD/xcp_oncology/z_scs_nira/dbr_pcr3002scs/re_pcr3002scs/tsfae06.sas] 23FEB2025, 23:11

Adverse events leading to dose interruption

Anaemia was the most common cause for dose interruption in the nira+AAP group (27.4%), followed by neutropenia (10.4%), hypertension (8.6%), thrombocytopenia (8.4%), and hypokalemia (8.1%). All other TEAEs leading to dose interruption occurred with <5% frequency. Data not shown.

Adverse events leading to dose reduction

The most common cause of dose-level reduction of study treatment was anaemia in the nira+APP arm (13.5%). All other TEAEs leading to dose-level reduction of study treatment occurred with <2% frequency in either treatment arm. Data not shown.

Post marketing experience

AKEEGA (niraparib plus abiraterone acetate fixed-dose combination therapy, plus prednisone or prednisolone) received the first regulatory approval on 19 April 2023 in the European Union.

No new safety signals were identified from the cumulative review of postmarketing spontaneous cases. The safety profile of niraparib/AA FDC in the postmarketing setting was consistent with the safety profile established during the clinical studies. Routine pharmacovigilance activities will continue to be performed to monitor the safety of niraparib/AA FDC. There are no changes to the identified or potential risks.

2.5.1. Discussion on clinical safety

The safety assessment is mainly based on 347 patients (All HRR, includes 191 BRCA) treated daily with niraparib 200 mg and AAP (1,000 mg + 5 mg) and 348 patients (All HRR, includes 196 BRCA) treated with pbo+AAP (1,000 mg + 5 mg) in the pivotal study AMPLITUDE (DCO: 07 Jan 2025).

Further, integrated data from the AMPLITUDE (mHSPC) study with safety data from the MAGNITUDE Cohort 1 (mCRPC) study have also been provided. The Combined (mHSPC + mCRPC) safety dataset comprised a pool of 1118 patients, 559 patients (All HRR) treated with nira+AAP and 559 patients (All HRR) treated with pbo+AAP.

Overall, despite some differences, safety data of patients in the BRCA subgroup were generally similar to those of the All HRR population which were also commonly similar with respect to the supportive data from MAGNITUDE Cohort 1 and Combined population. The overall safety profile of Akeega presented in the SmPC with 559 patients is based on pooled data from study AMPLITUDE [n=347] and study MAGNITUDE cohort 1 [n=212]).

Patient exposure

At DCO (7th January 2025), a higher proportion of patients remained on treatment in the nira+AAP arm of AMPLITUDE compared with the pbo+AAP arm: 54.5% vs 43.7%. The most frequently reported reason for treatment discontinuation in both arms was progressive disease with a lower percentage in the nira+APP arm compared with the pbo+AAP arm: 26.8% vs 42.8%, which suggest that niraparib has a positive impact in terms of decreasing the probabilities of experiencing progressive disease. However, a higher proportion of patients in the nira+APP arm discontinued the treatment due to AEs in comparison with the PBO+APP arm [38 (11.0%) vs 24 (6.9%)], therefore the addition of niraparib increases the toxicity of the combination, as expected.

The duration of study treatment (median) was slightly longer in the nira+AAP arm than in the pbo+AAP arm: 25.3 months vs. 22.5 months, hence the combination treatment with niraparib does not appear to reduce the administration of AAP. More than a half of patients (54.8%) in the nira+AAP arm received the study treatment for 24 months or longer and this percentage is considerably higher in comparison with the PBO+APP arm (44.3%). Note that the proposed indication for this combination is a long-term treatment, in which patients are supposed to receive this treatment until progression or inacceptable toxicity. In this context, the duration of treatment could be considered as sufficient for an initial safety assessment, although it should be noted that

the safety evidence supporting the use of the combination for a period of time longer than 2 year is more limited.

Adverse events

Almost all patients experienced at least one AE in both arms (99.7% in the nira+AAP and 98.0% in the pbo+AAP). The incidence of AEs considered as related by the investigator was higher in the nira+AAP compared to the pbo+AAP arm (89.0% vs 73.9%). The percentages of patients who reported G3-4 AEs (75.2% vs 58.9%), SAEs (39.2% vs 27.6%), causally-related G3-4 AEs (55.6% vs 30.2%) and causally-related SAEs (12.7% vs 3.2%) were markedly higher in the nira+AAP arm than in the pbo+AAP arm. These differences between treatment arms were more than 10% and around 25% in the case of causally-related G3-4 AEs, hence the addition of niraparib is linked to a worse tolerability profile predictably considering that the baseline status of patients does not differ significantly between arms. These higher incidences of AEs which worsened the tolerability profile when adding niraparib to AAP were largely driven by haematological AEs, particularly anaemia, and hypertension.

There were no differences among the gene subgroups analysed based on the data submitted.The "Gastrointestinal disorders" SOC was the most commonly reported in the nira+AAP arm (67.7%) vs 50.6% in the pbo+AAP arm, being by PT "constipation" the more frequent (35.2% vs 16.4%), followed by "nausea" (30.8 vs. 14.4%), "vomiting" (16.1% vs. 8.6%), and "diarrhoea" (14.7% vs. 11.5%). "Anemia" belonging to "Blood and lymphatic system disorders" SOC, the second SOC most commonly reported, was the AE most commonly reported in the nira+AAP arm, accounting for 51.6%, vs. 23.9% in the pbo+AAP arm. The differences between arms were also markedly higher in the nira+AAP arm for the other haematological events. Thus, "neutropenia" was reported in 21.9% vs 8.0% patients, "thrombocytopenia" in 19.0% vs 5.7% patients, and "leukopenia" in 16.7% vs 5.2%. Despite these high incidences in AEs of the haematology parameters in the nira+AAP arm, the percentage of infections reported were similar in both treatment arms (54.2% vs. 50.0%), driven by "COVID-19" (18.7% vs. 20.4%) and "urinary tract infection" (11.2% vs. 10.6%).

Sepsis is a common adverse reaction of abiraterone and 1.4% of patients in the nira+AAP arm vs. 1.1% in the pbo+AAP arm reported an AE of sepsis in the pooled dataset (1.7% vs. 1.4% in the Amplitude study) with 1.3% vs. 0.7% of subjects (1.4% vs. 0.9% in the AMPLITUDE study) reporting an SAE of sepsis, respectively.

The third SOC most commonly reported in the niraparib arm was "vascular disorders": 57.9% in the nira+AAP arm vs. 46.3% in the pbo+AAP arm. This difference between arms in terms of frequency was mainly driven by "hypertension" and "hot flush", which were reported in 43.8% and 18.2% of patients in the nira+AAP arm vs. 32.5% and 13.8% of patients in the pbo+AAP arm, respectively.

The following PTs were also reported with a markedly higher frequency in the nira+AAP arm than in the pbo+AAP arm: "fatigue", "hypokalaemia", "weight decreased", "decreased appetite", "dizziness", "insomnia", dyspnoea, "blood creatinine increased". All these adverse events are known adverse drug reactions (ADRs) of niraparib.

Unexpectedly, there were two hepatic parameters which were reported with a higher frequency in the placebo arm than in the niraparib arm: "AST increased" (8.1% in the nira+AAP arm vs. 14.4% in the pbo+AAP arm) and "ALT increased" (6.3% in the nira+AAP arm vs. 15.5% in the pbo+AAP arm). When assessing causality, it seems that these two abnormalities were mostly linked to

abiraterone, although the reason why these parameters were more altered in the placebo arm than in the niraparib arm is unknown. This finding was reported previously in the MAGNITUDE study.

The higher frequency of G3-4 TEAEs in the nira+AAP arm compared to the pbo+AAP arm (75.2% vs. 58.9%) was mainly due to higher incidences of TEAEs in the "blood and lymphatic system disorders" (41.2% vs. 8.9%) and in particular anaemia (29.1% vs. 4.6%) and neutropenia (9.5% vs 2.0%). Similar findings were observed in the MAGNITUDE Cohort [anaemia (30% vs. 7.6%) and neutropenia (6.6% vs. 1.4%)]. G3-4 hypertension and hypokalemia were also reported commonly in the nira+AAP arm (26.5% and 11.5% respectively), and the incidences were higher than in the MAGNITUDE Cohort 1 nira+AAP arm (16.5% and 5.7% respectively).

TEAEs considered related to niraparib or placebo were reported in 289 (83.3%) patients in the nira+AAP arm and 211 (60.6%) patients in the pbo+AAP arm; while TEAEs considered related to AA and prednisone were reported in 266 (76.7%) patients in the nira+AAP arm and 235 (67.5%) patients in pbo+AAP arm. The higher frequency of G3-4 Related TEAEs in the nira+AAP arm compared to the pbo+AAP arm (55.6% vs. 30.2%) was mainly due to higher incidences of TEAEs in the "blood and lymphatic system disorders" (36.0% vs. 3.4%) and in particular anaemia (26.5% vs. 1.7%) and neutropenia (8.4% vs 1.4%). Haematological adverse events, including anaemia and neutropenia, are well-known ADRs associated with niraparib and other PARP inhibitors. G3-4 hypertension (17.6% vs. 14.4%) and hypokalemia (8.0% vs. 8.6%) were also reported commonly.

Serious adverse events

SAEs were reported higher in the nira+AAP arm with more than 10% of difference compared to pbo+AAP arm (39.2% vs 27.6%). This increase is substantial, even when considering the median age of patients (around 67 years old). This suggests that the addition of niraparib implies a considerably worse toxicity profile.

The higher incidence of SAEs in the nira+AAP arm compared with the pbo+AAP arm was mainly driven by the SOC "Infections and infestations" [47 (13.5%) vs. 29 (8.3%)], "Blood and lymphatic systems disorders" [25 (7.2%) vs. 5 (1.4%)] and "Cardiac disorders" [18 (5.2%) vs. 15 (4.3%)]. The most common reported SAE in the nira+AAP arm was anemia [20 (5.8%) vs. 4 (1.1%) in the placebo arm], pneumonia [12 (3.5%) vs. 10 (2.9%)], urinary tract infection [9 (2.6%) vs. 6 (1.7%)] and hypokalaemia [8 (2.3%) vs. 2 (0.6 %)]. One patient with no prior history of neutropenia during the study treatment, had pneumonia with concurrent neutropenia in the nira+AAP arm that was attributed to progressive disease in the bone in a patient with radiographic progression. In the pbo+AAP the SAEs which occurred with higher frequency were haematuria (1.4%), following by anemia, acute kidney injury, spinal cord compression and pathological fracture (1.1% each).

SAE of sepsis was reported in 5 (1.4%) vs. 3 (0.9%) of patients in the nira+AAP and pbo+AAP arm respectively. SAEs of arrhythmia were reported in 9 (2.6%) vs. 5 (1.4%) of patients in the nira+AAP and pbo+AAP arm respectively. Anaemia concurrent with tachyarrhythmia was reported in 8 (2.3%) vs. 1 (0.3%) patient.

Deaths

During the study reporting period, 84 (24.2%) deaths occurred in the nira+AAP and 108 (31.0%) in the pbo+AAP arm. As of the DCO date, many deaths occurred during the follow-up period, 63 (18.2%) in the nira+AAP arm vs. 94 (27%) in the pbo+AAP; while deaths reported on study treatment were 21 (6.1%) vs. 14 (4.0%). The most common cause of death on study treatment as well as during the follow up was progressive disease, with 55 (15.9%) deaths in the nira+AAP arm and 75 (21.6%) in the pbo+AAP arm. The incidences of reported "Other" deaths were 13 (3.7%)

vs. 25 (7.2%), respectively. The MAH clarified that the category of "Other" deaths corresponds to deaths occurred outside of the AE reporting period (>30 days after the last dose of study treatment or after start of subsequent anticancer therapy). The "Other" deaths reported include sepsis (3 nira+AAP; 2 pbo+AAP), cerebral hemorrhage (2 nira+AAP; 1 pbo+AAP), pneumonia (1 nira+AAP; 3 pbo+AAP), cardiac arrest (0 nira+AAP; 3 pbo+AAP) and one patient´s death in the nira+AAP arm with both hemorrhagic stroke and sepsis.

The incidence of AEs with outcome of death was twice in the nira+AAP treated patients compared to pbo+AAP arm [14 (4.0%) vs. 7 (2.0%), respectively]. In terms of SOCs, the most common AE leading to death were infections and infestations in the nira+AAP arm compared with the pbo+AAP arm [5 (1.4%)] vs 1 (0.3%)], following by cardiac disorders [4 (1.2%) vs 3 (0.9%)] and general disorders and administration site conditions [4 (1.2%) vs 1 (0.3%)].

Deaths due to "infections and infestations" SOC in the nira+AAP arm were driven by COVID-19 pneumonia (n=2), pneumocystis jirovecii pneumonia (n=1), pneumonia (n=1), sepsis (n=1). The 4 patients who died of pneumonia had underlying pre-existing medical history risk factors including cardiac disease, and the patient who died due to sepsis had discontinued niraparib 1 year prior to the sepsis event but continued to receive AAP on study. In "cardiac disorders" the deaths in the nira+AAP arm were due to cardiac arrest (n=2), cardio-respiratory arrest (n=1), cardiogenic shock (n=1). The patient with cardiorespiratory arrest had a fall a few days before starting study treatment followed by G2 asthenia, G1 peripheral edema, and an early death at study day 24. The patient died of cardiogenic shock had a pre-existing medical history of aortic aneurysm with G4 aortic aneurysm reported on the day of death. In case of "general disorders and administration site conditions" SOC, deaths were driven by sudden death (n=3) and multiple organ dysfunction syndrome (n=1) in the nira+AAP arm. The three patients who experienced sudden death, all had cardiac medical history risk factors and died at home in their sleep, one of them was considered treatment-related by the investigator. The patient died of multiple organ dysfunction syndrome had underlying cardiac valvular disease after a cardiac procedure.

AESIs

Generally, AESIs were similar to those experienced by mCRPC patients with some differences in incidences of reported AEs as in the hypertension grouped term (44.7% vs. 34.0% in MAGNITUDE Cohort 1, in the nira+AAP arm) and hypokalemia (26.5% in AMPLITUDE All HRR vs. 16.0% in MAGNITUDE Cohort 1, in the nira+AAP arm). This pronounced imbalance between mHSPC (AMPLITUDE) and mCRPC (MAGNITUDE Cohort 1) populations may be associated with mineralcorticoid effects due the fact that, as pointed out before, prednisone dose (5 mg in AMPLITUDE vs. 10 mg in MAGNITUDE Cohort 1) which is administered with AA to mitigate the mineralcorticoid effects of AA. In addition, the rates of arrhythmias were also imbalanced between AMPLITUDE (19.6% vs. 8.0%) and MAGNITUDE Cohort 1 (13.2% vs. 7.6%). The treatment dose of niraparib and abiraterone was similar for both studies. The MAH stated that all patients had preexisting risk factors and that the difference in incidences of arrhythmias between mHSPC and mCRPC patients may be explained because of the shorter exposure to ADT on AMPLITUDE where cardiovascular disease (CVD) risk may be observed earlier into ADT treatment, particularly for those with pre-existing cardiovascular risk factors. According to the literature (O'Farrell 2015), the risk of CVD seems higher particularly during the first months of ADT and especially in patients with CV events history. However, O'Farrell study was an observational study where the lifestyle factors were not considered and residual confounders which could not be accounted for. On the other hand, although mHSPC patients are less exposed to ADT and the cardiovascular risk factors could be increased during the first months of treatment, mCRPC patients were also treated with ADT, hence an increase of the cardiovascular effects should have been observed among first month's

exposure too. Although the reasons for this imbalance could not be fully clarified, this was not further pursued. Section 4.4 and 4.8 were accordingly updated to reflect these findings.

The addition of niraparib to SoC resulted in higher risk of AESIs in All HRR AMPLITUDE, 88.2% in the nira+AAP arm vs. 75.0% in the pbo+AAP arm. This imbalance is driven mainly by anemia, hypertension, neutropenia, arrhythmia and thrombocytopenia that were the most commonly reported AESIs (≥ 20%). All these AESIs are known ADRs of Akeega and are addressed in 4.8 of the SmPC.

Anemia was reported in 51.6% of patients in the nira+AAP arm, 28.5% were G3 events and 0.6% were G4. Blood transfusion for the TEAEs of anemia were administered to 25.1% of participants in the nira+AAP arm, with 14.7% who requiring more than 1 transfusion.

Neutropenia and thrombocytopenia were reported in 21.9% and 19.0% of patients in the nira+AAP arm, respectively. G3 events of neutropenia and thrombocytopenia were reported in 8.1% and 4.3% of patients respectively. G4 events of neutropenia and thrombocytopenia were reported in 1.4% patients and 2.6% patients respectively.

There were patients who had an event of neutropenia with a concurrent event of infection, 11 (3.2%) in the nira+AAP arm and 3 (0.9%) in the pbo+AAP arm. Three events of neutropenia in the nira+AAP arm and 1 event in the pbo+AAP arm were temporally associated with SAEs of infection. In the nira+AAP arm, one patient had G4 pneumonia that was attributed to underlying progressive disease, one patient had neutropenia reported in the context of a *Clostridium difficile* infection, and the third event of neutropenia occurred in one subject with a medical history of G1 urinary retention and had a G3 episode of urinary tract infection preceded by neutropenia. There were no G3 or higher TEAEs of febrile neutropenia or neutropenic sepsis reported. Platelet transfusion was administered to 1.7% patients in the nira+AAP arm vs 0.6% in pbo+AAP. Bleeding event (the main concern of thrombocytopenia) within 7 days was reported in 66 (19.0%) patients in the nira+AAP arm vs. 49 (14.3%) reported a bleeding event.

Regarding major adverse cardiovascular events, MACE (Ischemic Heart Disease, Cardiac Failure, Arrhythmias, Cerebrovascular Disorders), a noticeable imbalance in incidence rate between arms is observed for the AESI of arrhythmia, 19.6% of patients in the nira+AAP arm and 8.0% in the pbo+AAP arm, driven mainly by sinus tachycardia (6.1% vs. 0.6%) and atrial fibrillation (4.9% vs. 1.7%); in both arms, most of these events were Grade 1 or 2 in severity. However, G3 and G4 arrhythmias were reported in 12 (3.5%) and 1 (0.3%) patient in the nira+AAP arm compared to 6 (1.7%) and 1 (0.6%) of patients in the pbo+AAP arm. Arrhythmia is already included as ADR in section 4.8 of the SmPC of Akeega.

Cerebrovascular events were reported with a slightly lower frequency in the nira+AAP arm than in the pbo+APP arm [12 (3.5%) vs. 14 (4.0%)]. G3 were reported in 4 (1.2%) vs. 6 (1.7%) patients, G4 in 1 (0.3%) in each treatment arm. A half of the events in the nira+AAP arm 6 (1.7%) were considered SAEs, however not related to the drug study.

The AESI of myelodysplastic syndrome (MDS) may initially present with concurrent and/or unresolving cytopenias. One case of MDS was reported in the nira+AAP arm in the AMPLITUDE study. The already existing warning in section 4.4 of the SmPC was updated to reflect the occurrence of this AE in the AMPLITUDE study. Additionally, a change in the RMP was implemented to upgrade this safety concern from "potential" to "identified" and MDS has been added as ADR in section 4.8.

Osteoporosis (PT only) was reported higher in the nira+AAP arm, 8 (2.3%) vs. 2 (0.6%), and the incidence was also higher compared to MAGNITUDE Cohort 1, 1 (0.9%) vs. 2 (2.4%) of patients in the nira+AAP and pbo+AAP arm respectively.

A rhabdomyolysis/myopathy G1 was reported in 1 (0.3%) patient in the nira+AAP arm and no one in pbo+AAP arm. One event was reported in the pbo+AAP arm of MAGNITUDE Cohort 1.

Increased incidence for secondary primary malignancies was observed with nira+AAP (4.0%) vs. 2.0% in pbo+AAP arm.

Adverse drug reactions

Three new ADRs (PTs) have been added based on the AMPLITUDE study: gastritis, lethargy, and hot flush, all were reported in a higher frequency in the nira+AAP arm as compared with the pbo+AAP arm: hot flush (18.2% vs. 13.8%), gastritis (3.2% vs. 1.1%), lethargy (2.6% vs. 0.6%). Moreover, several ADRs have been added to the SmPC as a result of the integrated safety data from AMPLITUDE and MAGNITUDE Cohort 1 studies including hyperbilirubinaemia, hepatitis, pruritus and urethral haemorrhage. Besides, MDS, a known ADR of niraparib and PARPi, has been added to section 4.8 of the SmPC since one case was reported in the AMPLITUDE study.

Laboratory findings

Regarding haematology laboratory abnormalities during treatment, an increased rate of laboratory values indicating G3 hematologic toxicities was observed in the nira+AAP vs. pbo+AAP arm. The imbalance in haematology values was due to anaemia (29.4% vs. 4.0%) predominantly, decreased lymphocyte count (18.7% vs 10.1%) and decreased neutrophil count (9.5% vs 2.3%). G4 abnormalities (≥1%) were decreased lymphocyte count (1.7% in both arms), decreased neutrophil count (1.4% vs 0.9%), decreased platelet count (2.6% vs 0.9%), and decreased white blood cell count (0.6% in each treatment arm). Haematology laboratory parameters were also significantly increased in the niraparib arm being anaemia the most commonly reported G3 abnormality too in MAGNITUDE Cohort 1.

Hepatic function laboratory abnormalities of G3-4 were more frequently reported in the pbo+AAP arm, including ALT increased (2.3% vs 4.9%) and AST increased (1.8% vs. 2.6%). Note that G3 or hepatotoxicity laboratory findings ("ALT increased" and "AST increased") were also reported markedly more frequently in the placebo arm in MAGNITUDE Cohort 1. Regarding these data, the MAH clarified that these increases in ALT and ALT may be due to risk factors of the population enrolled in the placebo arm. Moreover, the MAH argued that increases in AST and ALT liver enzymes are already included as common ADRs and that there is also a hepatoxicity warning in the SmPC, which is acknowledged. Of note, no cases meeting Hy's Law criteria were reported either with the nira+AAP or pbo+AAP.

Markedly abnormal treatment emergent increases in diastolic blood pressure and in systolic blood pressure were reported deeply in the niraparib arm compared to placebo arm. Similar findings were observed across MAGNITUDE Cohort 1.

Safety in special populations

Concerning age, significant differences were observed among age subgroups <65 (n=116 in the nira+AAP arm, n= 135 in the pbo+AAP arm) and ≥75 years of age (n= 84 in the nira+AAP arm, n= 74 in the pbo+AAP arm), particularly in the nira+AAP arm in the Grade 3-4 TEAEs (nira+AAP: 62.9% vs 82.1%; pbo+AAP: 55.6% vs 63.5%); SAEs (nira+AAP: 25.9% vs 53.6%; pbo+AAP: 25.2% vs 28.4%); TEAEs leading to discontinuation (nira+AAP: 6.9% vs 29.8%; pbo+AAP: 7.4% vs 21.6%); and TEAEs leading to death (nira+AAP: 0.9% vs 13.1%; pbo+AAP: 1.5% vs 2.7%). As

expected, an increase in the severity of TEAEs was observed as patients are older. However, there is an imbalance in the number of patients in the older age subgroup (≥75 years of age), and age is an unstratified subgroup analysis. Therefore, these results should be interpreted with caution.

Regarding race some differences were observed particularly in Grade 3-4 TEAEs, Asian patients experienced a higher incidence of G3 or G4 AEs (79.2% vs. 47.8%) compared to White patients (72.7% vs. 60.7%) in the nira+AAP arm. Due to the imbalance in the number of White (who were predominant) and Asian patients, no conclusion could be drawn. The MAH provided more information about these differences, claiming that there is apparently evidence that support that Asian patients may be more susceptible to haematological toxicities (the majority of G3-4 TEAEs reported). However, it has not been possible to establish a causal rationale for these differences.

Discontinuation due to AEs

AE leading to any study treatment (niraparib/placebo or AA/placebo or prednisone) discontinuation, dose interruption or reduction was more frequent for patients in nira+AAP arm than in pbo+AAP arm (respectively, 14.7% and 10.3%; 66.9% and 42.2%; 21.9% and 6.9%).

Anaemia was the most commonly reported AE leading to permanent discontinuation of study treatment, dose interruption or dose reduction and was reported at a higher incidence in the nira+AAP treatment arm than the pbo+AAP arm (respectively, 2.6% and 0.6%; 27.4% and 2.3%; 13.5% and 0.3%). Despite the fact that more than a half of the patients in the nira+AAP experienced anaemia in the nira+AAP arm (51.6%; G3-4. 29.1%), only 8 (2.3%) patients discontinued niraparib treatment due to TEAEs of anaemia. However, 25.1% of patients needed blood transfusions and 27.4% interrupted dose due to anaemia.

In addition to anaemia, neutropenia, hypertension, thrombocytopenia, and hypokalemia were common causes for dose interruption and were reported higher in the nira+AAP arm than in the pbo+AAP arm.

2.5.2. Conclusions on clinical safety

Overall, despite some differences, the safety profile of niraparib in combination with AAP appears quite consistent across the All HRR population and the BRCA subgroup, as well as with previous data from niraparib in combination with APP for mCRPC patients in MAGNITUDE Cohort 1 study. Three new ADRs have been identified or niraparib+AAP: hot flush, gastritis, and lethargy.

The combination of niraparib and abiraterone/prednisone is associated with a worsening of the toxicity profile of abiraterone/prednisone alone, although it seems to be manageable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Annex II C has been updated with the deletion of the sentence related to the first submission of the PSUR.

2.6. Risk management plan

The MAH submitted an updated RMP Version 3.2 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 is acceptable.

The CHMP endorsed the Risk Management Plan version version 3.2 with the following content:

Safety concerns

Table 102: Summary of Safety Concerns

Important Identified Risks	Severe hypertension
	Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
Important Potential Risks	Second primary malignancies (SPM) other than MDS and AML
Missing Information	Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart disease or cardiac ejection fraction measurement of <50%

The important potential risk "Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)" was reclassified as an important identified risk.

Pharmacovigilance plan

Table 103 Ongoing and planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
PCSONCA0485: Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA Ongoing	• **Primary:** (1) To estimate the incidence rate of (a) MDS/AML and (b) other SPMs in a cohort of adult patients with mCRPC and treated with AKEEGA. (2) To compare the incidence of (a) MDS/AML and (b) other SPMs in a cohort of adult male patients with mCRPC and treated with AKEEGA with a clinically comparable cohort of BRCA mutated patients treated with AR pathway inhibitors indicated for mCRPC. • **Secondary:** To assess clinical characteristics and characterize potential risk factors among patients with mCRPC who develop MDS/AML or other SPMs in a cohort of adult male patients with mCRPC and treated with AKEEGA.	Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) Second primary malignancies (SPM) other than MDS and AML	Start of data collection	Q3 2024
			Interim reports	Q3 2025, Q3 2026, Q3 2027, and Q3 2028
			End of data collection and start of final data analysis	Q2 2029
			Final report of study results	Q4 2029

No changes to the Pharmacovigilance plan were necessary as a result of this extension of indication.

Risk minimisation measures

Routine risk minimization activities are sufficient to manage the safety concerns of AKEEGA.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4., 4.8 and 5.1, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet (PL) is updated accordingly.

In addition, the list of local representatives in the PL has been revised.

Please refer to Attachment 1 which includes all changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The approved indication is:

"Akeega is indicated with prednisone or prednisolone in combination with androgen deprivation therapy (ADT) for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) and BRCA 1/2 mutations (germline and/or somatic)."

3.1.1. Disease or condition

Prostate cancer is the fourth most frequently diagnosed cancer and a leading cause of cancer death in men worldwide, with an estimated 1.5 million new cases (7.3% of all new cancers) in 2022 (Bray 2024). In Europe, prostate cancer is the most common cancer in men, with 473,144 new cases, representing the 20% of all cancers in men; and 115,194 (10.5%) of cancer deaths in 2022 (IARC 2022).

3.1.2. Available therapies and unmet medical need

In the EU, standard treatment for all patients with mHSPC irrespective of any HRR gene mutations includes doublet therapy with the addition of either docetaxel or an AR-pathway inhibitor to androgen deprivation therapy (abiraterone, enzalutamide, darolutamide or apalutamide) or triplet therapy with all three combined (i.e. darolutamide + docetaxel + ADT) (Parker C, et al. ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020)

Radiotherapy to the primary tumour combined with the systemic treatment is recommended for patients with low-volume disease. ADT alone is recommended as first-line systemic treatment in men who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel.

Alterations in HRR-associated genes have been shown to lead to poor outcomes in prostate cancer patients with existing therapies.

There are currently no treatment options available that specifically target the HRR pathway in patients with mHSPC and BRCA 1/2 mutations. There is thus a clinical unmet need for new therapies that may help improve outcomes in this patient population and delay the progression to mCRPC, a uniformly fatal disease.

3.1.3. Main clinical studies

The evidence in support of this application is based on the results of the study AMPLITUDE. This is a randomized, double-blind, placebo-controlled, multicenter study of niraparib in combination with abiraterone and prednisone daily (nira+AAP) compared with placebo plus abiraterone and prednisone (pbo+AAP) daily in subjects with deleterious germline or somatic HRR gene-mutated metastatic hormone-sensitive prostate cancer (mHSPC).

Patients were randomized 1:1 to nira+AAP or pbo+AAP, and were stratified by HRR gene alteration (BRCA2 vs. CDK12 vs. all other pathogenic alterations), prior docetaxel use (yes vs. no), and volume of disease at screening (high vs. low). Patients enrolled had to have at least one of the following deleterious germline or somatic HRR gene alterations: BRCA2, BRCA1, CDK12, CHEK2, FANCA, PALB2, BRIP1, RAD51B or RAD54L. All patients had to be on ADT if not surgically castrated.

In this study there were three pre-specified populations, based on the gene alterations: the BRCA population, the HRR effector population and the All HRR population. The three were included in the multiplicity testing procedure and formally tested.

The primary endpoint was radiographic progression-free survival (rPFS) by investigator based on RECIST 1.1 for soft tissue disease and PCWG3 criteria for bone disease. Key secondary endpoints (i.e., multiplicity-protected) were time to symptomatic progression (TSP) and overall survival (OS)

3.2. Favourable effects

In the BRCA subgroup, rPFS by investigator was statistically significant [HR: 0.51 (95% CI: 0.370, 0.717); p<0.0001]. Median rPFS was not reached in the nira+AAP arm, while it was 25.99 (95% CI: 22.11, 41.17) in the placebo arm.

The secondary endpoint TSP also met statistical significance [HR: 0.444 (95% CI: 0.290, 0.681)]. OS did not reach statistical significance at IA2 [HR: 0.80 (95% CI: 0.58, 1.11)], although a trend favouring nira+AAP was observed [the IF at IA2 was 63.3% (145/229)].

Sensitivity analyses were consistent with the primary analyses.

3.3. Uncertainties and limitations about favourable effects

Results in the subgroup of patients with BRCA1 mutations show limited benefits, however due to the limitations of this analysis and the small number of patients, excluding those patients from the indication is not justified.

3.4. Unfavourable effects

Overall, the safety profile of niraparib in combination with abiraterone and prednisone (nira+AAP) based on the AMPLITUDE study, is well characterised and quite consistent across the All HRR population and the BRCA subgroup, as well as with previous data from nira+APP in mCRPC patients in MAGNITUDE Cohort 1 study.

Nira+APP increased treatment-related AEs, AEs of Grade 3-4, SAEs, and AEs leading to treatment discontinuation or to dose modifications compared to PBO+APP treatment. The frequencies of patients who reported causally-related AEs (89.0% vs 73.9%), G3-4 AEs (75.2% vs 58.9%), causally-related G3-4 AEs (55.6% vs 30.2%), SAEs (39.2% vs 27.6%), and causally-related SAEs (12.7% vs 3.2%) were markedly higher in the niraparib+APP arm than in the PBO+APP arm. These differences between treatment arms were more than 10% and around 25% in the case of causally-related G3-4 AEs, and were largely driven by hematological AEs, particularly anemia, and hypertension. In terms of Grade 3-4 AEs and SAEs, anaemia was the most common reported SAE in nira+APP and it was managed by dose modifications or interruptions. These AEs are previously known ADRs for niraparib.

Three new ADRs were identified for the niraparib combination treatment in the AMPLITUDE study (nira+APP vs. PBO+APP): hot flush (18.2% vs. 13.8%), gastritis (3.2% vs. 1.1%), lethargy (2.6% vs. 0.6%).

Of note, an increased incidence of hypertension and hypokalaemia (already known ADRs of both niraparib and abiraterone) was observed with respect to the previous data in mCRPC patients in MAGNITUDE Cohort 1 study. This difference may be explained by an increase in mineralocorticoid adverse effects of abiraterone due to the lower dose of prednisone (5 mg in AMPLITUDE vs. 10 mg in MAGNITUDE Cohort 1).

Regarding deaths, treatment emergent adverse events leading to death occurred two times more in the niraparib arm than in the placebo arm [14 (4.0%) vs. 7 (2.0%) patients]. This imbalance between arms was determined firstly by "infections and infestations" following by "cardiac disorders" and "general disorders and administration site conditions" [sudden death (n=3) and multiple organ dysfunction syndrome (n=1)] in the niraparib+APP arm.

A higher percentage of patients in the niraparib arm had 1 or more AEs leading to discontinuation of any component of the combination (niraparib/placebo or AA/placebo or prednisone). The most common reason for discontinuation of study treatment, dose interruption or dose reduction was anaemia which was reported at a higher incidence in the niraparib+APP treatment arm than the PBO+APP arm Besides anaemia, neutropenia, hypertension, thrombocytopenia, and hypokalaemia were common cause for dose interruption and were reported higher in the niraparib+APP arm than in the PBO+APP arm.

The AESIs were similar to those experienced by mCRPC patients in MAGNITUDE Cohort 1 (anaemia, hypertension, hypokalaemia, neutropenia, arrhythmia, and thrombocytopenia).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 104: Effects Table for Akeega in patients with mHSPC (data cut-off: 07-Jan-2025)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
BRCA mutated population (N=387)						
rPFS (primary endpoint)	Radiographic progression free survival. Investigator assessment	Median, months (95% CI)	NE (41.20, NE)	25.99 (22.11, 41.17)	HR: 0.515 (95% CI: 0.370, 0.717); p<0.0001	CSR (final rPFS analysis)
TSP (key secondary endpoint)	Time to symptomatic progression	Median, months (95% CI)	NE (NE, NE)	NE (39.72 NE)	HR: 0.444 (95% CI: 0.290, 0.681); p=0.0001	CSR (TSP IA1; IF: 80.9%)
OS (key secondary endpoint)	Overall survival	Median, months (95% CI)	52.0	47.6	HR: 0.80 (95% CI: 0.58, 1.11) *Descriptive results.	IA2 topline report DCO 03-Oct-2025 (OS

						IA2; IF: 63.3%)
Unfavourable Effects						
All HRR population (N=696)						
AEs of Grade 3-4	High grade AE	%	75.2	58.9		CSR
SAEs	Serious AEs	%	39.2	27.6		
Death due to AEs	Adverse events leading to death	%	4.0	2.0		
AEs leading to discontinuation	Adverse events leading to discontinuation of study treatment	%	14.7	10.3		
AEs leading to dose interruption	Adverse events leading to interruption of study treatment	%	66.9	42.2		

Abbreviations: CI=confidence interval; CSR= clinical study report; HR=hazard ratio; NE=not estimable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the AMPLITUDE study the combination of niraparib+AAP demonstrated a statistically significant improvement in rPFS by investigator compared with AAP alone in adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) and BRCA 1/2 mutations (germline and/or somatic). TSP, key secondary endpoint, was also met. OS statistical significance was not reached at IA2 however a positive trend is observed. Sensitivity analyses were overall consistent with the primary analysis.

The clinical benefit in the All HRR population appears to be driven by the BRCA subgroup. In the Non-BRCA subgroup no apparent benefit is observed between treatment arms in either rPFS or OS. Considering these results and in light of the additive toxicity of niraparib and the uncertainties surrounding all the included HRR gene mutations (some of them proactively excluded from the clinical study due to an expected lack of efficacy) a restriction of the indication to BRCA mutated patients was agreed.

From a safety point of view, the safety profile of niraparib+AAP appears to be consistent across the All HRR population and the BRCA1/2 mutation positive patients subgroup, and with previous safety data from the mCRPC setting (MAGNITUDE study). Addition of niraparib to abiraterone translates into a worse tolerability profile compared to placebo+abiraterone, with an increase in treatment-related AEs, SAEs, AEs of grade 3-4 and AEs leading to treatment discontinuation and overlapping of toxicities. This is to be expected. Several ADRs have been identified in the nira+AAP arm and included in the product information based on the new data available (hot flush, gastritis and lethargy, hyperbilirubinaemia, hepatitis, pruritus, urethral haemorrhage and MDS). The safety profile of nira+AAP in the new claimed indication is considered well characterised and overall manageable.

3.7.2. Balance of benefits and risks

Niraparib + abiraterone has demonstrated a statistically significant and clinically relevant improvement in rPFS in patients mHSPC and BRCA 1/2 mutations (germline and/or somatic) supported by TSP and other secondary endpoints. Statistical significance for OS was not reached in any of the studied populations, however a positive trend has been observed. The safety profile of nira+AAP in the new claimed indication is considered well characterised and manageable.

3.8. Conclusions

The overall B/R of Akeega in adult patients with metastatic hormone-sensitive prostate cancer and BRCA 1/2 mutations (germline and/or somatic) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include AKEEGA with prednisone or prednisolone for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) and BRCA1/2 mutations (germline and/or somatic), based on interim results from study 67652000PCR3002 (AMPLITUDE); this is a phase 3 randomized, placebo-controlled, double-blind study of niraparib in combination with abiraterone acetate and prednisone versus abiraterone acetate and prednisone for the treatment of participants with deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-sensitive prostate cancer (mCSPC). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.2 of the RMP has also been agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation(s) proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation EMA/VR/0000282377 amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.