Capivasertib (breast cancer)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Medical and scientific advice

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AKT1	protein kinase B
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CDK	cyclin-dependent kinase
CTCAE	Common Terminology Criteria for Adverse Events
ddPCR	digital droplet polymerase chain reaction
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ER	oestrogen receptor
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IHC	immunohistochemistry
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NGS	next generation sequencing
PFS	progression-free survival
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PTEN	phosphatase and tensin homolog
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug capivasertib (in combination with fulvestrant). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 October 2024.

Research question

The aim of the present report is to assess the added benefit of capivasertib in combination with fulvestrant (hereinafter referred to as "capivasertib + fulvestrant") compared with the appropriate comparator therapy (ACT) in adult patients with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)/protein kinase B (AKT1)/phosphatase and tensin homolog (PTEN) alterations following recurrence or progression on or after an endocrine-based regimen.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of capivasertib (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, after recurrence of the disease during or after (neo-)adjuvant endocrine therapy, no treatment to date in locally advanced or metastatic stage[b, c]	▪ Tamoxifen (only for premenopausal women who have not received tamoxifen in previous [neo-]adjuvant endocrine therapy; only for postmenopausal women if aromatase inhibitors are not suitable) or ▪ letrozole or ▪ exemestane (only for women with progression following anti-oestrogen therapy) or ▪ anastrozole or ▪ fulvestrant or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant

Table 2: Research questions of the benefit assessment of capivasertib (multipage table)

Research question	Therapeutic indication	ACT[a]
2	Men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, after recurrence of the disease during or after (neo-)adjuvant endocrine therapy, no treatment to date in locally advanced or metastatic stage[b]	▪ tamoxifen or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)
3	Women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage[b, d]	Treatment of physician's choice, taking into account a change of endocrine therapy to ▪ tamoxifen ▪ letrozole[e] ▪ exemestane[e] ▪ anastrozole ▪ fulvestrant[e] ▪ everolimus in combination with exemestane (only for women without symptomatic visceral metastases who have progressed after a nonsteroidal aromatase inhibitor) ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ ribociclib in combination with fulvestrant ▪ abemaciclib in combination with fulvestrant ▪ palbociclib in combination with fulvestrant
4	Men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage[b]	Treatment of physician's choice[f], taking into account a change of endocrine therapy to ▪ tamoxifen ▪ aromatase inhibitor in combination with a GnRH analogue ▪ fulvestrant ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)

Table 2: Research questions of the benefit assessment of capivasertib (multipage table)

Research question	Therapeutic indication	ACT[a]
a. Presented is the respective ACT specified by the G-BA. b. The following conditions are assumed for the present therapeutic indication: ▫ For patients who have already received a CDK4/6 inhibitor, retreatment with a CDK4/6 inhibitor, anastrozole or letrozole is not an option. ▫ An(other) endocrine therapy is indicated for the patients and, in particular, there is no indication for chemotherapy to achieve a necessary, rapid remission. ▫ (Secondary) resection or radiotherapy with curative intent is not indicated. ▫ There has been a change in treatment with respect to the drugs used for initial endocrine-based therapy. c. Pre/perimenopausal patients are assumed to receive ovarian suppression with a GnRH analogue. d. Pre/perimenopausal patients are assumed to continue ovarian suppression with a GnRH analogue. e. For this patient group, treatment with fulvestrant, letrozole and exemestane, despite off-label use, is generally preferable to the approved endocrine therapies for the indication area after pretreatment with an endocrine therapy other than anti-oestrogens, in particular after pretreatment with aromatase inhibitors, according to §6 (2), sentence 3, number 3, AM-NutzenV. In accordance with the G-BA, it is therefore appropriate to determine the above-mentioned drugs as ACT for this indication area, even when used off-label. f. The guidelines recommend the drugs tamoxifen, fulvestrant, aromatase inhibitor + GnRH analogue, as well as CDK4/6 inhibitors for the male patient group. However, in the therapeutic indication, aromatase inhibitors and fulvestrant are only approved for women. Thus, the use of aromatase inhibitors and fulvestrant in the male patient group represents an off-label use. In view of the treatment algorithm, there is a relevant indication area in the present therapeutic indication for the male patient group for which the approved drugs are not an option. In this indication area, the use of fulvestrant and aromatase inhibitors + GnRH analogue is therefore generally preferable to tamoxifen and palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole), according to §6 (2), sentence 3, number 3, AM-NutzenV. In accordance with the G-BA, it is therefore appropriate to determine the off-label use of the above-mentioned drugs as ACT. AKT1: protein kinase B; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; CDK: cyclin-dependent kinase; ER: oestrogen receptor; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN: phosphatase and tensin homolog		

For better readability, the research questions defined by the G-BA are abbreviated below as follows:

- Research question 1: women, prior (neo-)adjuvant endocrine therapy
- Research question 2: men, prior (neo-)adjuvant endocrine therapy
- Research question 3: women, prior endocrine therapy in the locally advanced or metastatic stage
- Research question 4: men, prior endocrine therapy in the locally advanced or metastatic stage

The G-BA's most recent adjustments to the subdivision of the therapeutic indication into several research questions and the ACTs were made on 26 November 2024. This resulted in

the research questions and ACTs as presented in Table 2. In its dossier, the company referred to the research questions and their ACTs from the consultation with the G-BA on 24 April 2024. The company therefore addressed a total of 6 research questions or subpopulations in its dossier, differentiated by prior therapy, sex, and additionally by menopausal status (pre/perimenopausal versus postmenopausal) in women:

- Research question a1: pre/perimenopausal women, prior (neo-)adjuvant endocrine therapy
- Research question a2: postmenopausal women, prior (neo-)adjuvant endocrine therapy
- Research question a3: men, prior (neo-)adjuvant endocrine therapy
- Research question b1: pre/perimenopausal women, prior endocrine therapy in the locally advanced or metastatic stage
- Research question b2: postmenopausal women, prior endocrine therapy in the locally advanced or metastatic stage
- Research question b3: men, prior endocrine therapy in the locally advanced or metastatic stage

The company stated that it was following the ACT defined at that time, but described in Module 3 A, with reference to medical societies, that it did not consider differentiation according to menopausal status to be biologically or medically plausible. The present benefit assessment is conducted in comparison with the research questions and their ACTs specified by the G-BA on 26 November 2024.

The company determined the added benefit of capivasertib for its research questions a2 (postmenopausal women, prior [neo-]adjuvant endocrine therapy), b2 (postmenopausal women, prior endocrine therapy in the locally advanced or metastatic stage) and b3 (men, prior endocrine therapy in the locally advanced or metastatic stage) in comparison with fulvestrant. For the other research questions, the company stated that no data in comparison with the ACT were available.

The G-BA pointed out that the drugs anastrozole, fulvestrant and everolimus are explicitly approved for use in postmenopausal women. According to the Federal Institute for Drugs and Medical Devices (BfArM), the approvals for anastrozole, fulvestrant and everolimus do not formally exclude patients whose menopause has been induced by surgery or medication. The ACTs with anastrozole, fulvestrant or everolimus determined here therefore include patients who are physiologically in menopause or in whom the medical status of menopause has been induced by surgery or medication. The company used a different definition, as its analyses did not include pre- and perimenopausal patients whose menopause was induced by gonadotropin-releasing hormone (GnRH) analogues.

In summary, the current research questions of the G-BA no longer differentiate according to the patients' menopausal status. The consequences for the benefit assessment resulting from the absence of the group of the above-mentioned pre- and perimenopausal patients in the present analyses are explained below.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive the added benefit.

Evidence presented

CAPItello-291 study

The CAPItello-291 study is an ongoing, multicentre phase 3 RCT for the direct comparison of capivasertib + fulvestrant with placebo + fulvestrant. It included adult women (pre/perimenopausal and postmenopausal) and men with unresectable, locally advanced or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer. Patients with and without an PIK3CA/AKT1/PTEN alterations were enrolled. However, the PIK3CA/AKT1/PTEN alteration status was determined at enrolment.

To be eligible for enrolment, patients had to have a recurrence or progression during or after treatment with an aromatase inhibitor. In the case of neoadjuvant or adjuvant therapy, recurrence or progression must have occurred during therapy or within 12 months of the end of therapy. Furthermore, eligible patients were not allowed to have received more than 2 prior lines of endocrine therapy or more than one prior line of chemotherapy for inoperable locally advanced or metastatic disease. Patients were considered postmenopausal if one of the following criteria applied:

- age ≥ 60 years
- age < 60, amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments, chemotherapy, ovarian suppression, tamoxifen or similar
  - as well as oestradiol and follicle-stimulating hormone (FSH) levels within the normal postmenopausal range
- documented bilateral oophorectomy

The CAPItello-291 study comprises a global cohort and a China expansion cohort (named by the company, hereinafter referred to as "expansion cohort"), which recruited additional patients in China and Taiwan after randomization of the global cohort was completed. In the global cohort, the relevant subpopulation with PIK3CA/AKT1/PTEN alterations according to the approval of capivasertib comprises 155 patients in the intervention arm and 134 patients in the comparator arm. In the expansion cohort, the subpopulation with PIK3CA/AKT1/PTEN alterations comprises 24 patients in the intervention arm and 22 patients in the comparator

arm. Chinese and Taiwanese patients who were randomized into the expansion cohort before the planned end of recruitment into the global cohort are part of both the global cohort and the expansion cohort. To avoid double analysis of these patients, the company stated that they were assigned only to the global cohort in the analyses in Module 4 A of the dossier. The proportion of patients considered exclusively in the expansion cohort is unclear, as only information on the number of postmenopausal women according to the study definition is available. These were 14 patients in the intervention arm and 11 patients in the comparator arm.

In accordance with their randomization, patients in the intervention arm received approval-compliant treatment with capivasertib. Analogous placebo was administered in the comparator arm. Patients in both treatment arms also received intramuscular therapy with fulvestrant. In addition to the study medication, pre- and perimenopausal patients were to receive concomitant treatment with a menopause-inducing GnRH analogue from Day 1 of the first cycle at the latest until the end of the study. Men could also receive treatment with a GnRH analogue at the discretion of the investigator.

The primary outcome of the CAPItello-291 study was progression-free survival (PFS). Outcomes in the categories of mortality, morbidity, health-related quality of life, and side effects were additionally recorded.

FAKTION study

The FAKTION study is a 2-part study with an initial dose escalation phase and a double-blind, multicentre phase 2 RCT conducted in the United Kingdom. As the company was not the sponsor of the study, it obtained its information from 2 publications. For the early benefit assessment, only the randomized part of the FAKTION study is considered below. This part investigated the direct comparison of capivasertib + fulvestrant versus placebo + fulvestrant. Adult, postmenopausal patients with inoperable, locally advanced or metastatic, ER-positive, HER2-negative breast cancer were enrolled.

Patients were categorized as postmenopausal if they met one of the following criteria:

- Amenorrhoeic throughout and after therapy with a 3rd generation aromatase inhibitor, but without a GnRH analogue, as well as oestradiol and FSH levels within normal postmenopausal ranges at screening for the FAKTION study. If FSH was not in the normal postmenopausal range, the patients could be considered eligible after consultation provided they had been clinically postmenopausal for ≥ 5 years.
- The patient had been treated for early or metastatic breast cancer with a 3rd generation aromatase inhibitor and GnRH analogue, with no resumption of menstruation after

treatment discontinuation for ≥ 6 months. In addition, oestradiol and FSH levels at screening in the FAKTION study had to be in normal postmenopausal ranges.

- The patient had received an aromatase inhibitor and GNRH analogue combined and subsequently had bilateral oophorectomy.

To be enrolled, patients also had to have either progressive disease in the locally advanced or metastatic stage whilst receiving a 3rd generation aromatase inhibitor, or relapsed with metastatic disease whilst receiving a 3rd generation aromatase inhibitor in the adjuvant setting. Patients were not allowed to have received more than 3 lines of endocrine therapy or more than one prior line of chemotherapy for locally advanced or metastatic disease.

A total of 69 patients were randomized in the intervention arm and 71 in the comparator arm. The subpopulation with PIK3CA/AKT1/PTEN alterations relevant to the benefit assessment comprises 39 patients in the intervention arm and 37 patients in the comparator arm.

In accordance with their randomization, patients in the intervention arm received mostly approval-compliant treatment with capivasertib. Analogous placebo was administered in the comparator arm. In addition, patients in both treatment arms received intramuscular therapy with fulvestrant.

The primary outcome of the FAKTION study is PFS. Overall survival and side effect outcomes were also recorded.

Research question 1 (women, prior [neo-]adjuvant endocrine therapy

Results

Analyses presented by the company not suitable for the benefit assessment

The company identified the studies CAPItello-291 and FAKTION for the direct comparison of capivasertib + fulvestrant versus placebo + fulvestrant, for which it presented analyses with patients with PIK3CA/AKT1/PTEN alteration(s) in accordance with the approval of capivasertib.

The FAKTION subpopulation with PIK3CA/AKT1/PTEN alterations comprises 8 patients (10.5%) who had not received prior endocrine therapy in the locally advanced or metastatic stage and are therefore assigned to research question 1. However, based on the publicly available data, no separate analyses are available for patients of research question 1. Overall, there are therefore no suitable data from the FAKTION study for the relevant subpopulation of research question 1 (women, prior [neo-]adjuvant endocrine therapy).

In Module 4 A, the company used results from the CAPItello-291 populations with PIK3CA/AKT1/PTEN alterations exclusively for postmenopausal women as defined in the study protocols (i.e. excluding pre/perimenopausal women whose menopause was induced by

GnRH analogues). In principle, however, there are also data from the CAPItello-291 study for pre/perimenopausal women with drug-induced menopause, who can also be assigned to research question 1. Thus, analyses of the available evidence from the CAPItello-291 study are only available for part of the subpopulation relevant to research question 1 (women, prior [neo-]adjuvant endocrine therapy). The company derived an added benefit for patients of research question 1 by transferring the evidence presented by the company for research question 3.

The analyses on the CAPItello-291 study presented by the company are not suitable for the early benefit assessment of capivasertib in combination with fulvestrant in comparison with the ACT in women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer and recurrence of the disease during or after (neo-)adjuvant endocrine therapy, who had not yet received any treatment in the locally advanced or metastatic stage.

Unclear proportion of patients from the CAPItello-291 study not taken into account for research question 1

In accordance with the approval, fulvestrant as monotherapy is a suitable comparator therapy for postmenopausal patients of research question 1 (women, prior [neo-]adjuvant endocrine therapy). In the present therapeutic indication, patients are considered to be postmenopausal who are physiologically in menopause or in whom the medical status of menopause has been induced by surgery or medication.

In accordance with the inclusion criteria of the CAPItello-291 study, all pre/perimenopausal patients received treatment with a GnRH analogue for the duration of the study, which induced the clinical status of postmenopause. These patients therefore represent part of the relevant patient population of research question 1 (women, prior [neo-]adjuvant endocrine therapy). The company did not present analyses on this subpopulation of research question 1 in Module 4 A of its dossier, but only prepared results for patients defined as postmenopausal in the CAPItello-291 study.

Due to the proportion of pre/perimenopausal patients in the global cohort and an unclear proportion of pre/perimenopausal patients in the expansion cohort, there is a proportion of at least 4.9% to a maximum of 26.4% of which no analyses are available for the subpopulation of the CAPItello-291 study relevant to research question 1 (women, prior [neo-]adjuvant endocrine therapy). This means that the proportion can be in a potentially relevant range. For this reason, no suitable data from the CAPItello-291 study are available for the benefit assessment of capivasertib + fulvestrant for research question 1 (women, prior [neo-]adjuvant endocrine therapy).

Derivation of added benefit through transfer of evidence

To derive an added benefit for postmenopausal patients with prior (neo-)adjuvant endocrine therapy (research question 1), the company transferred the results from postmenopausal patients of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) to postmenopausal patients of research question 1.

According to the company, a transfer of the results from patients of research question 3 to patients of research question 1 is possible solely for the reason that both patient populations received the same prior endocrine therapy.

The approach of the company is not appropriate.

Although all patients included in CAPItello-291 and FAKTION had received prior therapy with an aromatase inhibitor, the company's rationale did not take into account that some of the patients of research question 3 received further endocrine therapies or chemotherapies. It is unclear whether the total number of treatment lines received has an impact on the effects of the current treatment. It is also unclear whether the disease stage at which the patients were treated with endocrine therapy has an influence on the effects and thus whether patients with prior endocrine therapy in the locally advanced or metastatic stage (research question 3) differ from patients with prior (neo-)adjuvant endocrine therapy (research question 1).

Irrespective of this, the data presented for research question 3 are unsuitable for the benefit assessment.

Results on added benefit

Since no suitable data are available for the present research question 1, there is no hint of added benefit of capivasertib in combination with fulvestrant in comparison with the ACT; an added benefit is therefore not proven.

Research question 2 (men, prior [neo-]adjuvant endocrine therapy)

Results

The check of the completeness of the study pool revealed no RCT for the direct comparison of capivasertib + fulvestrant with the ACT for research question 2 (men, prior [neo-]adjuvant endocrine therapy). Overall, no data are available on the comparison of capivasertib + fulvestrant with the ACT for research question 2.

Results on added benefit

Since no data are available for the present research question 2, there is no hint of added benefit of capivasertib in combination with fulvestrant in comparison with the ACT; an added benefit is therefore not proven.

Research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage)

Results

Analyses presented by the company not suitable for the benefit assessment

The company identified the studies CAPItello-291 and FAKTION for the direct comparison of capivasertib + fulvestrant versus placebo + fulvestrant, for which it presented analyses with patients with PIK3CA/AKT1/PTEN alteration(s) in accordance with the approval of capivasertib.

The analyses for the FAKTION study include not only patients of research question 3 (89.5%), but also patients who can be assigned to research question 1 (10.5%). Due to the small proportion of these patients who can be assigned to research question 1 and the lack of possibility for further separation, it is appropriate to consider this subpopulation in research question 3.

A meta-analytical summary of CAPItello-291 and FAKTION is basically appropriate. However, the analyses on CAPItello-291 and FAKTION presented by the company are not suitable for the early benefit assessment of capivasertib in combination with fulvestrant in comparison with the ACT in women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage.

Lack of consideration of a relevant number of patients from the CAPItello-291 study in meta-analyses for research question 3

In accordance with the approval, fulvestrant as monotherapy is a suitable comparator therapy for postmenopausal patients of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage). In the present therapeutic indication, patients are considered to be postmenopausal who are physiologically in menopause or in whom the medical status of menopause has been induced by surgery or medication.

In accordance with the inclusion criteria of the CAPItello-291 study, all pre/perimenopausal patients received treatment with a GnRH analogue for the duration of the study, which induced the clinical status of postmenopause. These patients therefore represent part of the relevant patient population of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage). The company did not present analyses on this subpopulation of research question 3 in Module 4 A of its dossier, but only prepared results for patients defined as postmenopausal in the CAPItello-291 study.

The company's information on the global cohort of the CAPItello-291 study shows that 23 pre/perimenopausal patients who can be assigned to research question 3 (women, prior

endocrine therapy in the locally advanced or metastatic stage) were included in the intervention arm and 27 in the comparator arm. However, it is not clear from the available information how many pre/perimenopausal patients of the expansion cohort of the CAPItello-291 study belong to the relevant subpopulation of research question 3. The number of these patients ranges between 0 and 5 in the intervention arm and between 0 and 7 in the comparator arm.

To derive the added benefit of capivasertib + fulvestrant for patients of research question 3, the company used different analyses depending on the outcome and data situation.

For all outcomes except overall survival and PFS, the company's analyses were based on a meta-analytical summary of the global cohort and the expansion cohort of the CAPItello-291 study, if possible according to the company. In cases where the company stated that it was unable to conduct an effect estimation for the expansion cohort due to the small number of patients, the company only used the global cohort to derive the added benefit. For the outcome of overall survival, the company used a meta-analytical summary of the global cohort (CAPItello-291), the expansion cohort (CAPItello-291) and the FAKTION study.

Depending on the outcome, the company's approach to the meta-analytical summary resulted in different proportions of patients not included in the analyses.

For patient-relevant outcomes in categories other than mortality, which were based exclusively on analyses of the CAPItello-291 study, taking into account the proportion of pre/perimenopausal patients in the global cohort and the unclear proportion of pre/perimenopausal patients in the expansion cohort of the CAPItello-291 study, a proportion of at least 18.4% to a maximum of 27.9% was excluded from the analyses. Due to this range, it can be assumed that a relevant proportion of available evidence is not considered. Overall, therefore, no suitable data are available for these outcomes for research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage).

Based on the proportion of pre/perimenopausal patients in the global cohort and the unclear proportion of pre/perimenopausal patients in the expansion cohort, a proportion of at least 14.4% and a maximum of 17.3% is not taken into account in the analyses for the outcome of overall survival.

However, based on the analyses presented by the company, which only consider patients defined as postmenopausal in the studies, there is a statistically significant difference in favour of capivasertib + fulvestrant compared with placebo + fulvestrant for the outcome of overall survival, which would result in a major extent. However, it is unclear what influence the consideration of the available evidence on pre/perimenopausal patients has on the observed effect in the outcome overall survival. In addition, the analyses presented by the company on

morbidity, health-related quality of life and side effects already show statistically significant differences to the disadvantage of capivasertib + fulvestrant compared with placebo + fulvestrant without taking pre/perimenopausal patients into account. Despite the major effect in overall survival, no added benefit can be derived for patients with prior endocrine therapy in the locally advanced or metastatic stage, as it is not sufficiently certain that this advantage in overall survival based on the available data outweighs the disadvantageous effects when taking into account the missing evidence from pre/perimenopausal patients.

Overall, therefore, no suitable data are available for the early benefit assessment of capivasertib + fulvestrant for research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage).

Results on added benefit

Since no suitable data are available for the present research question 3, there is no hint of added benefit of capivasertib in combination with fulvestrant in comparison with the ACT; an added benefit is therefore not proven.

Research question 4 (men, prior endocrine therapy in the locally advanced or metastatic stage)

Results

The company identified the CAPItello-291 study for the direct comparison of capivasertib + fulvestrant versus the ACT. However, since only 2 men were included in the intervention arm of the global cohort study CAPItello-291, no conclusions on added or lesser benefit can be drawn for men with prior endocrine therapy in the locally advanced or metastatic stage based on this evidence.

To derive an added benefit, the company transferred the results of postmenopausal patients of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) to men of research question 4.

The approach of the company is not appropriate.

Irrespective of this, the data presented for research question 3, which the company transferred to patients of research question 4, are not suitable for the benefit assessment.

Results on added benefit

Since no suitable data are available for the present research question 4, there is no hint of added benefit of capivasertib in combination with fulvestrant in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of capivasertib in combination with fulvestrant.

Table 3: Capivasertib in combination with fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, after recurrence of the disease during or after (neo-)adjuvant endocrine therapy, no treatment to date in locally advanced or metastatic stage[b, c]	▪ Tamoxifen (only for premenopausal women who have not received tamoxifen in previous [neo-]adjuvant endocrine therapy; only for postmenopausal women if aromatase inhibitors are not suitable) or ▪ letrozole or ▪ exemestane (only for women with progression following anti-oestrogen therapy) or ▪ anastrozole or ▪ fulvestrant or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant	Added benefit not proven

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Capivasertib in combination with fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
2	Men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, after recurrence of the disease during or after (neo-)adjuvant endocrine therapy, no treatment to date in locally advanced or metastatic stage[b]	▪ tamoxifen or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)	Added benefit not proven
3	Women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage[b, d]	Treatment of physician's choice, taking into account a change of endocrine therapy to ▪ tamoxifen ▪ letrozole[e] ▪ exemestane[e] ▪ anastrozole ▪ fulvestrant[e] ▪ everolimus in combination with exemestane (only for women without symptomatic visceral metastases who have progressed after a nonsteroidal aromatase inhibitor) ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ ribociclib in combination with fulvestrant ▪ abemaciclib in combination with fulvestrant ▪ palbociclib in combination with fulvestrant	Added benefit not proven

Table 3: Capivasertib in combination with fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
4	Men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage[b]	Treatment of physician's choice[f], taking into account a change of endocrine therapy to ▪ tamoxifen ▪ aromatase inhibitor in combination with a GnRH analogue ▪ fulvestrant ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The following conditions are assumed for the present therapeutic indication:
- For patients who have already received a CDK4/6 inhibitor, retreatment with a CDK4/6 inhibitor, anastrozole or letrozole is not an option.
- An(other) endocrine therapy is indicated for the patients and, in particular, there is no indication for chemotherapy to achieve a necessary, rapid remission.
- (Secondary) resection or radiotherapy with curative intent is not indicated.
- There has been a change in treatment with respect to the drugs used for initial endocrine-based therapy.

c. Pre/perimenopausal patients are assumed to receive ovarian suppression with a GnRH analogue.
d. Pre/perimenopausal patients are assumed to continue ovarian suppression with a GnRH analogue.
e. For this patient group, treatment with fulvestrant, letrozole and exemestane, despite off-label use, is generally preferable to the approved endocrine therapies for the indication area after pretreatment with an endocrine therapy other than anti-oestrogens, in particular after pretreatment with aromatase inhibitors, according to §6 (2), sentence 3, number 3, AM-NutzenV. In accordance with the G-BA, it is therefore appropriate to determine the above-mentioned drugs as ACT for this indication area, even when used off-label.
f. The guidelines recommend the drugs tamoxifen, fulvestrant, aromatase inhibitor + GnRH analogue, as well as CDK4/6 inhibitors for the male patient group. However, in the therapeutic indication, aromatase inhibitors and fulvestrant are only approved for women. Thus, the use of aromatase inhibitors and fulvestrant in the male patient group represents an off-label use. In view of the treatment algorithm, there is a relevant indication area in the present therapeutic indication for the male patient group for which the approved drugs are not an option. In this indication area, the use of fulvestrant and aromatase inhibitors + GnRH analogue is therefore generally preferable to tamoxifen and palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole), according to §6 (2), sentence 3, number 3, AM-NutzenV. In accordance with the G-BA, it is therefore appropriate to determine the off-label use of the above-mentioned drugs as ACT.

AKT1: protein kinase B; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; CDK: cyclin-dependent kinase; ER: oestrogen receptor; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN: phosphatase and tensin homolog

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of capivasertib in combination with fulvestrant (hereinafter referred to as “capivasertib + fulvestrant”) compared with the ACT in adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations following recurrence or progression on or after an endocrine-based regimen.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of capivasertib (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, after recurrence of the disease during or after (neo-)adjuvant endocrine therapy, no treatment to date in locally advanced or metastatic stage[b, c]	▪ Tamoxifen (only for premenopausal women who have not received tamoxifen in previous [neo-]adjuvant endocrine therapy; only for postmenopausal women if aromatase inhibitors are not suitable) or ▪ letrozole or ▪ exemestane (only for women with progression following anti-oestrogen therapy) or ▪ anastrozole or ▪ fulvestrant or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant
2	Men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, after recurrence of the disease during or after (neo-)adjuvant endocrine therapy, no treatment to date in locally advanced or metastatic stage[b]	▪ tamoxifen or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)

Table 4: Research questions of the benefit assessment of capivasertib (multipage table)

Research question	**Therapeutic indication**	**ACT[a]**
3	Women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage[b, d]	Treatment of physician's choice, taking into account a change of endocrine therapy to ▪ tamoxifen ▪ letrozole[e] ▪ exemestane[e] ▪ anastrozole ▪ fulvestrant[e] ▪ everolimus in combination with exemestane (only for women without symptomatic visceral metastases who have progressed after a nonsteroidal aromatase inhibitor) ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ ribociclib in combination with fulvestrant ▪ abemaciclib in combination with fulvestrant ▪ palbociclib in combination with fulvestrant
4	Men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage[b]	Treatment of physician's choice[f], taking into account a change of endocrine therapy to ▪ tamoxifen ▪ aromatase inhibitor in combination with a GnRH analogue ▪ fulvestrant ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)

Table 4: Research questions of the benefit assessment of capivasertib (multipage table)

Research question	Therapeutic indication	ACT[a]
a. Presented is the respective ACT specified by the G-BA. b. The following conditions are assumed for the present therapeutic indication: ▫ For patients who have already received a CDK4/6 inhibitor, retreatment with a CDK4/6 inhibitor, anastrozole or letrozole is not an option. ▫ An(other) endocrine therapy is indicated for the patients and, in particular, there is no indication for chemotherapy to achieve a necessary, rapid remission. ▫ (Secondary) resection or radiotherapy with curative intent is not indicated. ▫ There has been a change in treatment with respect to the drugs used for initial endocrine-based therapy. c. Pre/perimenopausal patients are assumed to receive ovarian suppression with a GnRH analogue. d. Pre/perimenopausal patients are assumed to continue ovarian suppression with a GnRH analogue. e. For this patient group, treatment with fulvestrant, letrozole and exemestane, despite off-label use, is generally preferable to the approved endocrine therapies for the indication area after pretreatment with an endocrine therapy other than anti-oestrogens, in particular after pretreatment with aromatase inhibitors, according to §6 (2), sentence 3, number 3, AM-NutzenV. In accordance with the G-BA, it is therefore appropriate to determine the above-mentioned drugs as ACT for this indication area, even when used off-label. f. The guidelines recommend the drugs tamoxifen, fulvestrant, aromatase inhibitor + GnRH analogue, as well as CDK4/6 inhibitors for the male patient group. However, in the therapeutic indication, aromatase inhibitors and fulvestrant are only approved for women. Thus, the use of aromatase inhibitors and fulvestrant in the male patient group represents an off-label use. In view of the treatment algorithm, there is a relevant indication area in the present therapeutic indication for the male patient group for which the approved drugs are not an option. In this indication area, the use of fulvestrant and aromatase inhibitors + GnRH analogue is therefore generally preferable to tamoxifen and palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole), according to §6 (2), sentence 3, number 3, AM-NutzenV. In accordance with the G-BA, it is therefore appropriate to determine the off-label use of the above-mentioned drugs as ACT. AKT1: protein kinase B; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; CDK: cyclin-dependent kinase; ER: oestrogen receptor; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN: phosphatase and tensin homolog		

For better readability, the research questions defined by the G-BA are abbreviated below as follows:

- Research question 1: women, prior (neo-)adjuvant endocrine therapy
- Research question 2: men, prior (neo-)adjuvant endocrine therapy
- Research question 3: women, prior endocrine therapy in the locally advanced or metastatic stage
- Research question 4: men, prior endocrine therapy in the locally advanced or metastatic stage

The G-BA's most recent adjustments to the subdivision of the therapeutic indication into several research questions and the ACTs were made on 26 November 2024. This resulted in

the research questions and ACTs as presented in Table 4. In its dossier, the company referred to the research questions and their ACTs from the consultation with the G-BA on 24 April 2024. The company therefore addressed a total of 6 research questions or subpopulations in its dossier, differentiated by prior therapy, sex, and additionally by menopausal status (pre/perimenopausal versus postmenopausal) in women:

- Research question a1: pre/perimenopausal women, prior (neo-)adjuvant endocrine therapy
- Research question a2: postmenopausal women, prior (neo-)adjuvant endocrine therapy
- Research question a3: men, prior (neo-)adjuvant endocrine therapy
- Research question b1: pre/perimenopausal women, prior endocrine therapy in the locally advanced or metastatic stage
- Research question b2: postmenopausal women, prior endocrine therapy in the locally advanced or metastatic stage
- Research question b3: men, prior endocrine therapy in the locally advanced or metastatic stage

The company stated that it was following the ACT defined at that time, but described in Module 3 A, with reference to medical societies, that it did not consider differentiation according to menopausal status to be biologically or medically plausible. The research questions with the corresponding ACTs addressed by the company can be found in I Appendix B of the full dossier assessment. The present benefit assessment is conducted in comparison with the research questions and their ACTs specified by the G-BA on 26 November 2024 (see Table 4).

The company determined the added benefit of capivasertib for its research questions a2 (postmenopausal women, prior [neo-]adjuvant endocrine therapy), b2 (postmenopausal women, prior endocrine therapy in the locally advanced or metastatic stage) and b3 (men, prior endocrine therapy in the locally advanced or metastatic stage) in comparison with fulvestrant. For the other research questions, the company stated that no data in comparison with the ACT were available.

The G-BA pointed out that the drugs anastrozole, fulvestrant and everolimus are explicitly approved for use in postmenopausal women. According to the BfArM, the approvals for anastrozole, fulvestrant and everolimus do not formally exclude patients whose menopause has been induced by surgery or medication. The ACTs with anastrozole, fulvestrant or everolimus determined here therefore include patients who are physiologically in menopause or in whom the medical status of menopause has been induced by surgery or medication. The

company used a different definition, as its analyses did not include pre- and perimenopausal patients whose menopause was induced by GnRH analogues (see below).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1 (women, prior [neo-]adjuvant endocrine therapy

I 3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on capivasertib (status: 8 August 2024)
- bibliographical literature search on capivasertib (last search on 31 July 2024)
- search in trial registries/trial results databases for studies on capivasertib (last search on 31 July 2024)
- search on the G-BA website for capivasertib (last search on 7 August 2024)

To check the completeness of the study pool:

- search in trial registries for studies on capivasertib (last search on 22 October 2024); for search strategies, see I Appendix A of the full dossier assessment

The company identified the studies CAPItello-291 [3-8] and FAKTION [9-12] for the direct comparison of capivasertib + fulvestrant versus placebo + fulvestrant, for which it presented analyses with patients with PIK3CA/AKT1/PTEN alteration(s) in accordance with the approval of capivasertib [13].

According to the Summary of Product Characteristics (SPC), fulvestrant as monotherapy, which was used as comparator in CAPItello-291 and FAKTION, is explicitly approved in postmenopausal women [14] and is therefore an ACT only for these women. In Module 4 A and the associated Appendix 4 G, in accordance with the original consultation by the G-BA on 24 April 2024, the company only presented results for women who were classified as postmenopausal according to the study protocol (for the definition in the studies, see I 3.1.1.1 and I 3.1.1.2). The company excluded from its analyses pre- and perimenopausal women whose menopause was induced by GnRH analogues in the CAPItello-291 study. The G-BA pointed out that, in addition to patients who are physiologically in menopause or in whom the medical status of menopause has been induced by surgery, patients in whom the medical status of menopause has been induced by medication are also classified as postmenopausal in the present therapeutic indication.

The consequences for the benefit assessment resulting from the absence of pre- and perimenopausal patients with drug-induced menopause are explained below. The studies CAPItello-291 and FAKTION and the company's approach for deriving an added benefit for patients of research question 1 are described first.

No additional relevant study was identified from the check of the completeness of the study pool.

I 3.1.1 Evidence presented

I 3.1.1.1 CAPItello-291 study

The CAPItello-291 study is an ongoing, multicentre phase 3 RCT for the direct comparison of capivasertib + fulvestrant with placebo + fulvestrant. It included adult women (pre/perimenopausal and postmenopausal) and men with unresectable, locally advanced or metastatic HR-positive, HER2-negative breast cancer. Patients with and without an PIK3CA/AKT1/PTEN alterations were enrolled. However, the PIK3CA/AKT1/PTEN alteration status was determined at enrolment, using the FoundationOne CDx (F1CDx) test.

To be eligible for enrolment, patients had to have a recurrence or progression during or after treatment with an aromatase inhibitor. In the case of neoadjuvant or adjuvant therapy, recurrence or progression must have occurred during therapy or within 12 months of the end of therapy. In the locally advanced or metastatic stage, however, the aromatase inhibitor did not have to be part of the most recent therapy. Furthermore, eligible patients were not allowed to have received more than 2 prior lines of endocrine therapy or more than one prior line of chemotherapy for inoperable locally advanced or metastatic disease. At enrolment, patients also had to have Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1. Patients were considered postmenopausal if one of the following criteria applied:

- age ≥ 60 years
- age < 60, amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments, chemotherapy, ovarian suppression, tamoxifen or similar, as well as oestradiol and FSH levels within the normal postmenopausal range
- documented bilateral oophorectomy

Randomization in the CAPItello-291 study was in a 1:1 ratio, stratified according to liver metastases (yes versus no), prior treatment with cyclin-dependent kinase (CDK)4/6 inhibitors (yes versus no), and geographic location (region 1 [United States, Canada, Western Europe, Australia, and Israel] versus region 2 [Latin America, Eastern Europe, and Russia] versus region 3 [Asia]). The CAPItello-291 study comprises a global cohort and a China expansion cohort (named by the company, hereinafter referred to as “expansion cohort”), which recruited additional patients in China and Taiwan after randomization of the global cohort was completed. The global cohort comprises a total of 355 patients in the intervention arm and 353 patients in the comparator arm. The expansion cohort comprises a total of 71 patients in the intervention arm and 63 patients in the comparator arm. In the global cohort, the relevant

subpopulation with PIK3CA/AKT1/PTEN alterations according to the approval of capivasertib comprises 155 patients in the intervention arm and 134 patients in the comparator arm. In the expansion cohort, the subpopulation with PIK3CA/AKT1/PTEN alterations comprises 24 patients in the intervention arm and 22 patients in the comparator arm. Chinese and Taiwanese patients who were randomized into the expansion cohort before the planned end of recruitment into the global cohort are part of both the global cohort and the expansion cohort. To avoid double analysis of these patients, the company stated that they were assigned only to the global cohort in the analyses in Module 4 A of the dossier, and that the expansion cohort was reduced by these patients. The number of patients within the population with PIK3CA/AKT1/PTEN alterations who would be considered exclusively in the expansion cohort is unclear, as only information on the number of postmenopausal women according to the study definition is available. These were 14 patients in the intervention arm and 11 patients in the comparator arm.

In accordance with their randomization, patients in the intervention arm received approval-compliant capivasertib 400 mg orally twice daily on Days 1–4 of each week of the 28-day treatment cycles [13]. Analogous placebo was administered in the comparator arm. Patients in both treatment arms also received intramuscular therapy with 500 mg fulvestrant on Day 1 of Weeks 1 and 3 of the first cycle and on Day 1 of each subsequent 28-day treatment cycle. The dosage of fulvestrant corresponds to the specifications in the SPCs of capivasertib and fulvestrant [13,14]. Treatment with the study medication was conducted until disease progression, unacceptable toxicity, withdrawal of consent, or death. In addition to the study medication, pre- and perimenopausal patients were to receive concomitant treatment with a menopause-inducing GnRH analogue from Day 1 of the first cycle at the latest until the end of the study. Men could also receive treatment with a GnRH analogue at the discretion of the investigator. With few exceptions, supportive therapy at the discretion of the investigator was generally allowed (see also Table 10 of the full dossier assessment). There is no information on how many patients in the relevant subpopulations of the individual research questions (according to the G-BA) had metastases located in bone and locomotor sites and received osteoprotective therapy in accordance with guideline recommendation [15-17]. The study documents only contain information on the total population with PIK3CA/AKT1/PTEN alterations of the CAPItello-291 global cohort with metastases located in bone and locomotor sites. Only 60% of these patients received osteoprotective therapy. Data on the expansion cohort are not available for the population with PIK3CA/AKT1/PTEN alterations. Up to 2 dose reductions of capivasertib or placebo were permitted in case of adverse events (AEs). Dose reduction of fulvestrant was not allowed, however.

The primary outcome of the CAPItello-291 study was PFS. Outcomes in the categories of mortality, morbidity, health-related quality of life, and side effects were additionally recorded.

For the global cohort of the CAPItello-291 study, data are available for 2 time points of analysis: a prespecified data cut-off from 15 August 2022, which was planned after the occurrence of disease progression in 77% of the study population or the population with PIK3CA/AKT1/PTEN alterations, and a non-prespecified analysis from 27 March 2023, which was not explicitly requested by the regulatory authorities and was prepared as part of a Day 120 Safety Update Report for the Food and Drug Administration (FDA). A prespecified data cut-off from 8 May 2023 is currently available for the expansion cohort. As for the global cohort, this was planned after the occurrence of disease progression in 77% of the study population or the population with PIK3CA/AKT1/PTEN alterations. The final data cut-off of the CAPItello-291 study is planned after the death of 70% of the study population or the population with PIK3CA/AKT1/PTEN alterations.

For a characterization of the CAPItello-291 study, see also Table 9 and Table 10 in I Appendix B of the full dossier assessment.

I 3.1.1.2 FAKTION study

The FAKTION study is a 2-part study with an initial dose escalation phase and a subsequent double-blind, multicentre phase 2 RCT conducted in the United Kingdom. As the company was not the sponsor of the study, it obtained its information from 2 publications [9,10]. The current status of the study is unknown (estimated study completion according to clinicaltrials.gov: December 2023) [12]. For the early benefit assessment, only the randomized part of the FAKTION study is considered below. This part investigated the direct comparison of capivasertib + fulvestrant versus placebo + fulvestrant. Adult, postmenopausal patients with inoperable, locally advanced or metastatic, ER-positive, HER2-negative breast cancer were enrolled.

Patients were categorized as postmenopausal if they met one of the following criteria:

- Amenorrhoeic throughout and after therapy with a 3rd generation aromatase inhibitor, but without a GnRH analogue, as well as oestradiol and FSH levels within normal postmenopausal ranges at screening for the FAKTION study. If FSH was not in the normal postmenopausal range, the patients could be considered eligible after consultation provided they had been clinically postmenopausal for ≥ 5 years.
- The patient had been treated for early or metastatic breast cancer with a 3rd generation aromatase inhibitor and GnRH analogue, with no resumption of menstruation after treatment discontinuation for ≥ 6 months. In addition, oestradiol and FSH levels at screening in the FAKTION study had to be in normal postmenopausal ranges.
- The patient had received an aromatase inhibitor and GNRH analogue combined and subsequently had bilateral oophorectomy.

To be enrolled, patients also had to have either progressive disease whilst receiving a 3rd generation aromatase inhibitor in the locally advanced or metastatic stage, or relapsed with metastatic disease whilst receiving a 3rd generation aromatase inhibitor in the adjuvant setting. However, the aromatase inhibitor did not have to be part of the most recent therapy immediately before enrolment. Patients were not allowed to have received more than 3 lines of endocrine therapy or more than one prior line of chemotherapy for locally advanced or metastatic disease. Patients with ECOG PS ≤ 2 were eligible.

Randomization was in a 1:1 ratio using minimization based on the characteristics of PIK3CA alteration status (altered versus wild type), PTEN expression status (0/1+ in < 10% of tumour cells versus > 1+ or 1+ in ≥ 10% of tumour cells [discrepant information between Module 4 A and the study documents, information according to the statistical analysis plan]), measurable versus non-measurable disease and primary versus secondary resistance to a 3rd generation aromatase inhibitor. The intervention arm included a total of 69 patients, and the comparator arm included 71 patients. The PIK3CA alteration status was determined by pyrosequencing or digital droplet polymerase chain reaction (ddPCR); the PTEN level was determined by immunohistochemistry (IHC). These molecular analyses were also used to assign the patients to the subpopulation with PIK3CA/AKT1/PTEN alterations. For the publication by Howell et al., a prespecified, additional analysis of the biosamples for further relevant mutations of the PIK3CA/AKT1/PTEN signalling pathway was carried out to allow a more comprehensive identification of the so-called “expanded pathway-altered subgroup”. Patients were assigned to this more comprehensive subpopulation if the analysed biosamples tested positive for one of the expanded alterations using pyrosequencing, ddPCR or next generation sequencing (NGS) [9]. The tests used for the NGS analyses were the FoundationOne CDx (F1CDx) NGS Clinical Trial Assay (for tissue samples) and the GuardantOMNI RUO (for plasma samples). The analyses of the FAKTION subpopulation with PIK3CA/AKT1/PTEN alterations in Module 4 A of the dossier are based on this patient population identified by expanded testing. The FAKTION subpopulation with PIK3CA/AKT1/PTEN alterations comprises a total of 39 patients in the intervention arm and 37 patients in the comparator arm.

In accordance with their randomization, patients in the intervention arm received mostly approval-compliant treatment with capivasertib [13]. This corresponded to oral administration of 400 mg capivasertib twice daily on Days 1–4 of each week of the 28-day treatment cycles, starting on Day 15 of Cycle 1. Analogous placebo was administered in the comparator arm. Patients in both treatment arms also received intramuscular therapy with 500 mg fulvestrant on Day 1 of Weeks 1 and 3 of the first cycle and on Day 1 of Week 1 of each subsequent 28-day treatment cycle. The dosage of fulvestrant corresponds to the specifications in the SPCs of capivasertib and fulvestrant [13,14]. Treatment was conducted until disease progression, unacceptable toxicity, or withdrawal of consent. With few exceptions, supportive therapy at the discretion of the investigator was generally allowed. No

information is available on how many patients with bone metastases received osteoprotective therapy. This therapy is recommended for patients with metastases located in bone and locomotor sites [15-17]. If AEs occurred, up to 3 dose reductions of capivasertib or placebo were permitted (3rd dose reduction only after consultation with the principal investigator). Deviating from this, the approval of capivasertib allows for a maximum of 2 dose reductions, with the dose of the 2nd dose reduction (200 mg) being lower than the 240 mg administered after the 2nd dose reduction in the FAKTION study [13]. However, in the entire study population, only a few patients required ≥ 2 dose reductions [10]. Contrary to the SPCs, which do not provide for a dose reduction of fulvestrant, fulvestrant could be reduced to 250 mg in the FAKTION study after consultation with the principal investigator [13,14]. Information on subsequent antineoplastic therapies is not reported for the FAKTION study.

The primary outcome of the FAKTION study is PFS. Overall survival and side effect outcomes were also recorded.

Data cut-offs from 30 January 2019 and 25 November 2021 are available. The company's analyses are based on the publication by Howell et al. [9] for the data cut-off of 25 November 2021.

I 3.1.2 Approach of the company

I 3.1.2.1 CAPItello-291 study

The present therapeutic indication for capivasertib includes adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations following recurrence or progression on or after an endocrine-based regimen [13]. The CAPItello-291 and FAKTION subpopulations relevant for the early benefit assessment thus exclusively comprise patients with confirmed PIK3CA/AKT1/PTEN alteration. In addition, research question 1 only comprises patients with prior (neo-)adjuvant endocrine therapy who have not yet received therapy in the locally advanced or metastatic stage.

In Module 4 A, the company used results from the CAPItello-291 populations with PIK3CA/AKT1/PTEN alterations exclusively for postmenopausal women as defined in the study protocols (i.e. excluding pre/perimenopausal women whose menopause was induced by GnRH analogues). In principle, however, there are also data from the CAPItello-291 study for pre/perimenopausal women with drug-induced menopause, who can also be assigned to research question 1 (see Section I 2).

In Appendix 4 G of the dossier, the company presented analyses of patients classified as postmenopausal according to the CAPItello-291 study protocol of research question 1 (women with prior [neo]adjuvant endocrine therapy) only as supplementary information and

separately for the global cohort (13 versus 18 patients) and the expansion cohort (3 versus 5 patients) (for the number of patients in research question 1, see also Table 5). The company derived an added benefit for patients of research question 1 by transferring the evidence presented by the company for research question 3 (see Section I 3.1.2.3). Analyses of pre/perimenopausal patients undergoing therapy with a GnRH analogue are not available. Thus, analyses of the available evidence from the CAPItello-291 study are only available for part of the subpopulation relevant to research question 1 (women, prior [neo-]adjuvant endocrine therapy).

I 3.1.2.2 FAKTION study

For the FAKTION study, the company described that 8 of the 76 included patients with PIK3CA/AKT1/PTEN alteration(s) (10.5%) could be assigned to research question 1 (a2 of the company), but that it only had access to the data published as part of the full publications due to its involvement in the external funding of the study, and that a separate analysis of the results for research question 1 was not available. Since, at 89.5% of patients, a large proportion of the study's subpopulation with PIK3CA/AKT1/PTEN alterations was attributable to research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage), the company presented the results of the FAKTION study under research question 3 (b2 of the company).

I 3.1.2.3 Derivation of added benefit through transfer of evidence

To derive an added benefit for postmenopausal patients with prior (neo-)adjuvant endocrine therapy (research question 1), the company transferred the results from postmenopausal patients of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) to postmenopausal patients of research question 1. The company justified its approach with the fact that due to the small number of patients in this subpopulation, the effect estimates from the CAPItello-291 study alone could not be used to derive the added benefit and that, in its view, patients with recurrence during or after endocrine therapy in the (neo-)adjuvant treatment stage (subpopulation a2 of the company) did not differ therapeutically from patients with recurrence during or after the same endocrine therapy in the locally advanced or metastatic treatment stage (subpopulation b2 of the company). The company therefore did not consider the stage at which treatment with a particular endocrine therapy was started as relevant for the treatment decision, but the drugs used in prior therapy. It added, that this was also shown in the lack of heterogeneity in the meta-analysis between the subpopulations a2 and b2 of the global cohort of the CAPItello-291 study and the FAKTION study, which the company additionally presented. The company did not consider the patients in the expansion cohort in its meta-analytical summary.

I 3.1.3 Assessment of the company's approach and consequence for the benefit assessment

I 3.1.3.1 Unclear proportion of patients from the CAPItello-291 study not taken into account for research question 1

In accordance with the approval, fulvestrant as monotherapy is a suitable comparator therapy for postmenopausal patients of research question 1 (women, prior [neo-]adjuvant endocrine therapy). In the present therapeutic indication, analogous to the explanation in Section I 2, patients are considered to be postmenopausal who are physiologically in menopause or in whom the medical status of menopause has been induced by surgery or medication.

In accordance with the inclusion criteria of the CAPItello-291 study, all pre/perimenopausal patients received treatment with a GnRH analogue for the duration of the study. These patients therefore represent part of the relevant patient population of research question 1 (women, prior [neo-]adjuvant endocrine therapy). The company did not present analyses on this subpopulation of research question 1 in Module 4 A of its dossier, but only prepared results for patients defined as postmenopausal in the CAPItello-291 study.

Table 5 shows the distribution of patients relevant to research question 1 by menopausal status and CAPItello-291 cohort, as well as the proportion of patients not included in the analyses presented by the company for research question 1.

Table 5: Overview of the number of patients of research question 1 and proportions missing in the analyses

Menopausal status	**Cohort (CAPItello-291)**	**Number of patients [intervention vs. comparison]**	**Proportion of missing patients[a]**		
Pre/perimenopausal	Global cohort	0 vs. 2[b]		Intervention vs. comparator	Total
	Expansion cohort	min: 0 vs. 0[b] max: 5 vs. 7[b]			
Postmenopausal	Global cohort	13 vs. 18	Scenario 1:	0.0% vs. 8.0%	4.9%
	Expansion cohort	3 vs. 5	Scenario 2:	23.8% vs. 28.1%	26.4%

a. It is unclear how many pre/perimenopausal patients of the expansion cohort can be assigned to research question 1. A distinction is therefore made between 2 extreme scenarios:
- Scenario 1: none of the patients can be assigned to research question 1
- Scenario 2: all of the patients can be assigned to research question 1 and no patient is already included in the global cohort for the analysis

b. Institute's calculation.

max: maximum; min: minimum

The information provided by the company shows that 2 pre/perimenopausal patients of the global cohort of the CAPItello-291 study can be assigned to the comparator arm of the relevant subpopulation of research question 1 (women, prior [neo-]adjuvant endocrine therapy). However, it is not clear from the available information how many pre/perimenopausal patients of the expansion cohort of the CAPItello-291 study belong to the relevant subpopulation of research question 1 (women, prior [neo-]adjuvant endocrine therapy). The number of these patients ranges between 0 and 5 in the intervention arm and between 0 and 7 in the comparator arm. Taking into account this range of the expansion cohort and the 2 pre/perimenopausal patients of the global cohort belonging to the relevant subpopulation, there are no analyses of a proportion of at least 4.9% to a maximum of 26.4% of the subpopulation of the CAPItello-291 study relevant to research question 1 (women, prior [neo-]adjuvant endocrine therapy). The proportion is unclear, but can be in a potentially relevant range. Due to this unclear proportion of patients excluded from the analyses, no suitable data from the CAPItello-291 study are available for the benefit assessment of capivasertib + fulvestrant for research question 1 (women, prior [neo-]adjuvant endocrine therapy).

I 3.1.3.2 Non-consideration of the FAKTION study for research question 1

As described above, the FAKTION subpopulation with PIK3CA/AKT1/PTEN alterations included 8 patients (10.5%) who had not received prior endocrine therapy in the locally advanced or metastatic stage [9]. Based on the publicly available data, no separate analyses are available for these patients.

Due to the high proportion of patients (89.5%) assigned to research question 3, the company's approach of considering the available analyses there is understandable. Overall, there are therefore no suitable data from the FAKTION study for the relevant subpopulation of research question 1 (women, prior [neo-]adjuvant endocrine therapy).

I 3.1.3.3 Derivation of added benefit through transfer of evidence

The company justified its approach of transferring results of patients from research question 3 to patients from research question 1 with uninformative effect estimates due to few patients included in the analysis of research question 1. The company further argued that, in its view, patients with recurrence during or after endocrine therapy in the (neo-)adjuvant treatment stage (research question 1) in the CAPItello-291 study did not differ therapeutically in terms of prior endocrine therapy from patients with recurrence during or after the same endocrine therapy in the locally advanced or metastatic treatment stage (research question 3).

According to the company, a transfer of the results from patients of research question 3 to patients of research question 1 is possible solely for the reason that both patient populations received the same prior endocrine therapy.

The approach of the company is not appropriate.

Although all patients included in CAPItello-291 and FAKTION had received prior therapy with an aromatase inhibitor, the company's rationale did not take into account that some of the patients of research question 3 received further endocrine therapies or chemotherapies. It is unclear whether the total number of treatment lines received has an impact on the effects of the current treatment. It is also unclear whether the disease stage at which the patients were treated with endocrine therapy has an influence on the effects and thus whether patients with prior endocrine therapy in the locally advanced or metastatic stage (research question 3) differ from patients with prior (neo-)adjuvant endocrine therapy (research question 1). The company provided no further information to support the transfer of evidence.

In principle, data are available on patients who can be assigned to research question 1. In relation to the patients classified as postmenopausal according to the study protocol, there are 39 patients (31 patients from the global cohort and 8 patients from the expansion cohort, see Table 5). In addition, 2 pre/perimenopausal patients from the global cohort and up to 12 pre/perimenopausal patients from the expansion cohort are also relevant for research question 1. Overall, data on at least 41 and a maximum of 53 patients with recurrence during or after endocrine therapy in the (neo-)adjuvant treatment stage are available from the CAPItello-291 study.

Irrespective of this, the lack of heterogeneity in the meta-analyses presented by the company for overall survival and PFS is not a sufficient reason to transfer the evidence from research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) to research question 1.

Regardless of this, the data presented for research question 3 are not suitable for the benefit assessment (see Section I 5).

In general, the available data on women with recurrence during or after endocrine therapy in the (neo-)adjuvant treatment stage should be used for the present research question 1.

I 3.1.3.4 Summary

Based on the uncertainties described regarding the unclear proportion of disregarded evidence from the CAPItello-291 study and the lack of suitable data from the FAKTION study, there are no suitable data overall for the derivation of an added benefit of capivasertib in combination with fulvestrant compared with the ACT fulvestrant for research question 1 (women, prior [neo-]adjuvant endocrine therapy). The transfer of results from research question 3 to research question 1 is not appropriate. In principle, data are available on patients who can be assigned to research question 1.

I 3.1.4 Further points of criticism

No data on AE outcomes at the prespecified data cut-off for the relevant subpopulation

As described in Section I 3.1.1.1, for the CAPItello-291 study, in addition to the data cut-off from 15 August 2022 decisive for the present dossier assessment, the company presented an analysis from 27 March 2023 prepared for the FDA as part of a Day 120 Safety Update Report, which, as the company itself stated, was not prespecified. This analysis as part of a Day 120 Safety Update Report is a regular part of the approval procedure in the FDA's assessment process and was not explicitly requested. The analyses on AE outcomes in the relevant subpopulation of research question 1 (women, prior [neo-]adjuvant endocrine therapy) presented by the company in Module 4 A are based exclusively on this analysis; corresponding analyses on AEs based on the prespecified data cut-off of 15 August 2022 decisive for the dossier assessment are not available. This means that analyses are not available for all relevant outcomes for the relevant data cut-off from 15 August 2022, as required in the module template.

Meta-analytical summary of the results of the CAPItello-291 study

As described above, the CAPItello-291 study comprises both a global cohort and an expansion cohort. Separate study protocols are available for each cohort, but they do not differ notably, so that the 2 cohorts of the CAPItello-291 study can be considered as one study population in the present situation. Besides, according to the company, patients who were randomized into the expansion cohort before the planned end of recruitment into the global cohort are part of both the global cohort and the expansion cohort. In the analyses of Module 4 A of the dossier, these patients were assigned exclusively to the global cohort according to the company's information. In places where the company considered all patients in the CAPItello-291 study of a research question together in its dossier, the meta-analytical summary is based on the aggregated effect estimates of the individual cohorts. For some outcomes, the company stated that an effect estimation for the expansion cohort was not possible due to low event numbers. As a result, only the results of the global cohort of the CAPItello-291 study were included in the relevant outcomes. The approach of the company is not appropriate. In the present situation, as described above, the 2 cohorts of the CAPItello-291 study can be considered as one study population. One way to consider the expansion cohort even in cases where no effect estimation is possible for the expansion cohort alone is a meta-analytical summary of all patients in the CAPItello-291 study at the level of individual patient data. This should also take into account pre/perimenopausal women, as they are also to be classified as postmenopausal due to treatment with GnRH agonists.

Subgroup analyses for the CAPItello-291 study

In Appendix 4 G of its dossier, the company presented supplementary subgroup analyses of postmenopausal women with prior (neo-)adjuvant endocrine therapy according to the study

protocol, separated by global cohort and expansion cohort of the CAPItello-291 study, for research question 1. Pre/perimenopausal patients were not taken into account in the subgroup analyses presented. However, due to the drug-induced menopause, these patients are also to be classified as postmenopausal and are therefore relevant for the present research question (see Section I 2). The company presented no subgroup analyses on a priori defined characteristics, e.g. separately according to the characteristics of bone metastases (yes versus no) or visceral metastases (yes versus no), in Module 4 A. The company justified this with the fact that these patients were already comprised by further subgroup analyses, some of which were conducted post hoc. According to the module template, however, for patient-relevant outcomes, all subgroup analyses planned a priori and defined in the study protocol must be presented in Module 4 A of the dossier.

Besides the presentation of all predefined subgroup analyses, subgroup analyses with regard to the biological menopausal status (pre/perimenopausal versus postmenopausal) should also be presented for the relevant subpopulation of research question 1 (women, prior[neo-]adjuvant endocrine therapy).

I 3.2 Results on added benefit

No suitable data are available to assess the added benefit of capivasertib in combination with fulvestrant in comparison with the ACT in women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer and recurrence of the disease during or after (neo-)adjuvant endocrine therapy, who have not yet received any treatment in the locally advanced or metastatic stage. For these patients, there is no hint of an added benefit of capivasertib in combination with fulvestrant compared with the ACT; an added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

As the company presented no suitable data for the assessment of the added benefit of capivasertib in combination with fulvestrant compared with the ACT in women of research question 1, an added benefit for these patients is not proven.

The assessment described above does not correspond to that of the company, which derived a non-quantifiable added benefit based on a transfer of the results from the patients classified as postmenopausal according to the study protocol of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) to postmenopausal women of research question 1 (women, [neo-]adjuvant endocrine therapy). The company did not provide any information on the certainty of conclusions.

I 4 Research question 2 (men, prior [neo-]adjuvant endocrine therapy)

I 4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on capivasertib (status: 8 August 2024)
- bibliographical literature search on capivasertib (last search on 31 July 2024)
- search in trial registries/trial results databases for studies on capivasertib (last search on 31 July 2024)
- search on the G-BA website for capivasertib (last search on 7 August 2024)

To check the completeness of the study pool:

- search in trial registries for studies on capivasertib (last search on 22 October 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool revealed no RCT for the direct comparison of capivasertib + fulvestrant with the ACT for research question 2 (men, prior [neo-]adjuvant endocrine therapy). Overall, no data are available on the comparison of capivasertib + fulvestrant with the ACT for research question 2.

I 4.2 Results on added benefit

No data are available to assess the added benefit of capivasertib in combination with fulvestrant in comparison with the ACT in men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer and recurrence of the disease during or after (neo-)adjuvant endocrine therapy, who have not yet received any treatment in the locally advanced or metastatic stage. For these patients, there is no hint of an added benefit of capivasertib in combination with fulvestrant compared with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

As the company presented no data to assess the added benefit of capivasertib in combination with fulvestrant in comparison with the ACT in men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer and recurrence of the disease during or after (neo-)adjuvant endocrine therapy, who have not yet received any treatment in the locally advanced or metastatic stage, an added benefit for these patients is not proven.

The assessment described above concurs with that by the company.

I 5 Research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage)

I 5.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on capivasertib (status: 8 August 2024)
- bibliographical literature search on capivasertib (last search on 31 July 2024)
- search in trial registries/trial results databases for studies on capivasertib (last search on 31 July 2024)
- search on the G-BA website for capivasertib (last search on 7 August 2024)

To check the completeness of the study pool:

- search in trial registries for studies on capivasertib (last search on 22 October 2024); for search strategies, see I Appendix A of the full dossier assessment

For the direct comparison of capivasertib + fulvestrant versus the ACT, the company identified the studies CAPItello-291 [3-8] and FAKTION [9-12], for which it presented analyses with patients with PIK3CA/AKT1/PTEN alteration(s) in accordance with the approval of capivasertib [13]. In its analyses for research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage), the company used different meta-analytical summaries depending on the outcome and data availability, combining the CAPItello-291 global cohort, the CAPItello-291 expansion cohort, and the FAKTION study.

According to the SPC, fulvestrant as monotherapy, which was used as comparator in CAPItello-291 and FAKTION, is explicitly approved in postmenopausal women [14] and is therefore an ACT only for these women. In Module 4 A of its dossier, the company only presented analyses of women with prior endocrine therapy in the locally advanced or metastatic stage who were classified as postmenopausal according to the study protocols of the 2 studies. No analyses of pre/perimenopausal patients whose menopause was induced by GnRH analogues in the CAPItello-291 study are available. However, such patients were also included in the CAPItello-291 study and are to be classified as postmenopausal (see Section I 2). This means that some of the patients relevant to research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) were not included in the analyses of the CAPItello-291 study. The analyses presented by the company are not suitable for the present benefit assessment (see Section I 5.1.3).

No additional relevant study was identified from the check of the completeness of the study pool.

I 5.1.1 Evidence presented

I 5.1.1.1 CAPItello-291 and FAKTION

A detailed description of CAPItello-291 and FAKTION can be found in Section I 3.1 of the dossier assessment.

The relevant subpopulation of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) comprises different numbers of patients depending on the outcome. For the results of the outcome of overall survival, which also include those of the FAKTION study, the number of patients is at least 347 and at most 359. For all other outcomes in which the FAKTION study is not taken into account, the minimum number of patients is 271 and the maximum 283. For a detailed presentation of patient numbers according to menopausal status and study or cohort of the CAPItello-291 study, see Section I 5.1.3.1.

Implementation of the treatment of physician's choice

For women with prior endocrine therapy in the locally advanced or metastatic stage in the therapeutic indication of capivasertib, the G-BA specified treatment of physician's choice, taking into account a change of endocrine therapy to several treatment options (see Table 4). The company used fulvestrant as a comparator. The company did not provide an explicit justification for choosing fulvestrant as treatment of physician's choice for patients of research question 3. However, independent of the research questions and without reference to the studies, it described that the optimal sequence and integration of available endocrine drugs are influenced by the choice of prior therapies, response, duration of response, tolerability, patient preference and individual patient and disease characteristics, citing various guidelines [15,17-20]. For the CAPItello-291 study, it explained that, according to the inclusion criteria, the entire study population had been pretreated with aromatase inhibitors, a large proportion with CDK4/6 inhibitors and around half with tamoxifen, and that the first-time treatment with fulvestrant as part of the study ensured that a treatment switch to the previous endocrine or endocrine-based therapy had taken place. The company provided no corresponding information for the FAKTION study.

According to the notes on the ACT, retreatment with CDK4/6 inhibitors or anastrozole or letrozole is not an option for patients. It is also assumed that there has been a change in treatment with respect to the drugs used for initial endocrine-based therapy. This was the case with the use of fulvestrant.

To be enrolled in the FAKTION study, patients had to have either progressive disease whilst receiving a 3rd generation aromatase inhibitor in the locally advanced or metastatic stage, or relapsed with metastatic disease whilst receiving a 3rd generation aromatase inhibitor in the adjuvant setting. According to national and European guidelines, the use of fulvestrant is a suitable treatment option for patients with recurrence or progression after previous endocrine therapy, e.g. with an aromatase inhibitor [15,17,20].

Overall, the use of fulvestrant in CAPItello-291 and FAKTION is a sufficient implementation of treatment of physician's choice, taking into account a change of endocrine therapy for research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage).

I 5.1.2 Approach of the company

I 5.1.2.1 CAPItello-291 study

The present therapeutic indication for capivasertib includes adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations following recurrence or progression on or after an endocrine-based regimen [13]. The CAPItello-291 subpopulation relevant for the early benefit assessment thus exclusively comprises patients with confirmed PIK3CA/AKT1/PTEN alteration. In addition, research question 3 only comprises patients who have received prior endocrine therapy in the locally advanced or metastatic stage.

In Module 4 A, the company used results from the CAPItello-291 populations with PIK3CA/AKT1/PTEN alterations exclusively for postmenopausal women as defined in the study protocols (i.e. excluding pre/perimenopausal women whose menopause was induced by GnRH analogues). In principle, data from the CAPItello-291 study are available on pre/perimenopausal women with drug-induced menopause, who can also be assigned to research question 3 and thus represent part of the relevant patient population for research question 3 (women with prior endocrine therapy in the locally advanced or metastatic stage).

I 5.1.2.2 FAKTION study

The present therapeutic indication for capivasertib includes adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations following recurrence or progression on or after an endocrine-based regimen [13]. The FAKTION subpopulation relevant for the early benefit assessment thus exclusively comprises patients with confirmed PIK3CA/AKT1/PTEN alteration. In addition, research question 3 only comprises patients who have received prior endocrine therapy in the locally advanced or metastatic stage.

As already described in Section I 3.1.1.2 and Section I 3.1.2.2, the company only has access to publicly available information on the FAKTION study due to its involvement in the external funding. In the subpopulation with PIK3CA/AKT1/PTEN alteration(s), 68 of the 76 patients (89.5%) had prior endocrine therapy in the locally advanced or metastatic stage and can therefore be assigned to research question 3. The remaining 8 patients can be assigned to research question 1. Separate analyses are not available. A further differentiation of the patient population reported in Howell et al. on the basis of the prior therapy received according to research questions 1 and 3 (prior [neo-]adjuvant endocrine therapy versus prior endocrine therapy in the locally advanced or metastatic stage) is therefore not possible. Since the vast majority of patients in the subpopulation with PIK3CA/AKT1/PTEN alteration described in Howell et al. (89.5%) received prior endocrine therapy in the locally advanced or metastatic stage, the company considered the subpopulation with PIK3CA/AKT1/PTEN-alteration reported in Howell et al. in research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage). Only results for overall survival and PFS in the relevant subpopulation of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) are available from the FAKTION study.

I 5.1.2.3 Derivation of added benefit depending on the data situation

To derive the added benefit of capivasertib + fulvestrant for patients of research question 3, the company used different analyses depending on the outcome and data situation.

For all outcomes except overall survival and PFS, the company's analyses were based on a meta-analytical summary of the global cohort and the expansion cohort of the CAPItello-291 study, if possible according to the company. In cases where the company stated that it was unable to conduct an effect estimation for the expansion cohort due to the small number of patients, the company only used the global cohort to derive the added benefit.

For the outcome of overall survival, the company used a meta-analytical summary of the global cohort (CAPItello-291), the expansion cohort (CAPItello-291) and the FAKTION study. Pre- and perimenopausal women from the CAPItello-291 study whose menopause was induced by GnRH analogues were not included in the analysis (see above).

I 5.1.3 Assessment of the company's approach and consequence for the benefit assessment

I 5.1.3.1 Lack of consideration of a relevant number of patients from the CAPItello-291 study for research question 3

Table 6 shows the distribution of patients relevant to research question 3 by menopausal status and study or cohort, as well as the proportion of patients not included in the analyses presented by the company.

Table 6: Overview of the number of patients of research question 3 and proportions missing in the analyses

Menopausal status	Cohort	Number of patients [intervention vs. comparison]	Proportion of missing patients[a]		
				Intervention vs. comparator	Total
Pre/perimenopausal	Global cohort	23 vs. 27[b]	Scenario 1:	12.5% vs. 22.5%	18.4%
	Expansion cohort	min: 0 vs. 0[b] max: 5 vs. 7[b]	Scenario 2:	17.9% vs. 26.8%	21.9%
Postmenopausal	Global cohort	117 vs. 87	Scenario 3:	22.5% vs. 27.5%	24.7%
	Expansion cohort	11 vs. 6	Scenario 4:	25.0% vs. 31.5%	27.9%
	FAKTION[c]	39 vs. 37	Scenario 5:	12.1% vs. 17.2%	14.4%
			Scenario 6:	14.4% vs. 20.7%	17.3%

a. It is unclear how many pre/perimenopausal patients of the expansion cohort can be assigned to research question 3. The calculation of the proportions of missing patients also takes into account whether, according to the company, an effect estimation in the postmenopausal expansion cohort was possible for a meta-analytical summary (for all outcomes except overall survival, where an effect estimation was possible). In addition, patients from the FAKTION study must be taken into account only in the overall survival outcome. A distinction is therefore made between a total of 6 extreme scenarios:
- Scenario 1: outcomes other than overall survival; none of the patients can be assigned to research question 3; an effect estimation for the expansion cohort was possible according to the company
- Scenario 2: outcomes other than overall survival; all of the patients can be assigned to research question 3 and no patient is already included in the global cohort for the analysis; an effect estimation for the expansion cohort was possible according to the company
- Scenario 3: outcomes other than overall survival; none of the patients can be assigned to research question 3; an effect estimation for the expansion cohort was not possible according to the company
- Scenario 4: outcomes other than overall survival; all of the patients can be assigned to research question 3 and no patient is already included in the global cohort for the analysis; an effect estimation for the expansion cohort was not possible according to the company
- Scenario 5: overall survival outcome; none of the patients can be assigned to research question 3
- Scenario 6: overall survival outcome; all of the patients can be assigned to research question 3 and no patient is already included in the global cohort for the analysis

b. Institute's calculation.

c. Patient numbers also include patients assigned to research question 1 (6 patients in the intervention arm and 2 patients in the comparator arm). Separate analyses of the patients of research question 3 are not available, but exclusive consideration of these patients would lead to higher proportions of missing patients.

max: maximum; min: minimum

The company's information on the global cohort of the CAPItello-291 study shows that 23 pre/perimenopausal patients who can be assigned to research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) were included in the intervention arm and 27 in the comparator arm. However, it is not clear from the available information how many pre/perimenopausal patients of the expansion cohort of the CAPItello-291 study belong to the relevant subpopulation of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage). The number of these patients ranges between 0 and 5 in the intervention arm and between 0 and 7 in the comparator arm. Depending on the outcome, the company's approach to the meta-analytical summary resulted in different, partly relevant proportions of patients not included in the analyses (see Table 6).

I 5.1.3.2 Consideration of the analysis of the FAKTION study for research question 3 is appropriate

The analysis for the FAKTION study includes not only patients of research question 3 (89.5%), but also patients who can be assigned to research question 1 (10.5%). Due to the small proportion of these patients who can be assigned to research question 1 and the lack of possibility for further separation of the subpopulation used for the meta-analysis, it is appropriate to consider this subpopulation in the meta-analysis of research question 3.

I 5.1.3.3 Meta-analytical summary of CAPItello-291 and FAKTION possible in principle

In addition to the previously mentioned aspect that the analyses of the FAKTION study include a small proportion of patients who can be assigned to research question 1, CAPItello-291 and FAKTION differ with regard to various inclusion criteria. For example, the definition of the characteristic "ER-positive" differed. Patients in the CAPItello-291 study were defined as ER-positive if ≥ 1% of tumour cells stained positive or the Allred IHC score was ≥ 3/8. In the FAKTION study, patients were defined as ER-positive only if ≥ 10% of tumour cells stained positive or the Allred IHC score was ≥ 4/8. No information is available on how many patients in the CAPItello-291 study had ≥ 1 to < 10% positively stained tumour cells. According to Schrodi et al., the proportion of patients with ER-positive breast cancer with staining intensity ranging from ≥ 1 to < 10% appears to be low (approx. 2%) [21], however. Therefore, the differing definitions of ER positivity are considered negligible.

The relevant subpopulations of research question 3 of CAPItello-291 and FAKTION also differ in terms of prior therapy with CDK4/6 inhibitors. While in the CAPItello-291 study around 75% of the subpopulation relevant to research question 3 (excluding pre/perimenopausal patients) had undergone this prior therapy, no patient in the FAKTION study had been pretreated with a CDK4/6 inhibitor. However, current guidelines do not provide a uniform recommendation for the mandatory use of CDK4/6 inhibitors in the relevant subpopulation [15,17,20]. In

principle, therefore, the differences with regard to prior CDK4/6 inhibitor therapy do not preclude a meta-analytical summary of CAPItello-291 and FAKTION.

The 2 studies also differ with regard to the identification of patients who can be assigned to the respective subpopulation with PIK3CA/AKT1/PTEN alteration. In the CAPItello-291 study, the PIK3CA/AKT1/PTEN alteration status was determined using the FoundationOne CDx (F1CDx) test. In the FAKTION study, PIK3CA/AKT1/PTEN alterations could be confirmed by pyrosequencing, ddPCR or the NGS tests FoundationOne CDx (F1CDx) NGS Clinical Trial Assay (for tissue samples) or the GuardantOMNI RUO (for plasma samples). Although partially different tests were used in the 2 studies, it is assumed that patients with alteration(s) of the PIK3CA/AKT1/PTEN signalling pathway were identified with sufficient certainty in both studies.

There were also initial differences with regard to the definition of postmenopausal status. According to the definition in the CAPItello-291 study, patients could be classified as postmenopausal solely based on their age, whereas in the FAKTION study, postmenopausal status was always linked to amenorrhoea following previous drug therapy (see study descriptions in Section I 3.1). However, taking into account all inclusion criteria for the CAPItello-291 study, it can be seen that the patients included in this study who were initially classified as postmenopausal solely on the basis of age had also been pretreated with endocrine therapy (aromatase inhibitor). Therefore, the definitions of postmenopausal status overall differed only slightly between the studies. These differences do not preclude a meta-analytical summary of the 2 studies.

The delayed start of capivasertib therapy by 14 days compared with fulvestrant in the intervention arm of the FAKTION study in comparison with the CAPItello-291 study, where capivasertib was started on Day 1 of the first treatment cycle, also does not preclude a meta-analytical summary of CAPItello-291 and FAKTION, as it is not assumed that a 14-day delay in the start of treatment with capivasertib has a decisive influence on the results of the outcome of overall survival.

A meta-analytical summary of the results of the CAPItello-291 global cohort and expansion cohort and the FAKTION study is appropriate despite the differences described.

I 5.1.3.4 Lack of suitability of the presented analyses for the benefit assessment

Depending on the outcome, the company's approach to the meta-analytical summary resulted in different proportions of patients not included in the analyses (see Table 6).

For outcomes in categories other than mortality, taking into account the range of pre/perimenopausal patients in the expansion cohort (0–5 or 0–7) and a total of 50 pre/perimenopausal patients in the global cohort who belong to the relevant

subpopulation for research question 3, a proportion of at least 18.4% to a maximum of 27.9% was excluded from the analyses. Due to this range, it can be assumed that a relevant proportion of available evidence is not considered. Overall, therefore, no suitable data are available for outcomes that are exclusively based on analyses of the CAPItello-291 study for research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage).

Based on the range of pre/perimenopausal patients in the expansion cohort (0–5 or 0–7) and the total of 50 pre/perimenopausal patients in the global cohort, a proportion of at least 14.4% and a maximum of 17.3%, was not taken into account in the analyses for the outcome of overall survival.

However, based on the analyses presented by the company, which only consider patients defined as postmenopausal in the studies, there is a statistically significant difference in favour of capivasertib + fulvestrant compared with placebo + fulvestrant for the outcome of overall survival, which would result in a major extent (see I Appendix D of the full dossier assessment). However, it is unclear what influence the consideration of the available evidence on pre/perimenopausal patients has on the observed effect in the outcome overall survival. In addition, the analyses presented by the company on morbidity, health-related quality of life and side effects already show statistically significant differences to the disadvantage of capivasertib + fulvestrant compared with placebo + fulvestrant without taking pre/perimenopausal patients into account. Despite the major effect in overall survival, no added benefit can be derived for patients with prior endocrine therapy in the locally advanced or metastatic stage, as it is not sufficiently certain that this advantage in overall survival based on the available data outweighs the disadvantageous effects when taking into account the missing evidence from pre/perimenopausal patients. Overall, therefore, no suitable data are available for the early benefit assessment of capivasertib + fulvestrant for research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage).

I 5.1.3.5 Summary

Based on the uncertainties described, which result from the proportion of disregarded evidence from the CAPItello-291 study, there are no suitable data overall to assess any added benefit or lesser benefit of capivasertib in combination with fulvestrant compared with the ACT for research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage).

I 5.1.4 Further points of criticism

No data on AE outcomes at the prespecified data cut-off for the relevant subpopulation

As described in Section I 3.1.1.1, for the CAPItello-291 study, in addition to the data cut-off from 15 August 2022 decisive for the present dossier assessment, the company presented an

analysis from 27 March 2023 prepared for the FDA as part of a Day 120 Safety Update Report, which, as the company itself stated, was not prespecified. This analysis as part of a Day 120 Safety Update Report is a regular part of the approval procedure in the FDA's assessment process and was not explicitly requested. The analyses on AE outcomes in the relevant subpopulation of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) presented by the company in Module 4 A are based exclusively on this unprespecified analysis; corresponding analyses based on the prespecified data cut-off of 15 August 2022 decisive for the dossier assessment are not available. This means that analyses are not available for all relevant outcomes for the relevant data cut-off from 15 August 2022, as required in the module template.

Meta-analytical summary of results

As already described in Section I 3.1.4 on research question 1, the global cohort and the expansion cohort of the CAPItello-291 study can be regarded as one study population. One way to consider the expansion cohort even in cases where no effect estimation is possible for the expansion cohort alone is a meta-analytical summary of all patients in the CAPItello-291 study at the level of individual patient data. This should also take into account pre/perimenopausal women, as they are also to be classified as postmenopausal due to treatment with GnRH agonists.

Subgroup analyses for the CAPItello-291 study

For research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage), the company considered different meta-analytical summaries in its dossier (see above), in each case without taking into account pre/perimenopausal women. The company presented subgroup analyses for these meta-analytical summaries in Appendix 4 G of the dossier. However, only forest plots for individual outcomes and characteristics are shown; a complete presentation of all subgroup analyses is not available. Based on the available information, it is also unclear on what basis the company made its selection of the forest plots presented.

In addition to the subgroup analyses of the meta-analytical summaries, the company's dossier presented subgroup analyses for the relevant subpopulation of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) separately for the global cohort and the expansion cohort of the CAPItello-291 study. Pre/perimenopausal patients were not taken into account in the subgroup analyses presented. However, due to the drug-induced menopause, these patients are also to be classified as postmenopausal and are therefore relevant for the present research question. The company presented no subgroup analyses on a priori defined characteristics, e.g. separately according to the characteristics of bone metastases (yes versus no) or visceral metastases (yes versus no), in Module 4 A. The company justified this with the fact that these patients were already comprised by further

subgroup analyses, some of which were conducted post hoc. According to the module template, however, for patient-relevant outcomes, all subgroup analyses planned a priori and defined in the study protocol must be presented in Module 4 A of the dossier.

Besides the presentation of all predefined subgroup analyses, subgroup analyses with regard to the biological menopausal status (pre/perimenopausal versus postmenopausal) should also be presented for the relevant subpopulation of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage).

No subgroup analyses are available for the FAKTION study in the publicly accessible data.

I 5.2 Results on added benefit

No suitable data are available to assess the added benefit of capivasertib in combination with fulvestrant in comparison with the ACT in women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage. For these patients, there is no hint of an added benefit of capivasertib in combination with fulvestrant compared with the ACT; an added benefit is therefore not proven.

I 5.3 Probability and extent of added benefit

As the company presented no suitable data to assess the added benefit of capivasertib in combination with fulvestrant in comparison with the ACT in women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage, an added benefit for these patients is not proven.

The assessment described above differs from that by the company, which, based on the CAPItello-291 study and the FAKTION study, derived proof of considerable added benefit for women classified as postmenopausal according to the study protocol, with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage.

I 6 Research question 4 (men, prior endocrine therapy in the locally advanced or metastatic stage)

I 6.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on capivasertib (status: 8 August 2024)
- bibliographical literature search on capivasertib (last search on 31 July 2024)
- search in trial registries/trial results databases for studies on capivasertib (last search on 31 July 2024)
- search on the G-BA website for capivasertib (last search on 7 August 2024)

To check the completeness of the study pool:

- search in trial registries for studies on capivasertib (last search on 22 October 2024); for search strategies, see I Appendix A of the full dossier assessment

In agreement with the company, the CAPItello-291 study [3] was identified for the direct comparison of capivasertib in combination with fulvestrant versus the ACT; for the study description, see Section I 3.1.1.1. However, since only 2 men were included in the intervention arm of the global cohort study CAPItello-291, no conclusions on added or lesser benefit can be drawn for men with prior endocrine therapy in the locally advanced or metastatic stage based on this evidence. No additional relevant study was identified from the check of the completeness of the study pool.

The company did not present the results for these 2 patients, as the results have no informative value. To derive an added benefit, the company transferred the results of postmenopausal patients of research question 3 (women, prior endocrine therapy in the locally advanced or metastatic stage) to men of research question 4. It justified its approach by stating that, according to the treatment recommendations of evidence-based medical guidelines, the treatment of men was analogous to that of postmenopausal women, which means that, from a clinical point of view, the results of postmenopausal women can be assumed to be transferable to men.

The approach of the company is not appropriate. Similar guideline recommendations are not sufficient as the sole justification for the transfer of evidence. The company did not provide any further information that would justify the transferability of the results from women of research question 3 to men of research question 4.

Irrespective of this, the data presented for research question 3, which the company transferred to patients of research question 4, are not suitable for the benefit assessment (see Section I 5).

I 6.2 Results on added benefit

No suitable data are available to assess the added benefit of capivasertib in combination with fulvestrant in comparison with the ACT in men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage. For these patients, there is no hint of an added benefit of capivasertib in combination with fulvestrant compared with the ACT; an added benefit is therefore not proven.

I 6.3 Probability and extent of added benefit

As the company presented no suitable data to assess the added benefit of capivasertib in combination with fulvestrant in comparison with the ACT in men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage, an added benefit for these patients is not proven.

The assessment described above differs from that by the company, which derived a non-quantifiable added benefit by transferring the results of postmenopausal women with prior endocrine therapy in the locally advanced or metastatic stage to men with prior endocrine therapy in the locally advanced or metastatic stage. The company did not provide any information on the certainty of conclusions.

I 7 Probability and extent of added benefit – summary

Table 7 summarizes the result of the assessment of added benefit of capivasertib in combination with fulvestrant in comparison with the ACT.

Table 7: Capivasertib in combination with fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, after recurrence of the disease during or after (neo-)adjuvant endocrine therapy, no treatment to date in locally advanced or metastatic stage[b, c]	▪ Tamoxifen (only for premenopausal women who have not received tamoxifen in previous [neo-]adjuvant endocrine therapy; only for postmenopausal women if aromatase inhibitors are not suitable) or ▪ letrozole or ▪ exemestane (only for women with progression following anti-oestrogen therapy) or ▪ anastrozole or ▪ fulvestrant or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant	Added benefit not proven
2	Men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, after recurrence of the disease during or after (neo-)adjuvant endocrine therapy, no treatment to date in locally advanced or metastatic stage[b]	▪ tamoxifen or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)	Added benefit not proven

Table 7: Capivasertib in combination with fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
3	Women with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage[b, d]	Treatment of physician's choice, taking into account a change of endocrine therapy to ▪ tamoxifen ▪ letrozole[e] ▪ exemestane[e] ▪ anastrozole ▪ fulvestrant[e] ▪ everolimus in combination with exemestane (only for women without symptomatic visceral metastases who have progressed after a nonsteroidal aromatase inhibitor) ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) ▪ ribociclib in combination with fulvestrant ▪ abemaciclib in combination with fulvestrant ▪ palbociclib in combination with fulvestrant	Added benefit not proven
4	Men with PIK3CA/AKT1/PTEN-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, with disease progression during or after endocrine therapy that occurred in the locally advanced or metastatic stage[b]	Treatment of physician's choice[f], taking into account a change of endocrine therapy to ▪ tamoxifen ▪ aromatase inhibitor in combination with a GnRH analogue ▪ fulvestrant ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)	Added benefit not proven

Table 7: Capivasertib in combination with fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit

a. Presented is the respective ACT specified by the G-BA.
b. The following conditions are assumed for the present therapeutic indication:
- For patients who have already received a CDK4/6 inhibitor, retreatment with a CDK4/6 inhibitor, anastrozole or letrozole is not an option.
- An(other) endocrine therapy is indicated for the patients and, in particular, there is no indication for chemotherapy to achieve a necessary, rapid remission.
- (Secondary) resection or radiotherapy with curative intent is not indicated.
- There has been a change in treatment with respect to the drugs used for initial endocrine-based therapy.

c. Pre/perimenopausal patients are assumed to receive ovarian suppression with a GnRH analogue.
d. Pre/perimenopausal patients are assumed to continue ovarian suppression with a GnRH analogue.
e. For this patient group, treatment with fulvestrant, letrozole and exemestane, despite off-label use, is generally preferable to the approved endocrine therapies for the indication area after pretreatment with an endocrine therapy other than anti-oestrogens, in particular after pretreatment with aromatase inhibitors, according to §6 (2), sentence 3, number 3, AM-NutzenV. In accordance with the G-BA, it is therefore appropriate to determine the above-mentioned drugs as ACT for this indication area, even when used off-label.
f. The guidelines recommend the drugs tamoxifen, fulvestrant, aromatase inhibitor + GnRH analogue, as well as CDK4/6 inhibitors for the male patient group. However, in the therapeutic indication, aromatase inhibitors and fulvestrant are only approved for women. Thus, the use of aromatase inhibitors and fulvestrant in the male patient group represents an off-label use. In view of the treatment algorithm, there is a relevant indication area in the present therapeutic indication for the male patient group for which the approved drugs are not an option. In this indication area, the use of fulvestrant and aromatase inhibitors + GnRH analogue is therefore generally preferable to tamoxifen and palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole), according to §6 (2), sentence 3, number 3, AM-NutzenV. In accordance with the G-BA, it is therefore appropriate to determine the off-label use of the above-mentioned drugs as ACT.

AKT1: protein kinase B; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; CDK: cyclin-dependent kinase; ER: oestrogen receptor; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN: phosphatase and tensin homolog

The G-BA decides on the added benefit.

I 8 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Turner NC, Oliveira M, Howell SJ et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2023; 388(22): 2058-2070. https://doi.org/10.1056/NEJMoa2214131.

4. AstraZeneca. A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + Fulvestrant Versus Placebo + Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative (HR+/HER2−) Breast Cancer Following Recurrence or Progression On or After Treatment with an Aromatase Inhibitor (CAPItello-291); study D3615C00001; Interim Clinical Study Report [unpublished]. 2023.

5. AstraZeneca. A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + Fulvestrant Versus Placebo + Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative (HR+/HER2−) Breast Cancer Following Recurrence or Progression On or After Treatment with an Aromatase Inhibitor (CAPItello-291); Clinical Study Report for China Cohort; study D3615C00001; Interim Clinical Study Report [unpublished]. 2023.

6. AstraZeneca. A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + Fulvestrant Versus Placebo + Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative (HR+/HER2−) Breast Cancer Following Recurrence or Progression On or After Treatment with an Aromatase Inhibitor (CAPItello-291) [online]. [Accessed: 31.10.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-003629-78.

7. AstraZeneca. A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + Fulvestrant Versus Placebo + Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative (HR+/HER2−) Breast Cancer Following Recurrence or Progression On or After Treatment with an Aromatase Inhibitor (CAPItello-291) [online]. [Accessed: 31.10.2024]. URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-505042-25-00.

8. AstraZeneca. Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2- Breast Cancer (CAPItello-291) [online]. 2023 [Accessed: 31.10.2024]. URL: https://clinicaltrials.gov/study/NCT04305496.

9. Howell SJ, Casbard A, Carucci M et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. Lancet Oncol 2022; 23(7): 851-864. https://doi.org/10.1016/s1470-2045(22)00284-4.

10. Jones RH, Casbard A, Carucci M et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 2020; 21(3): 345-357. https://doi.org/10.1016/s1470-2045(19)30817-4.

11. Velindre NHS Trust. A phase 1b/2 randomised placebo controlled trial of fulvestrant +/- AZD5363 in postmenopausal women with advanced breast cancer previously treated with a third generation aromatase inhibitor [online]. [Accessed: 31.10.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000898-68.

12. Velindre NHS Trust. Fulvestrant +/- Akt Inhibition in Advanced Aromatase Inhibitor Resistant Breast Cancer (FAKTION) [online]. 2022 [Accessed: 31.10.2024]. URL: https://clinicaltrials.gov/study/NCT01992952.

13. AstraZeneca. TRUQAP 160 mg/-200 mg Filmtabletten [online]. 2024 [Accessed: 07.10.2024]. URL: https://www.fachinfo.de/.

14. Mylan. Fulvestrant Mylan 250 mg Injektionslösung [online]. 2023 [Accessed: 07.10.2024]. URL: https://www.fachinfo.de/.

15. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Mammakarzinom der Frau [online]. 2018 [Accessed: 12.11.2024]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/mammakarzinom-der-frau/@@pdf-latest?filename=mammakarzinom-der-frau.pdf.

16. Leitlinienprogramm Onkologie. Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, AWMF Registernummer: 032/054OL [online]. 2020 [Accessed: 13.11.2024]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf.

17. Gennari A, André F, Barrios CH et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021; 32(12): 1475-1495. https://doi.org/10.1016/j.annonc.2021.09.019.

18. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31(12): 1623-1649. https://doi.org/10.1016/j.annonc.2020.09.010.

19. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Onkopedia Leitlinie: Mammakarzinom des Mannes [online]. 2016 [Accessed: 02.08.2024]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/mammakarzinom-des-mannes/@@guideline/html/index.html.

20. Leitlinienprogramm Onkologie. S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.4, AWMF Registernummer: 032-045OL [online]. 2021 [Accessed: 12.11.2024]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mammakarzinom_4_0/Version_4.4/LL_Mammakarzinom_Langversion_4.4.pdf.

21. Schrodi S, Braun M, Andrulat A et al. Outcome of breast cancer patients with low hormone receptor positivity: analysis of a 15-year population-based cohort. Ann Oncol 2021; 32(11): 1410-1424. https://doi.org/10.1016/j.annonc.2021.08.1988.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-105.html.