BRCA-P: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, International Phase 3 Study to Determine the Preventive Effect of Denosumab on Breast Cancer in Women Carrying a *BRCA1* Germline Mutation

Local Protocol Amendment for UK

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PROTOCOL SIGNATURE PAGE

Protocol Title: **BRCA-P: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, International Phase 3 Study to determine the Preventive Effect of Denosumab on Breast Cancer in Women carrying a *BRCA1* Germline Mutation**

Protocol Number: ABCSG 50

EudraCT Number: 2017-002505-35

Global Trial Coordination: Austrian Breast & Colorectal Cancer Study Group

National Sponsor Name: _____

Declaration of Investigator

I confirm that I have read this study protocol and agree to conduct the study in accordance with the current protocol and its appendices. In addition, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the ICH Guideline on Good Clinical Practice and the appropriate national laws and regulations. I agree to handle all information concerning the study confidentially.

BRCA-P Site ID (5-digits): _____

_____	_____
First Name, Last Name	Date, Signature

1. PROTOCOL SYNOPSIS

Title

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center International Phase 3 Study to Determine the Preventive Effect of Denosumab on Breast Cancer in Women Carrying a *BRCA1* Germline Mutation ("BRCA-P")

Indication

Prevention of breast cancer in women with a *BRCA1* germline mutation

Study Type

Phase III, double-blind, prospective, randomized interventional prevention trial

Primary Objective

- To evaluate the reduction in the risk of any breast cancer (invasive or DCIS) in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo

Secondary Objectives

- To determine the reduction in the risk of invasive breast cancer in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo
- To determine the reduction in the risk of invasive triple negative breast cancer (TNBC) in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo
- To determine the reduction in the risk of ovarian, fallopian and peritoneal cancers (in women who have not undergone PBSO) in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo
- To determine the reduction in the risk of other (i.e. non-breast and non-ovarian) malignancies, including those known to be associated with *BRCA1* germline mutations in women with

germline *BRCA1* mutation who are treated with denosumab compared to placebo

- To determine the reduction in the risk of clinical fractures in pre- and postmenopausal women with germline *BRCA1* mutation who are treated with denosumab compared to placebo
- To compare rates of breast biopsies and rate of benign breast lesions in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo

Safety Objective

- To determine the safety profile of denosumab delivered at the study dose compared to placebo in pre- and postmenopausal women with germline *BRCA1* mutation

Exploratory Objective

- To determine the reduction in the risk of osteopenia and osteoporosis in pre- and postmenopausal women with germline *BRCA1* mutation during denosumab treatment compared to placebo at sites/ countries where DXA is SoC or funded
- To identify serological and other markers that allow early diagnosis of breast cancer in *BRCA1* mutation carriers
- To study the genetic, epigenetic, and phenotypic characteristics of cancers that occur during denosumab/placebo treatment
- To study changes in bone turnover markers in pre- and postmenopausal women during denosumab/placebo treatment
- To study changes in hormone biomarkers including RANKL, OPG, LH, FSH, E2 and progesterone
- To study changes in breast mammographic density, or breast background parenchymal enhancement on MRI using a BIRADs score
- To evaluate SNPs that have been associated with altered

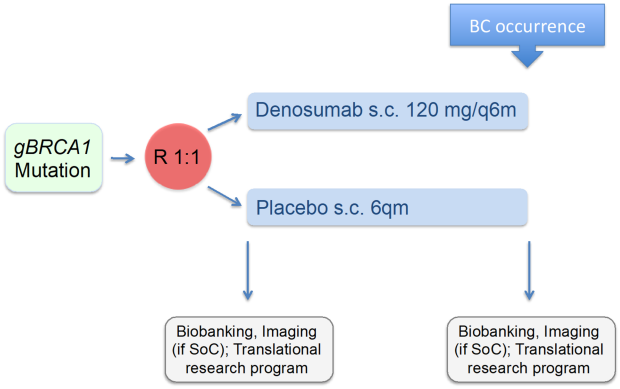
breast cancer risk, mammographic density, bone mineral density and any relationship to treatment effect

- To study the incidence of serous tubal in situ carcinoma (STIC), other precursor lesions and occult neoplasia in women who undergo risk-reducing bilateral salpingo-oophorectomy during the clinical trial
- To study differences in arms in Quality of Life in all subjects, as well as menopausal symptoms in perimenopausal and postmenopausal subjects through questionaires
- To study additional research questions / to perform additional analyses from biological material and / or clinical data that have been collected within this trial (upon decision of the steering committee and in alignment with the national study sponsors)

Sample Size 2,918 participants, 1:1 randomized

Treatment Arms Arm A (Experimental): Denosumab 120 mg s.c., q6m
Arm B (Placebo Comparator): Placebo s.c., q6m

Study Design



Study Duration 12 years in total (recruitment phase of 2 years and treatment phase of 5 years needed to yield 167 primary endpoint events, 5 years follow up)

STUDY GLOSSARY

Abbreviation/Acronym	Definition
ABCSG	Austrian Breast and Colorectal Cancer Study Group
ADH	Atypical ductal hyperplasia
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIT	Aromatase Inhibitor Therapy
AFF	Atypical Femur Fracture
ALH	Atypical lobular hyperplasia
BIRAD	Breast Imaging Reporting and Data System
BMD	Bone mineral denisity
BRCA	Breast Cancer Gene
BPM	Bilateral prophylactic mastectomy
CA	Competent Authority
CDM	Clinical Data Management
CI	Confidence interval
CHO	Chinese Hamster Ovary
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computertomography
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal Carcinoma *in situ*
IDMC	Independent Data Monitoring Committee
DFS	Disease-free survival
DXA	Dual X-Ray Absorptiometry
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
EDC	Electronic Data capture
(e)EOT	(Early) End of Treatment
ER	Estrogen receptor

Abbreviation/Acronym	Definition
E2	Estradiol
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HGSO	High grade serious ovarian
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobuline G
IP	Investigational product
ITT	Intent-to-Treat
IRB	Institutional Review Board
IxRS	Interactive voice and/or web-based response system
LH	Luteinizing Hormone
LTFU	Long-term follow-up
LCIS	Lobular carcinoma *in situ*
MedDRA	Medical Dictionary for Regulatory Activities
MG	Mammography
MRI	Magnetic Resonance Imaging
NGS	Next Generation Sequencing
OC	Oral contraceptive
ONJ	Osteonecrosis of the Jaw
OPG	Osteoprotegerin
OS	Overall survival
P	Progesterone
PBMC	Peripheral Blood Mononuclear Cells
PFS	Prefilled syringe
PgR	Progesterone receptor (gene)

Abbreviation/Acronym	Definition
PR	Progesterone receptor (protein)
PBSO	Prophylactic bilateral salpingo-oophorectomy including consecutively performed unilateral salpingo-oophorectomy
Q6M	Every 6 months
Q12M	Every 12 months
RANK/L	Receptor Activator for Nuclear factor Kappa B/ Ligand
REC	Research Ethics Committee
RRSO	Risk-reducing salpingo-oophorectomy
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious Adverse Event
SC	Subcutaneous
SERM	Selective Estrogen Receptor Modulator
SNP	Single Nucleotide Polymorphism
SP	Safety Population
STIC	Serous tubal *in situ* carcinoma
SoC	Standard of Care
SC	Steering Committee
TNBC	Triple negative breast cancer
TRC	Translational Research Committee
WHO	World Heath Organization

STUDY TERMS DEFINITION

Study Term	Definition
Clinical Fracture	A Clinical fracture is a clinically evident fracture with associated symptoms (e.g. pain)
End of Treatment	The end of treatment is the last day of investigational product administration. For the purpose of statistical analyses the end of treatment date is defined as exact 6 months after the last administration of investigational product
End of Treatment Visit	The End of Treatment Visit is defined as the visit/contact 6 months after the participant received the last dose of IP.
End of Study Visit	Participant's end of study visit is the last formal study visit, or last formal contact or an unscheduled study visit in case of early withdrawal from study.

Study Term	Definition
End of Study	End of study is the date when the last participant has completed the respective end of study visit, all data have been collected, and all data queries have been resolved.
Osteopenia	Osteopenia is a condition in which bone mineral density is lower than normal. Osteopenia is defined by the WHO as a bone mineral density T-score between −1.0 and −2.5.
Osteoporosis	Osteoporosis is a disease where increased bone weakness increases the risk of a broken bone. Osteoporosis is diagnosed when the bone mineral density T-score is less than or equal to 2.5 standard deviations below the mean (WHO).
Postmenopausal status	A postmenopausal state is defined as no menses for ≥12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of ≥12 months of amenorrhea, a single FSH measurement is insufficient
Woman of childbearing potential (WOCBP)	A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Invasive triple negative breast cancer (TNBC)	Triple-negative breast cancer (TNBC) do not express estrogen receptor (ER) or progesterone receptor (PR) at all, and do not overexpress human epidermal growth factor receptor 2 (HER2) diagnosed by immunohistochemistry as defined per ASCO CAP guidelines. The latest CAP/ASCO guideline[1] for ER and PR assessment has recommended a threshold of ≥1% for positivity.

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2. EXECUTIVE SUMMARY

In Europe and the USA, more than 1.3 million women are estimated to carry a germline mutation in the *BRCA1* or *BRCA2* genes. These women have up to 87% lifetime risk of developing breast cancer, with tumors usually developing at an early age. Currently, prophylactic surgery is the only proven procedure that significantly reduces breast cancer risk, and this can be associated with postoperative complications and a suboptimal cosmetic outcome. Medical prevention, if effective, could present a non-invasive alternative to mastectomy, but would need to be started relatively early in adulthood and potentially has to be offered beyond menopause. This strategy could also 'buy time' for women considering prophylactic mastectomy. There is accumulating evidence that the RANK/RANKL signaling pathway plays a pivotal role in breast tumorigenesis, particularly in the development of *BRCA1*-mutated tumors. Targeting the RANK pathway has been shown to attenuate breast epithelial proliferation *in vitro* and *in vivo*, and to profoundly reduce mammary tumor formation in mouse models.

In addition, since *BRCA* germline (*gBRCA*) mutations confer an increased risk for ovarian cancer, the vast majority of *gBRCA* women undergo prophylactic bilateral salpingo-oophorectomy (PBSO) at a young age. This has been shown to reduce ovarian cancer risk, but can significantly compromise bone, sexual and potentially cardiovascular and cognitive health. Many women who undergo PBSO therefore receive some form of osteoprotective therapy. Current medical breast cancer prevention strategies for *gBRCA* mutation carriers involve the use of tamoxifen or aromatase inhibitors, which - at least in the case of aromatase inhibitors - may further compromise bone health.

The RANKL inhibitor Denosumab is potentially an ideal chemopreventive agent for women with a *BRCA1* germline mutation because it: (a) could potentially reduce breast cancer risk, and (b) concomitantly protect bone health in those women who have already undergone PBSO or in naturally postmenopausal women. It has already been shown to have a positive benefit-risk profile in the treatment and prevention of bone loss in post-menopausal patients undergoing endocrine therapy for breast cancer.

2.1 Societal Impact

Mutations in *BRCA1* or *BRCA2* affect at least one in 400 women in the industrialized world. They are associated with up to 87% lifetime risk for the development of breast cancer, and a 15% to 50% lifetime risk for the development of ovarian cancer. There is now a widespread awareness that a positive family history of breast and/or ovarian cancer, particularly when early onset, could be due to the presence of a deleterious *BRCA1* or *BRCA2* germline mutation. As a result, affected women with a family history now commonly receive genetic testing. This is also being increasingly performed for women diagnosed before age 60 where their tumors exhibit 'BRCA-like' features, such as a TNBC phenotype. Genetic testing is progressively relevant for their medical management, due to important therapeutic options that include consideration of mastectomy and incorporation of platin-based chemotherapy or PARP inhibitors. Importantly, the identification of a mutation usually leads to 'cascade testing' of unaffected relatives to ascertain whether they harbor a pathogenic *BRCA* mutation. This has substantially increased the numbers of *BRCA1/2* mutation carriers who are yet unaffected by cancer.

Since both ovarian cancer and breast cancer can occur at a young age, carriers are usually advised to undergo prophylactic bilateral salpingo-oophorectomy (PBSO) at about age 40 (after completion of their family planning) in order to prevent ovarian cancer and to possibly reduce their risk of breast cancer. However, early PBSO compromises bone health and may require ongoing monitoring of bone mineral density throughout life and treatment with bone-protective therapies. Available non-surgical chemopreventive options such as aromatase inhibitors (AIs) are often associated with significant menopausal symptoms, and a further decline in bone health. Alternatively, non-hormonal chemopreventive strategies are thus urgently required.

BRCA mutation carriers are often highly motivated to pro-actively address their elevated cancer risk, which is exemplified by the willingness of carriers to undergo risk-reducing surgical procedures such as PBSO and bilateral mastectomy.

2.2 Background & Rationale

One out of 200-400 individuals is born with a *BRCA1* or *BRCA2* germline mutation. For women who carry a mutation in either of these breast cancer susceptibility genes, the risk to develop breast cancer by the age of 70 years is approximately 65% for *BRCA1* and 45% for *BRCA2*, respectively.[2,3] Typically, affected women develop tumors early in life with an estimated ~2% annual probability of developing breast cancer and ~1% annual probability of developing ovarian cancer (Table 1, 2). After unilateral breast cancer, the annual probability to develop contralateral breast cancer is estimated to be around 4%. In a recent update from a large, prospectively collected database of 15,170 *BRCA* mutation carriers, annual breast cancer incidence was 2% in *BRCA1* germline mutation carriers and 1.6% in *BRCA2* mutation carriers (Narod *et al.*, personal communication).

Table 1: Annual breast and ovarian cancer risk in healthy *BRCA1* mut. carriers

Cancer	Annual incidence	95% CI (range)
Breast cancer (BC)	**1.84 %**	95% CI 1.3%-2-6%; range 1.7%-3 (30-59 years)
20 – 29 years	0.87 %	
30 – 39 years	1.69 %	
40 – 49 years	1.99 %	
50 – 59 years	3.61 %	
60 – 69 years	0.74 %	
Ovarian cancer (OC)	**0.99 %**	95% CI 0.66%-15.1%
30 – 39 years	0.11 %	
40 – 49 years	0.74 %	
50 – 59 years	2.03 %	
60 – 69 years	5.59 %	
70 +	0.99 %	

Table 1 shows the annual risk to develop breast cancer and ovarian cancer in healthy *BRCA1* mutation carriers (adapted from Mavaddad and Liede).[4,5]

Table 2: Overall lifetime and 5-year cancer risks for *BRCA* mutation carriers

What are the cancer risks associated with *BRCA1/2?*		
Gene	***BRCA 1***	***BRCA 2***
Breast cancer, in unaffected woman (up to age 80)	60-90%	45-85%
Woman with breast cancer (unilateral) Lifetime risk of a new cancer in the other breast	50% 5-year risk of new breast cancer ~10%	50% 5-year risk of new breast cancer ~5-10%
Ovarian cancer, lifetime risk	40-60% Risk increases from age 40	10-30% Risk increases from mid 40s

Table 2 shows the overall lifetime and 5-year cancer risks for *BRCA* mutation carriers and the contralateral breast cancer risks in women who have already developed breast cancer (for comparison: lifetime breast cancer risk in non-*BRCA* mutation carriers in Europe is 12%, and ovarian cancer risk is 0.9-1.2%).

2.3 Breast Cancer Prevention in *BRCA1/2* Mutation Carriers

Breast cancer prevention for *BRCA1/2* mutation carriers has predominantly focused on surgical strategies, such as bilateral prophylactic mastectomy (BPM) and endocrine ablation by premenopausal bilateral salpingo-oophorectomy (PBSO). These procedures are associated with a substantially reduced risk of breast cancer. Of note, prophylactic BSO (PBSO) had initially been shown to reduce breast cancer risk by 50%, irrespective of whether the *BRCA1* or *BRCA2* genes are affected.[6] More recently, however, a thorough re-analysis which has addressed potential biases that had previously not been considered, has suggested that there may not be a preventive effect of PBSO on breast cancer risk in *BRCA1* mutation carriers, and in *BRCA2* carriers older than 50 years. Only *BRCA2* mutation carriers, who are younger than 50 appear to have some benefit from PBSO but the preventive effect is weaker than shown earlier.[7] Similar findings have been observed by other groups.[8]

In addition, in many countries the uptake of these highly effective prevention strategies is low and is compromised by a high rate of postoperative complications and sub-

optimal cosmetic outcome for bilateral prophylactic mastectomy.[9] This highlights the need for additional, non-surgical alternatives for breast cancer prevention, particularly for *BRCA1* mutation carriers.

2.4 Endocrine Prevention Strategies

The oral selective estrogen receptor (ER) modulator, tamoxifen, taken daily for 5 years, substantially reduces breast cancer risk for women who are at increased risk owing to their family cancer history, reproductive risk factors, or personal history of atypical hyperplasia or lobular carcinoma *in situ.*[10] Moreover, this benefit is sustained for up to 15 years after ceasing tamoxifen.[11] Mounting evidence, albeit observational, suggests that tamoxifen may also be efficacious for the prevention of breast cancer for *BRCA1* and *BRCA2* mutation carriers. An overview on its potential merits has been summarized by Phillips and Lindeman [12], and is detailed below:

For primary prevention, the only published data on the efficacy of tamoxifen for *BRCA1* and *BRCA2* mutation carriers come from a subgroup analysis of the NSABP-P1 breast cancer prevention trial. This trial randomized 13,388 women at increased risk of breast cancer to receive either tamoxifen 20 mg daily or placebo for 5 years. The risk ratio for breast cancer with tamoxifen was 1.67 (95% CI: 0.32–10.7) for *BRCA1* mutation carriers and 0.38 (95% CI: 0.06–1.56) for *BRCA2* mutation carriers. However, few mutation carriers were enrolled: only eight *BRCA1* and 11 *BRCA2* mutation carriers were identified among 288 study participants who developed breast cancer[13], so the confidence intervals were quite wide. Nevertheless, this study raised the possibility that tamoxifen could modulate breast cancer risk, at least for *BRCA2* mutation carriers.[12]

More data are available in the secondary prevention setting, although all of these studies were observational rather than randomized. The largest, comprising data from 2,464 mutation carriers, showed that tamoxifen use after a first breast cancer was associated with a reduced risk of contralateral breast cancer.[14] The hazard ratio was 0.38 (95% CI: 0.27–0.55; $p < 0.001$) for *BRCA1* mutation carriers and 0.33 (95% CI: 0.22–0.50; $p < 0.001$) for *BRCA2* mutation carriers. Several earlier studies also examined the association between tamoxifen use and contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers.[15-18] Although their power was limited due to study size, the point estimates for the hazard ratios for the risk of contralateral breast cancer with tamoxifen use were consistently less than 1 for all studies and for both

genes, consistent with tamoxifen being efficacious for contralateral breast cancer prevention for both *BRCA1* and *BRCA2* mutation carriers.

The differing hormonal phenotype of breast cancers arising in *BRCA1* and *BRCA2* mutation carriers is an issue that often arises in discussions about whether tamoxifen might provide benefit as a prevention agent. While the majority of breast cancers arising in *BRCA2* mutation carriers are ER positive, most breast cancers in *BRCA1* mutation carriers are ER negative at the time of diagnosis.[19] Data from the randomized primary prevention studies suggested that the benefit of tamoxifen was confined to the prevention of ER-positive breast cancer.[6] Paradoxically, however, the observational studies described above suggest that tamoxifen can reduce hormone receptor-negative tumors in *BRCA1* mutation carriers, consistent with the prevention properties afforded by PBSO. In fact, there is strong evidence that female hormones play a critical role in the early ontogeny of *BRCA1*-associated breast cancer: *BRCA1* has been shown to repress ERα-mediated transcription and may therefore alter estrogenic response.[20] Moreover, in mouse models activation of estrogen signaling has been shown to collaborate with *Brca1* loss to promote tumor development.[21] A link between estrogen and breast cancer development in *BRCA1* mutation carriers is also suggested by the finding that two single nucleotide polymorphisms located close to *ESR1* (which encodes ERα) are associated with breast cancer risk for *BRCA1* mutation carriers.[22] Furthermore, tamoxifen has been demonstrated to be effective in reducing proliferation of histologically normal breast tissue from *BRCA1/2* carriers when transplanted into nude mice, which further strengthens the role of estrogens in this setting.[23]

Finally, progesterone receptor (PR) expression may be altered in *BRCA1* and *BRCA2* mutation carriers. In one study, the estrogen-responsive PR-B isoform was reduced in breast tissue from mutation carriers.[24] On the other hand, total PR expression was reported to be elevated in *Brca1/p53*-deficient mice where the progesterone antagonist mifepristone (RU486) appeared to ameliorate mammary tumorigenesis.[25] In the future there may be other efficacious chemoprevention options for women with a mutation in *BRCA1* or *BRCA2*. Aromatase inhibitors and selective ER modulators other than tamoxifen have been shown to be effective for breast cancer prevention in women at increased risk on the basis of factors other than a *BRCA1* or *BRCA2* mutation. There are no data on their efficacy for mutation carriers. It seems likely, however, that they would confer similar chemoprevention properties to tamoxifen, although aromatase

inhibitors can only be used in the postmenopausal setting. The French LIBER Trial (NCT00673335) is a randomized phase III trial which is investigating whether letrozole, compared to placebo, is able to prevent breast cancer in postmenopausal women with a *BRCA1* or *BRCA2* mutation. The study has a planned sample size of 386 and its primary endpoint is survival without invasive cancer at 5 years. The estimated study completion date is planned for February 2022, with primary outcome measures to be reported in 2027.

2.5 Denosumab as Preventive Strategy in *BRCA1/2* Mutation Carriers

The emerging importance of progesterone/RANKL signaling as a key mediator of normal breast epithelial function raises the possibility that RANKL inhibition, using agents such as denosumab, could offer a novel approach for breast cancer prevention, although this has not been evaluated in the clinic.[26,27] It is noteworthy that female steroid hormones profoundly affect mammary epithelial cell function by both direct and indirect means.[28,29] A recent report has found that premenopausal *BRCA1* and *2* carriers have higher serum levels of estrogen and progestin across the menstrual cycle.[30] Indeed, mammary stem cells (which lack ERα and PR) appear to be indirectly activated by steroid hormones via paracrine signaling mediated by RANK ligand (RANKL), a progestin target.[31] These findings raise the possibility that PBSO and tamoxifen reduce breast cancer risk (at least in part) by the indirect inactivation of stem and/or progenitor cells in the breast.[32,33] This observation has potential relevance to *BRCA1* mutation carriers, where breast tumors are believed to arise from aberrant luminal progenitor cells.

Widschwendter *et al.* have recently examined serum RANKL and OPG levels across the menstrual cycle and their associations with hormonal responsiveness in the mammary gland. OPG was dysregulated in *BRCA* mutation carriers and inversely associated with breast cancer risk and mammary epithelial proliferation. In comparison to women without a *BRCA* mutation, OPG levels were particularly low through most of the menstrual cycle in mutation carriers, and an inverse correlation between serum OPG and luteal-phase P levels that was more marked in *BRCA* mutation carriers. Low serum OPG levels in an animal model were, in turn, associated with increased mammary epithelial cell proliferation, and significantly higher OPG levels were seen in

the absence of functional ovaries. Interestingly, while OPG levels in breast and serum were both decreased in presence of progesterone, RANKL serum levels did not appear to reflect local increases in breast tissue.[34] These data suggest that the net magnitude of RANK signaling in the breast upon progesterone exposure may be regulated by a local increase of RANKL which is paralleled by a decrease in both, local and systemic OPG thereby ultimately increasing the RANKL:OPG ratio in the breast tissue of mutation carriers.

There is further evidence from animal experiments which suggest a pivotal role of the RANK/RANKL pathway in breast carcinogenesis irrespective of the *BRCA* mutation status: RANK pathway activation by Progesterone (P)-mediated RANKL upregulation plays an important role in mammary carcinogenesis, in part by increasing mammary stem/progenitor cell proliferation.[35,36] Moreover, deleting *RANK* from the mammary epithelium decreases incidence and delays onset of P-mediated mammary cancer, indicating that RANK signaling suppression might be an excellent strategy for breast cancer prevention.[37] Whereas anti-progestin treatment inhibits mammary tumorigenesis in the animal model by decreasing ductal branching and alveolar proliferation, long-term treatment of premenopausal women with selective PgR modulators has not been tested sufficiently in humans and could potentially lead to substantial side-effects, including adverse effects on the endometrium.[25] Because OPG is not regulated throughout the menstrual cycle and luteal-phase P showed a much stronger inverse association in *BRCA*-mutation carriers vs controls, cell-autonomous factors might be involved in progesterone-OPG regulation. Taken together, there is now substantial evidence suggesting that the direct targeting of RANKL could overcome the low OPG levels present in mutation carriers and inhibit the RANK/RANKL axis, particularly in premenopausal women.

The pathophysiological role of the RANK/RANKL system, however, appears to be particularly important - and potentially independent of PgR - in *BRCA1* mutation carriers. Two seminal papers have just recently highlighted the pivotal role of RANK/RANKL in *BRCA1*-mutated breast cancer: using two different mouse models, Sigl *et al.* have shown that genetic inactivation of the key osteoclast differentiation factor RANK in the mammary epithelium markedly delayed onset, reduced incidence, and attenuated progression of *BRCA1;p53* mutation-driven mammary cancer. In their paper, the authors demonstrated that long-term pharmacological inhibition of the RANK ligand (RANKL) in mice abolished the occurrence of *Brca1* mutation-driven pre-

neoplastic lesions. Mechanistically, genetic inactivation of *Rank* or RANKL/RANK blockade impaired proliferation and expansion of both murine *Brca1;p53* mutant mammary stem cells and mammary progenitors from human *BRCA1* mutation carriers. In addition, genome variations within the RANK locus were significantly associated with risk of developing breast cancer in women with *BRCA1* mutations. Thus, RANKL/RANK control progenitor cell expansion and tumorigenesis in inherited breast cancer.[38]

In another paper, Nolan *et al.* investigated a role for the RANK/RANKL pathway in the pre-neoplastic phase of *BRCA1*-mutation carriers. They identified two subsets of luminal progenitors ($RANK^+$ and $RANK^-$) in histologically normal tissue of *BRCA1*-mutation carriers and showed that $RANK^+$ cells are highly proliferative, have grossly aberrant DNA repair and bear a molecular signature similar to that of basal-like breast cancer. These data suggest that $RANK^+$ and not $RANK^-$ progenitors are a key target population in these women. Inhibition of RANKL signaling by treatment with denosumab in three-dimensional breast organoids derived from pre-neoplastic $BRCA1^{mut/+}$ tissue attenuated progesterone-induced proliferation. Notably, proliferation was markedly reduced in breast biopsies from *BRCA1*-mutation carriers who were treated with denosumab. Furthermore, inhibition of RANKL in young adult *Brca1*-deficient mice substantially curtailed mammary tumorigenesis. Taken together, these both manuscripts have independently shown that RANKL blockade is a promising strategy in the prevention of breast cancer particularly in *BRCA1* mutant patients. This supports our previous results from ABCSG 18 in postmenopausal women, and supports our hypothesis of a particularly beneficial effect on premenopausal women since Nolan *et al.* observed that the frequency of RANKL expression was substantially lower in breast tissue from women aged >55 and in premenopausal women with prior tamoxifen use or oophorectomy.[39]

While considerably less information on the role of RANK/RANKL pathway is available for ovarian cancer, there is circumstantial evidence that PR signaling is important in endometrioid and high grade serious ovarian (HGSO) cancer, which is now believed to arise from Pax8-positive secretory cells in the distal fimbriae of the oviduct.[40] These secretory, as well as the ciliated cells in the oviduct, undergo cyclical changes that are under the direct influence of estrogen and progesterone.[41] Secondly, in a recent meta-analysis of 12 studies (n=2,933) conducted in ovarian cancer patients, Sieh *et al.,* showed that ER and particularly PR were prognostic biomarkers in endometrioid and

high-grade serous ovarian cancers: Strong PR expression was independently associated with improved disease-specific survival in high-grade serous carcinoma (HR 0.71, 95% C.I. 0.55.-0.91; p=0.0080), but low PR expression was not (HR 1.02, 95% C.I. 0.98-1.18; p=0.74), suggesting that PgR-mediated signaling is important in HGSO cancer.[42] Since HGSO cancers are the predominant subtype in *BRCA*-associated ovarian cancer, it seems reasonable to assume that a disruption of the PR/RANK/RANKL system could be pertinent to tumorigenesis and therapy for mutation carriers.

2.6 Rationale for Denosumab Dose and Schedule

There is some uncertainty regarding the optimal dose of denosumab for chemoprevention. Minimizing toxicity is a key consideration for a prevention study. Conversely, adequate RANKL inhibition will be required to inhibit breast epithelial proliferation, particularly in pre-menopausal women where progesterone and RANKL levels are high. Most of the currently available data on denosumab have been derived in postmenopausal women, where RANKL levels are lower including in breast tissue, where RANKL is produced locally by PR^+ luminal breast cells. This is a potentially important consideration, as the binding ratio of RANKL:denosumab is assumed to be 1:1.

The minimal dose of denosumab that will attenuate mammary epithelial proliferation is also an important consideration. In mouse models, 1 mg/kg of the RANKL inhibitor OPG-Fc was sufficient to abrogate progestin-induced proliferation in the mammary gland at 48 hrs. By contrast, 3 mg/kg was required to reduce the serum levels of the bone resorption marker TRAP 5b at 48 hrs. [36] Thus it is possible that the dose of denosumab that inhibits bone turnover will deliver an antiproliferative effect in the breast. In pre-clinical models, OPG-Fc administered at 10 mg/kg s.c. 3 times per week reduced pre-neoplastic lesions and mammary tumors in an MPA/DMBA model. [36] Nolan *et al.* carried out a pre-clinical chemoprevention study using a *BRCA1* mouse model, where tumors arise spontaneously (without progestin induction). In this model, OPG-Fc administered at 3 mg/kg sc. 3 times per week to young adult mice appeared to effectively reduce tumor incidence compared with mice treated with an isotype control antibody.[39] Thus a dose of denosumab that will effectually inhibit bone turnover could prove to be efficacious. However, a 'trade-off' in dosing may be required to

maximize safety, while ensuring that adequate denosumab levels are achieved in pre-menopausal women to neutralize the high RANKL levels in the breast throughout the menstrual cycle.

In contrast to patients with osteoporosis, who are treated with denosumab at 60 mg sc. every 6 months (Prolia® dose, equivalent to 120 mg p.a.), breast cancer patients with bone metastases are treated at 120 mg qmo (Xgeva® dose, equivalent to 1440 mg p.a.). The Prolia® dose appears to have a favorable toxicity profile, at least for post-menopausal patients with osteoporosis. In the FREEDOM trial, the incidence of atypical femoral fracture was rare (≥1 to <10/10,000 patients) and there were no cases of osteonecrosis of the jaw (ONJ). In contrast, the risk of ONJ with Xgeva® dosing appears to be ~1% in year 1, increasing to 4% p.a. thereafter. Safety data on patients treated with an intermediate dose (denosumab/Xgeva® 120 mg every three months) will be available from the D-Care study, due to report in 2017. Although denosumab can induce hypocalcaemia, patients generally tolerate denosumab well, particularly if calcium levels are normal at the commencement of therapy.

In the recently published clinical trial (ABCSG 18) of women with early breast cancer who received aromatase inhibitor therapy, denosumab when given at 60 mg, q6m appeared to be safe. In this study, 3,425 eligible patients were enrolled into the trial, of whom 3,420 were randomly assigned to receive denosumab 60 mg (n=1,711) or placebo (n=1,709) subcutaneously every 6 months for 3 years. The patient incidence of adverse events in the safety analysis set (all patients who received at least one dose of study drug) did not differ between the denosumab group (1,366 events, 80%) and the placebo group (1,334 events, 79%), nor did the numbers of serious adverse events (521 vs 511 [30% in each group]). The main adverse events were arthralgia and other aromatase-inhibitor related symptoms; no additional toxicity from the study drug was reported. Despite proactive adjudication of every potential case of osteonecrosis of the jaw (ONJ) by an international expert panel, no case of osteonecrosis of the jaw was identified. 93 patients (3% of the full analysis set) died during the study of which only 1 case had to be further investigated regarding the potential relationship to study drug administration. Moreover, compared with the placebo group, patients in the denosumab group had a significantly delayed time to first clinical fracture, which was the primary endpoint of this trial (hazard ratio [HR] 0.50 [95% CI 0.39-0.65], p<0·0001). The overall lower number of clinical fractures in the denosumab group (92) than in the placebo group (176) was similar in all patient subgroups, including in patients with a

bone mineral density T-score of -1 or higher at baseline (n=1,872, HR 0.44 [95% CI 0.31-0·64], p<0·0001) and in those with a bone mineral density T-score of less than -1 already at baseline (n=1,548, HR 0.57 [95% CI 0.40-0.82], p=0.002). The authors concluded that adjuvant denosumab 60 mg twice per year reduces the risk of clinical fractures in postmenopausal women with breast cancer receiving aromatase inhibitors, is safe and can be administered without any additional toxicity when compared to placebo.[43]

An analysis of disease-free survival (DFS) in women randomized into ABCSG 18, which was presented at SABCS 2015, revealed an improved DFS in postmenopausal denosumab-treated women, thus demonstrating that 60 mg of denosumab, offered q6m has an anti-tumoral effect as well, although it is not yet clear whether this benefit was confined to bone metastases.[44] Using 6-monthly doses of 60 mg (and possibly 120 mg) denosumab in *BRCA1* mutation carriers should thus be very safe.

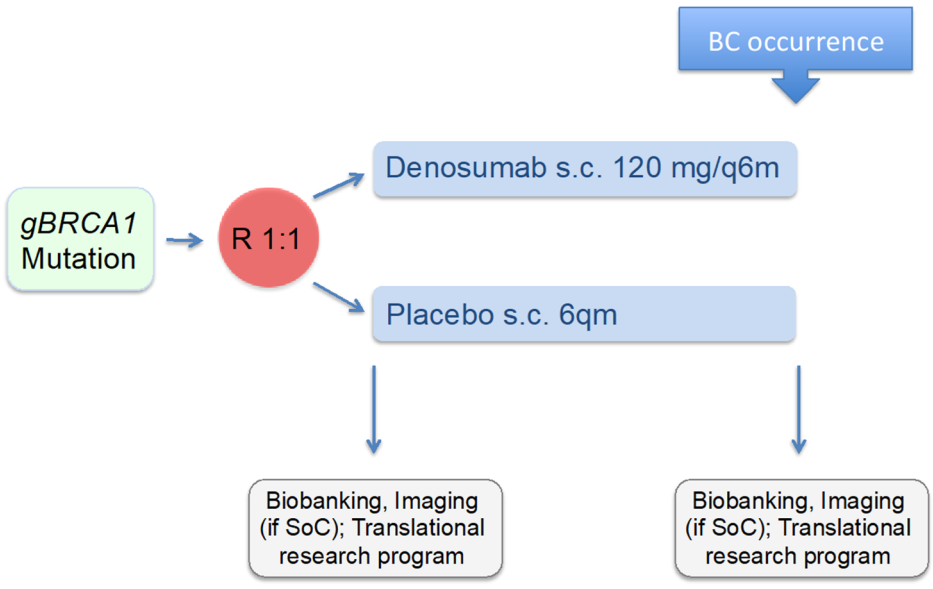
Following subcutaneous injection, denosumab achieves a rapid (serum levels are detectable within 1 hr) and prolonged absorption. The average maximum serum concentration was achieved between 7-14 days with various doses. Mean half-life is reported to be 28 days (range 14-55 days). In early studies in postmenopausal women, a single dose of denosumab (AMG162) at 1.0 mg/kg sustained serum levels of denosumab above 1,000 ng/ml for 90 days, however levels appreciably dropped to close to 100 ng/ml in the 6th month. A rapid reduction in bone resorption (determined by urinary NTX/creatinine) was observed, although levels began to rise in the sixth month.[45] By contrast, a single dose at 3.0 mg/kg kept denosumab levels above 5,000 ng/ml for 90 days. Bone resorption markers were repressed for 6 months. At 6 months, the range of percent changes in bone resorption observed was between -37% to -79% in the 1.0 mg/kg group and -56% to -94% in the 3.0 mg/kg group (compared to -48% to +62% in the placebo group). A return towards baseline occurred at 9 months for both the 1.0 and 3.0 mg/kg dose groups. In another study on patients with bone metastases from breast cancer (mean ages in various cohorts between 52-61), both the 1.0 and 3.0 mg/kg dose of denosumab sustained levels above 1,000 ng/ml and reduced bone resorption biomarkers for 90 days.[46] In a population pharmacokinetic study of 14 clinical studies (including 14,228 free serum samples from 1,076 subjects; 495 healthy subjects), denosumab levels fell to a mean of ~1,000 ng/ml by 18 weeks following a single 120 mg dose. By contrast, 120 mg dose each month resulted in mean values of ~20,000 ng/ml. [47]

Based on the above information, a dose greater than 60 mg sc. denosumab twice a year will be required to inhibit breast epithelial proliferation for a breast cancer prevention study, given the high levels of RANKL in pre-menopausal women. A 120 mg sc. every 6 months regimen could prove effective but may result in suboptimal serum levels of denosumab by 5-6 months. On the other hand, this strategy would allow for a period of bone turnover recovery and has also the advantage of reduced clinic visits for participants and improved patient compliance. Taken together, denosumab at a dose of 120 mg every six months is considered to be the preferred regimen for a prevention study.

2.7 Rationale for a blinded Placebo-controlled Study Design

Although the primary and secondary endpoints of the study can be measured fairly easily and precisely, it cannot be excluded that women randomized into a control arm (i.e. into the non-treatment arm) would be more likely to undergo prophylactic surgery (either PBM or PBSO, or both), or to have an alternative lifestyle and reproductive pattern (since pregnancy would not be contradicted as would be the case for denosumab-treated women). Also, women in the control arm might potentially be more inclined to forego trial-related visits at the study centers and rather opt for local (non-supervised) surveillance since they would not receive trial medication at the study site.

3. STUDY DESIGN



3.1 Study Type

International, multi-center, phase III, double-blinded, placebo-controlled, prospective, randomized interventional prevention trial.

3.2 Treatment Arms

Arm A (Experimental): Denosumab 120 mg s.c., q6m for 5 years
(Daily supplements, containing 500 mg elemental calcium and at least 400 I.U. vitamin D are highly recommended throughout study treatment)

Arm B (Placebo Comparator): Placebo s.c., q6m for 5 years
(Daily supplements, containing 500 mg elemental calcium and at least 400 I.U. vitamin D are highly recommended throughout study treatment)

3.3 Study Duration

The primary endpoint analysis is event-driven and will be performed when 167 primary endpoint events will have occurred. It is anticipated that, because of individual lifestyle changes, a considerable number of women may drop out for a number of reasons including family planning and adoption of alternative prevention strategies and hence a drop-out rate of 50% of participants at five years is assumed. Therefore, in order to observe the required number of events needed, 1,459 subjects per group (2,918 in total) will need to be randomized. The individual study treatment duration is 5 years. It is anticipated that 7 years are needed from first participant in to reach the required number of events. The individual follow-up period is 5 years after end of treatment per protocol. The overall study duration is anticipated to be 12 years and includes a 2 years enrollment phase, a 5 years treatment phase and 5 years follow up phase.

Participants will be followed up every 12 months after last administration of IP for 5 years, either by clinic visit, telephone contact, email or other means of communication, to determine the occurrence of oncological events, overall survival, clinical fractures and adverse events of special interests (oral events for ONJ adjudication and atypical femur fractures).

4. PARTICIPANT SELECTION – INCLUSION AND EXCLUSION CRITERIA

4.1 Inclusion Criteria

- Women with a confirmed deleterious or likely deleterious *BRCA 1* germline mutation (Variant class 4 or 5)
- Age ≥ 25 years and ≤ 55 years at randomization
- No evidence of breast cancer by MRI or MG and clinical breast examination within the last 6 months prior to randomization
- No clinical evidence of ovarian cancer at randomization
- Negative pregnancy test at randomization for women of childbearing potential
- Documentation that preventive breast surgery has been discussed as a potential treatment but is not planned at the time of randomization
- Women for whom preventive medications (tamoxifen, raloxifene or aromatase inhibitors) are not indicated as standard of care, or who have intolerance of or opt not to take these drugs.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Written informed consent before any study-specific procedure is performed

All individuals will be considered for inclusion in this study regardless of disability, marriage and civil partnership, maternity, race, religion and belief, and sexual orientation.

4.2 Exclusion Criteria

- Prior bilateral mastectomy
- History of ovarian cancer (including fallopian tube and primary peritoneal cancer)
- History of breast cancer
- History of invasive cancer except for basal cell or squamous cell skin cancer. History of the following are also allowed: carcinoma *in situ* of the cervix, stage 1 papillary or follicular thyroid cancer, atypical hyperplasia or LCIS (Lobular Carcinoma In Situ)

- Pregnant or lactating women (within the last 2 months prior to randomization)
- Unwillingness to use highly effective contraception method during and within at least 5 months after cessation of denosumab/placebo therapy in women of childbearing potential.
- Clinically relevant hypocalcaemia (history and current condition), or serum calcium <2.0 mmol/L (<8.0 mg/dL)

  Hypocalcemia defined by calcium below the normal range (a single value below the normal range does not necessarily constitute hypocalcemia, but should be 'corrected' before dosing the participant). Monitoring of calcium level in regular intervals (usually prior to IP administration) is highly recommended

- Tamoxifen, raloxifene or aromatase inhibitor use during the last 3 months prior to randomization or for a duration of more than 3 years in total (current and prior HRT is permitted)
- Prior use of denosumab
- Participant has a known prior history or current evidence of osteonecrosis or osteomyelitis of the jaw, or an active dental/jaw condition which requires oral surgery including tooth extraction within 3 months of enrollment
- Concurrent treatment with a bisphosphonate or an anti-angiogenic agent
- Any major medical or psychiatric condition that may prevent the participant from completing the study
- Hepatic impairment (defined as known chronic liver disease such as alcoholic cirrhosis or chronic autoimmune hepatitis or transaminases (aspartate aminotransferase or alanine aminotransferase) >1.5x upper limit of the laboratory normal range.
- Known active infection with Hepatitis B virus or Hepatitis C virus
- Known infection with human immunodeficiency virus (HIV)Use of any other investigational product (current or prior Aspirin or NSAIDs are permitted)
- Hypersensitivity to the active substance or to any of the excipients
- Known rare hereditary problems of fructose intolerance

5. OBJECTIVES

5.1 Primary Objective

- To evaluate the reduction in the risk of any breast cancer (invasive or DCIS) in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo

5.2 Secondary Objectives

- To determine the reduction in the risk of invasive breast cancer in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo

- To determine the reduction in the risk of invasive triple negative breast cancer (TNBC) in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo

- To determine the reduction in risk of ovarian, fallopian and peritoneal cancers (in women who have not undergone PBSO) in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo

- To determine the reduction in risk of other (i.e. non-breast and non-ovarian) malignancies, including those known to be associated with *BRCA1* germline mutations in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo

- To determine the reduction in the risk of clinical fractures in pre- and postmenopausal women with germline *BRCA1* mutation who are treated with denosumab compared to placebo

- To compare rates of breast biopsies and rate of benign breast lesions in women with germline *BRCA1* mutation who are treated with denosumab compared to placebo

5.3 Safety Objective

- To determine the safety profile of denosumab delivered at the study dose compared to placebo in pre- and postmenopausal women with germline *BRCA1* mutation

5.4 Exploratory Objective

According to local standards in particular countries/institutions, the respective analyses and assessments may be performed, also in consideration of available resources:

- To determine the reduction in the risk of osteopenia and osteoporosis in pre- and postmenopausal women with germline *BRCA1* mutation during denosumab treatment compared to placebo at sites/ countries where DXA is SoC or funded

- To identify serological and other markers that allow early diagnosis of breast cancer in *BRCA1* mutation carriers

- To study the genetic, epigenetic, and phenotypic characteristics of cancers that occur during denosumab/placebo treatment

- To study changes in bone turnover markers in pre- and postmenopausal women during denosumab/placebo treatment

- To study changes in hormone biomarkers including RANKL, OPG, LH, FSH, E2 and progesterone

- To study changes in breast mammographic density, or breast background parenchymal enhancement on MRI using a BIRADs score

- To evaluate SNPs that have been associated with altered breast cancer risk, mammographic density, bone mineral density and any relationship to treatment effect

- To study the incidence of serous tubal *in situ* carcinoma (STIC), other precursor lesions and occult neoplasia in women who undergo risk-reducing bilateral salpingo-oophorectomy during the clinical trial

To study differences in arms in Quality of Life in all subjects, as well as menopausal symptoms in perimenopausal and postmenopausal subjects through questionaires (refer to section 9.1.9)

- To study additional research questions / to perform additional analyses from biological material and / or clinical data that have been collected within this trial (upon decision of the steering committee and in alignment with the national study sponsors)

6. ENDPOINTS

6.1 Primary Endpoint

- Time to the occurrence of any breast cancer (invasive or DCIS)

6.2 Secondary Endpoints

- Time to invasive breast cancer
- Time to invasive triple negative breast cancer
- Time to ovarian, fallopian and peritoneal cancer (in women who have not undergone PBSO)
- Time to other (non breast or ovarian cancer) malignancies, including those known to be associated with *BRCA1* mutations
- Time to clinical fractures in pre- and postmenopausal women
- Frequency of breast biopsies and frequency of benign breast lesions

6.3 Safety Endpoint

- Incidence, nature and severity of adverse events (AEs) using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0)

6.4 Exploratory Endpoints

A baseline serum sample is mandatory and genomic DNA sample is optional. Patients should provide prospective consent at recruitment to allow research access to DNA and/or tissue samples collected for diagnostic purposes throughout the course of the study. Provision of serial serum or blood samples as well as digital mammogram and digital breast MRI scan data is recommended but is not a pre-requisite for participation in the trial. Participant will also be offered to complete Quality of Life questionnaires. If samples are collected, participating centers agree to adhere to common guidelines as agreed between the national sponsors. Mammography and/or MRI reports must be available at study site and may be requested by the respective national study sponsor.

The exploratory endpoints are as follow:

- Changes in T-scores
- Serological and other markers that allow early diagnosis of breast cancer in *BRCA1* mutation carriers
- Genetic, epigenetic, and phenotypic characteristics of cancers
- Changes in bone turnover markers
- Changes in hormone biomarkers including RANKL, OPG, LH, FSH, E2 and progesterone
- Changes in breast mammographic density, or breast background parenchymal enhancement on MRI using BIRADS score
- SNPs that have been associated with altered breast cancer risk, mammographic density and/or bone mineral density
- Incidence of serous tubal *in situ* carcinoma (STIC), other precursor lesions and occult neoplasia in women who undergo risk-reducing bilateral salpingo-oophorectomy
- Quality of Life in all participating participants, as well as menopausal symptoms in perimenopausal/postmenopausal participants

Additional data from biological material and / or clinical data that have been collected within this trial (upon decision of the steering committee and in alignment with the national study sponsors)

7. METHOD OF TREATMENT ASSIGNMENT/ PARTICIPANT RANDOMIZATION

7.1 Site Enrollment Requirements

Following regulatory and ethical approval for each participating site, it is the responsibility of the respective national sponsor to formally activate sites according to local regulations. Sites will only be able to enroll participants once formal site activation has been performed by the national sponsor.

7.2 Participant Randomization Procedure

After written informed consent has been obtained, the study site will register/randomize the participantvia an interactive voice and/or web-based response system (IxRS), which will allocate a unique subject identifier and the subject's blinded treatment group. Subjects screened but not randomized for any reason have to be registered as Screening Failure in IxRS.
Details of the randomization procedure will be described in a separate document.

7.3 Stratification Criteria at Baseline

Pre- vs postmenopausal status as defined in section 9.1.7.
A 1:1 ratio between pre- and postmenopausal women will be aimed at randomization. Therefore, in order to ensure a balanced study population, randomization for both menopausal strata will be capped at approximatealy 1,459 women randomized into either group. Perimenopausal women will be included in the premenopausal group.

7.4 Emergency Unblinding

A participant's treatment assignment should only be unblinded by the study site in emergencies when knowledge of the treatment assignment is essential for further management of the participant. Emergency unblinding may be performed by authorized site staff via IxRS (i.e. by principal investigators and sub-investigators with valid access to the IxRS). The principal investigator should promptly document and explain to ABCSG and the national sponsor any premature unblinding after the event.

8. IP DISCONTINUATION / WITHDRAWAL / END OF STUDY

8.1 Events during Study leading to IP Discontinuation / EOT Reasons

- **Bilateral prophylactic mastectomy** will lead to permanent discontinuation of denosumab / placebo.
- **Concurrent use of prohibited medication** will lead to permanent discontinuation of denosumab / placebo.
- **Oncologic Event** (DCIS or invasive breast or ovarian cancer) will lead to permanent discontinuation of denosumab / placebo.
- **Non-compliance** will lead to permanent discontinuation of denosumab / placebo (definition of non-compliance: missing 3 consecutive doses; please see section 11.2.1 for guidance on missed doses).
- **Adverse event** (e.g. AFF, ONJ), which by the Investigator's decision will require permanent discontinuation of denosumab / placebo.
- **Development of active hepatitis** with Hepatitis B virus or Hepatitis C virus, or the development of HIV.
- **Emergency Unblinding**
- **Other reason** (e.g. administrative decision), which by Investigator's decision will require permanent discontinuation of denosumab / placebo.

Participants will be followed up once a year by clinical visit, telephone visit or (e)mail until the End of Study (EOS).

8.2 Pregnancy during Treatment Phase

8.2.1 Planned Pregnancy

Participants planning pregnancy should inform their treating Investigator and will be withheld from further administration of denosumab/placebo The pregnancy should be scheduled for ≥5 months after the last administration of denosumab/placebo.

8.2.2 Unplanned Pregnancy

Women getting pregnant under active denosumab / placebo treatment have to inform

their treating Investigator immediately and will be withheld from further administration of denosumab / placebo.

8.2.3 Re-initiation of denosumab/placebo after pregnancy

Participants may re-initiate their denosumab / placebo treatment after discussion with their treating Investigator and after a weaning period of ≥ 2 months after lactation is completed. Re-initiation of study denosumab / placebo has to follow the participants' s' regular study schedule and must not exceed the maximum treatment period of 5 years after their first administration of denosumab / placebo. If participants decide not to re-initiate denosumab / placebo, they will continue to be documented in the eCRF at the corresponding treatment visits until initiation of the follow-up period per protocol.

8.2.4 Adequate contraception

Participating women of childbearing potential are required to use a highly effective contraception method during and within at least 5 months after cessation of denosumab/placebo therapy.

Adequate contraception is defined as:

- Surgical sterilisation (vasectomy or tubal ligation) provided (for vasectomy) that the vasectomised partner is the sole sexual partner of the WOCBP trial participant and received medical assessment of the surgical success; or true abstinence (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject); or
- Participant and partner use a highly effective method of birth control:
  - combined (oestrogen and progestogen) hormonal method (pills, vaginal ring, or skin patch) which will be associated with inhibition of ovulation.
  - single hormonal methods (progesterone) to stop release of the egg from the ovary (pills, shots/ injections, or implants placed under the skin by a healthcare provider)
  - a non-hormonal intrauterine device (IUD)
  - intrauterine hormonal-releasing system (IUS)

8.3 End of Study Reasons

- Death
- Consent withdrawal
- Lost to follow-up: in cases where sites cannot successfully contact a participant and are not able to receive appropriate basic publicly available information for greater than two years, the participant will be noted as lost to follow up with the date of last formal clinic visit, telephone contact, email or other means of communication
- Completion of protocol defined follow up period by participant

8.4 End of Treatment Visit / End of Study Visit

8.4.1 End of Treatment Visit

The End of Treatment Visit is defined as the visit / contact 6 months after the participant received the last dose of IP and may be conducted either by clinic visit, telephone contact, email or other means of communication. For the purpose of statistical analyses, the end of treatment date is defined as exactly 6 months after the last administration of investigational product and will be calculated as such and hence not seperately captured in the eCRF.

8.4.2 End of Study Visit

Participant's end of study visit is the last formal study visit, or last formal contact, or an unscheduled study visit in case of early withdrawal from study.

8.5 End of Study

End of study is the date when the last participant has completed the respective end of study visit, all data have been collected, and all data queries have been resolved.

9. STUDY ASSESSMENTS AND PROCEDURES

9.1 Baseline (Screening / Randomization / Day 1)

9.1.1 Informed Consent

Informed consent form (ICF) may be obtained greater than 30 days before randomization; however, it must be obtained prior to any protocol required procedure (i.e., Baseline), which is not performed as part of local SoC.

Signed and dated ICFs for all screened participants, even for those who are not subsequently randomized, must be maintained at the study site. All eligibility criteria must be confirmed prior to randomization.

9.1.2 Medical History, Demographic and Lifestyle Data

Medical history includes clinically significant diseases that are currently active or that were active within the previous 5 years, (major) surgeries with special emphasis on breast and reproductive tract biopsies/surgeries, as well as dental and fracture history. In addition, data on *BRCA1* mutation status, weight development, reproductive history, history of chest/breast imaging, history of concomitant medication and family cancer history will be collected. Demographic data will include age at time of randomization, marital status, level of eduction, smoking status, alcohol use, and self-reported race/ethnicity.

9.1.3 Physical Examination

All physical examinations should be performed by a physician or registered nurse or other qualified health care provider according to local regulations and SoC.

Each physical examination will include assessment of vital signs (temperature, heart rate, blood pressure, O2 saturations and respiratory rate), ECOG performance status, oral status, height (during baseline only) and weight. Clinically significant findings should be captured in the participant's medical history.

See Appendix A for ECOG performance status criteria.

9.1.4 Reporting of Concomitant Medication

Concomitant medications and treatments will be recorded from randomization up to the end of the treatment phase and documented in the eCRF.

9.1.5 MRI of the Breast, Mammography (MG) and Clinical Breast Examination

MRI of the breast and/or mammography and clinical breast examination should be performed according to local practice, but MRI or MG should have been performed within 6 months prior to randomization. Breast ultrasounds should be performed where the assessment is part of SoC and recorded in the eCRF accordingly.

9.1.6 Dual Energy X-Ray Absorptiometry (DXA) Assessment

Participants should undergo bone densitometry assessments of the lumbar spine and proximal femur performed by DXA at sites where this is SoC or funded per local practice and recorded in the eCRF accordingly.

9.1.7 Menopausal Status

A postmenopausal state is defined as no menses for ≥12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of ≥12 months of amenorrhea, a single FSH measurement is insufficient.

9.1.8 Laboratory Assessments

9.1.8.1 Routine Blood Samples

Blood samples including blood haematology (white blood cell count (WCC), haemoglobin, platelet count, red blood cell count, total neutrophil count, lymphocytes, monocytes, eosinophils, basophils), blood chemistry (serum creatinine, eGFR, AST or ALT , GGT, LDH, alkaline phosphatase (ALP), total bilirubin, sodium, potassium, corrected calcium, ionized (free) calcium, magnesium, phosphate, vitamin D, and urea) must be taken at baseline and prior to each dose of IMP/placebo (every 6 months) during the treatment period.

Serum calcium should also be assessed within two weeks of the initial dose of IMP/placebo, and in any other moment if suspected symptoms of hypocalcaemia occur. Additional monitoring of calcium level will be considered during therapy in participants with risk factors for hypocalcaemia (e.g. abnormal renal function), or if otherwise indicated based on the clinical condition of the participant.

9.1.8.2 Translational Blood Samples

Collection and adequate storage are the responsibility of the national sponsor(s). Local legislations regarding the collection of DNA samples and analysis have to be considered and a dedicated consent of the participant may have to be obtained.

- Mandatory Translational Blood Samples
  - Serum sample for translational research
- Genomic DNA sample

  Germline DNA may already be available from genetic analysis prior to randomization and must be made available for analyses by national sponsors. If germline DNA is not already available, additional blood samples for isolation of germline DNA has to be taken. Collection / isolation (if applicable) and proper storage of germline DNA samples is under the responsibility of the national sponsor. Optional Translational Blood Samples
    - May be obtained (e.g for isolation of cell free DNA and whole cell blood) and should be done and stored at sites where this is SoC or locally funded

9.1.8.3 Serum/urine pregnancy test

Serum or urine high sensitivity pregnancy test must be negative in women of childbearing potential, prior to every denosumab / placebo administration. This should be within 72 hours of the IP / placebo for a serum pregnancy test and within 24 hours of the IP/placebo for a urine pregnancy test. In addition, a high sensitivity urine pregnancy test must be performed 3 months +/- 14 days after each IP/placebo administration and can be performed at the participant's home with the results reported by telephone. Pregnancy tests should also be performed at any time when clinically indicated (e.g. unexplained amenorrhoea or when pregnancy is suspected). .

9.1.9 Quality of Life

Participants may complete self-reported questionnaires addressing aspects of the participants' physical and psychosocial well-being: the (1) SF-12, a generic quality of life measure[48], (2) Cancer Worry Scale to measure cancer-related anxiety[49] (3) Impact of Events Scale (IES)[50] to measure intrusive / avoidant thoughts about cancer and (4) the Greene Climacteric Scale[51], a standard measure of core climacteric symptoms (provided to perimenopausal/postmenopausal participants only).The questionnaires will be provided to participants at the baseline visit, if available in the respective language. Participants may be given choice of either completing the questionnaire(s) online or on paper.

9.2 Treatment Visits

Treatment visits are to be scheduled every 6 months (+/- 3 months) for five years.

9.2.1 Update on Medical History, Demographic and Lifestyle Data

At yearly visits, participants will be asked about updates on breast and reproductive tract biopsies/surgeries, as well as their outcome. In addition, changes since the last evaluation on their reproductive history and family cancer history will be captured. Updates to demographic data will include physical activity, smoking habits and alcohol use.

9.2.2 Physical Examination

During each treatment visit, a physical examination is required before administration of denosumab/placebo.

All physical examinations should be performed by a physician or registered nurse or other qualified health care provider according to local regulations and SoC. Clinically significant findings should be captured as an adverse event in the eCRF.

Each physical examination visit will include assessment of vital signs (temperature, heart rate, blood pressure, O2 saturations and respiratory rate), ECOG performance status, oral status and weight.

See Appendix A for ECOG performance status criteria.

9.2.3 Reporting of Concomitant Medication

Concomitant medications and treatments will be recorded at each treatment visit up to the end of treatment phase visit and documented in the respective eCRF.

9.2.4 MRI of the Breast, Mammography and Clinical Examination

Clinical breast examination, MRI of the breast and/or mammography should be performed according to local standard. Breast ultrasound (if standard of care) should be performed and recorded in the eCRF accordingly.

9.2.5 Dual Energy X-ray Absorptiometry (DXA) Assessment

DXA should be performed at yearly visits until EOT at sites where this is SoC or funded per local practice.

9.2.6 Menopausal Status

Menopausal status should be determined every 12 months according to the definition provided in section 9.1.7.

9.2.7 Laboratory Assessments

Blood samples (including full blood count, biochemistry,. vitamin D and Ca^{2+}) should be taken at baseline, within 2 weeks of the first dose of IMP/placebo and then every 6 months (prior to IMP/placebo). Blood samples should also be taken at the EOT visit .

9.2.7.1 Optional Translational Blood & Serum Samples

As outlined within the schedule of assessments; additional blood samples may be taken for translational research purpose at EOT and at tumor diagnosis, if applicable. These blood draws are optional and should be done at sites if performed as SoC or locally funded.

9.2.7.2 Serum/Urine Pregnancy Tests

Serum or urine high sensitivity pregnancy test must be negative in women of childbearing potential, prior to every denosumab / placebo administration. and

urine pregnancy tests must be performed monthly and **be** negative throughout the trial and for five months after the last dose of denosumab/placebo..

9.2.8 Oncologic Event Recording

Endpoint ascertainment for breast cancer (invasive or DCIS), for ovarian cancer and for other incident cancers should be performed by histological diagnosis in core or excisional surgical biopsies. Annual MRI and/or mammography should be standard state of the art imaging modalities for *BRCA1* mutation carriers in all participating sites. Mammograms and MRI will be read and assessed according to local standards at all institutions. For the confirmation of locoregional or metastatic disease, imaging as per clinical routine (such as CT scan, mammography, breast ultrasound, MRI, bone scintigraphy, etc.) is acceptable. If locoregional or metastatic disease is diagnosed by any of the described methods, a histological confirmation should be attempted.

9.2.9 Clinical Fracture Recording

Clinical fractures should be ascertained by x-ray.

At each yearly study visit, the investigator should assess if the participant has any relevant symptoms of clinical fractures. If new symptoms are reported by the participant, the investigator will use clinical judgment to determine if these symptoms warrant further investigation and whether a diagnostic x-ray should be performed. All clinical fractures except those of the skull, face, fingers and toes must be documented in the eCRF accordingly.

A copy of any radiologic report must be included in the participant's study records. All clinical fractures, except those of the skull, face, fingers, and toes, which are typically not associated with osteoporosis, will be included in the analyses of clinical fractures.

9.2.10 Atypical Femur Fracture

The occurrence of atypical femur fracture (AFF) will be proactively assessed during each clinical visit. In case of AFF occurrence, IP treatment interruption or discontinuation will be considered until the condition resolves and contributing risk factors are mitigated, where possible.

AFF is defined as atypical femoral fracture (femur midshaft fracture, femur subtrochanteric, femur distal) associated with minimal trauma (fall from standing height

or less).

9.2.11 Osteonecrosis of the Jaw Assessment (ONJ)

ONJ will be proactively assessed during each clinical visit. Suspected cases of ONJ should be ascertained by a dentist and treated according to SoC.The initial treatment start or further treatment administration during the course of the trial should be delayed in participants with unhealed open soft tissue lesions in the mouth. IP treatment interruption or discontinuation will be considered until the condition resolves and contributing risk factors are mitigated where possible.

A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab/placebo.

The following risk factors should be considered when evaluating a woman's risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy
- Co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: e.g. corticosteroids
- Poor oral hygiene, periodontal disease, poorly fitting dentures, pre-existing dental disease, invasive dental procedures (e.g. tooth extractions)

All participants should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with denosumab/placebo. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab/placebo administration. Denosumab/placebo administration should therefore be delayed until full recovery from surgery (i.e. invasive dental procedures).

9.2.12 Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The

possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections.

9.2.13 Quality of Life

Participants may complete self-reported questionnaires (the (1) SF-12[48], a generic quality of life measure, (2) Cancer Worry Scale[49], (3) Impact of Events Scale (IES)[50] and (4) the Greene Climacteric Scale[51], (provided to perimenopausal / postmenopausal participants only), as well as a BRCA-P questionnaire (5). These will be provided to the participant at the following treatment visits: 6 months, 12 months, and every 12 months following that). Participants may be given a choice of either completing the questionnaire online or on paper.

9.2.14 End of treatment Visit / Contact

6 months after the participantreceived the last dose of IP, information on adverse events, fractures, oncologic events and oral events (ONJ) should be collected either by clinic visit, telephone contact, email or other means of communication.

If a fracture or oncologic event occurred, medical event reports must be made available.

9.3 Follow Up Visits

Follow up visits should be performed either as clinic visit, telephone contact, email or other means of communication on a yearly basis.

9.3.1 Oncologic Event Recording

At each yearly follow up visit/contact, the investigator should ask the participant regarding the occurrence of new oncological events. The Investigator should aim to retrieve a copy of any confirmatory report for the event and include them in the participant's study records.

9.3.2 Clinical Fracture Recording

At each yearly follow up visit/contact, the investigator should ask the participant regarding the occurrence of new clinical fractures and whether a diagnostic x-ray was

performed. The Investigator should aim to retrieve a copy of any confirmatory report for the event and include them in the participant's study records.

9.3.3 Atypical Femur Fracture

The occurrence of atypical femur fracture (AFF) should be proactively assessed during each clinical visit, phone or email contact. The Investigator should aim to retrieve a copy of any confirmatory report for the event and include them in the participant's study records.

9.3.4 Osteonecrosis of the Jaw Assessment (ONJ)

ONJ should be proactively assessed during each clinical visit, phone or email contact. Participants should be advised that suspected cases of ONJ should be ascertained by a dentist and treated according to SoC. The Investigator should aim to retrieve a copy of any relevant report for suspected ONJs and include them in the participant's study records.

10. SCHEDULE OF ASSESSMENTS / STUDY FLOWCHART

	Baseline	Treatment visits		EOT Visit	Follow Up
	Screening / Randomization / Day 1 visit	Half- yearly visit (QM6) 6,18,30,42,54m	Yearly visit (QM12) 12,24,36,48,60m	6 months after last dose of IP	Yearly visit/contact (QM12) for 5 years
Informed consent(s)	x[1]				
Eligibility criteria, including documented evidence for pathogenic mutation in *BRCA1*	x				
Medical history, demographic & lifestyle data	x		x		
Physical examination	x	x	x	x	
Clinical breast examination, where SoC	x		x		
Concomitant medications collection	x	x	x		
MRI or MG (if performed according to local standard)	x[2]		x[3]		
Breast Ultrasound (if performed according to local standard)	x[4]		x[4]		
Bone Density Scan (DXA)	x[5]		x[6]		x[6]
Pregnancy test (in women of childbearing potential) every 3 months	x[7]	x[7]	x[7]		

	Baseline	Treatment visits		EOT Visit	Follow Up
	Screening / Randomization / Day 1 visit	Half- yearly visit (QM6) 6,18,30,42,54m	Yearly visit (QM12) 12,24,36,48,60m	6 months after last dose of IP	Yearly visit/contact (QM12) for 5 years
Blood sample (see below)[8]	x[8]	x	x[9]	x	
Serum sample for translational research	x[10]		x[11]		x[11]
Optional Translational Blood Sample (e.g for isolation of cell free DNA and whole cell blood)	x[12]		x[12]	x[12]	
Germline DNA sample	x[13]				
Denosumab 120 mg s.c./Placebo s.c. administration	x	x	x		
Oncologic event recording	x	x	x	x	x
Clinical fracture recording	x	x	x	x	x
Adverse Events / Safety evaluation Using CTCAE v4.0	x	x	x	x	
AEs of special interests (ONJ/ AFF)		x	x	x	x
Tumor sample (if applicable)		x[14]	x[14]	x[14]	x[14]
Access to archival breast tissue or BSO sample (if applicable)		x[15]	x[15]	x[15]	x[15]
QoL Questionnaire (optional)	x[16]	x[16]	x[16]		

1 Signed informed consent(s) must be obtained before any study specific screening assessments are performed

2 MG and MRI should not be older than 6 months

3 Either MG or MRI should be performed every 12 months (if according to local standard).

4 Breast ultrasound is not mandatory, but if conducted, result should be recorded

5 Participants should undergo a baseline bone densitometry assessment of the lumbar spine and proximal femur performed by DXA where this is SoC or funded per local practice

6 DXA will be performed at yearly visits until EOT at sites where this is SoC or funded per local practice

7 Serum or urine high sensitivity pregnancy test in women of childbearing potential prior to every denosumab / placebo administration. High sensitivity urine pregnancy test 3 months +/- 14 days after each IP/placebo administration and can be performed at the participant's home with the results reported by telephone.

8 Blood sample at baseline including blood haematology (white blood cell count (WCC), haemoglobin, platelet count, red blood cell count, total neutrophil count, lymphocytes, monocytes, eosinophils, basophils), blood chemistry (serum creatinine, eGFR, AST or ALT, GGT, LDH, alkaline phosphatase (ALP), total bilirubin, sodium, potassium, corrected calcium, ionized (free) calcium, magnesium, phosphate, vitamin D, urea and optional assessment of FSH, LH, E2, Pg)). Additional Ca^{2+} level should be taken within two weeks after the initial dose and if symptoms of hypocalcaemia occur. Additional regular monitoring of calcium levels should be considered during therapy in women with risk factors for hypocalcaemia. Participantsshould be encouraged to report symptoms indicative of hypocalcaemia. If hypocalcaemia occurs while receiving denosumab/placebo, additional calcium supplementation and additional monitoring may be necessary.

9 It is recommended that serum samples (including biochemistry, e.g. vitamin D, Ca2+) are taken yearly until EOT

10 A baseline serum sample for translational research is **mandatory**. Collection and proper storage of serum sample is under the responsibility of the national sponsor

11 Serum sample yearly and at tumor diagnosis of any solid tumor if available and if SoC or locally funded

12 Optional Translational Blood Sample: Additional blood samples (e.g for isolation of cell free DNA and whole blood) may be taken for translational research pupose. This blood draw is optional and should be done and stored at sites if performed as SoC or locally funded

13 Germline DNA may be already available from genetic analysis prior randomization and must be made available for analyses by national sponsors. If germline DNA is not already available additional blood samples for isolation of germline DNA has to be taken. Collection/ isolation (if applicable) and proper storage of germline DNA sample is under the responsibility of the national sponsor

14 A tumor tissues sample and corresponding histological report of any solid tumor should be collected if applicable

15 Access to archival breast tissue or BSO sample if patients undergo prophylactic surgery

16 Electronic or paper copy completion of questionnaire

11. STUDY TREATMENT AND TREATMENT PROCEDURES

11.1 Investigational product overview / terms and descriptions

Densosumab / placebo is the only investigational product (IP) of this trial and will be provided free of charge by Amgen. It is highly recommended that all participants receive daily calcium and vitamin D supplements (locally provided).

11.2 Investigational Product Dosage, Administration, and Schedule

Participants will be randomized 1:1 to receive 120 mg of denosumab or placebo every 6 months (time window for IP administration: +/- 3 months). Women will remain on study treatment until the required number of events is reached or until 5-year treatment is completed. Denosumab and placebo will be administered as a SC injection.
All doses should be administered by a licensed health care professional after all other study visit procedures have been completed.

11.2.1 Missed Dose

If a scheduled s.c. injection is missed, the participant should return to the site as soon as possible for investigational product administration (no later than 3 months after the scheduled dose). If more than 3 months have elapsed since the scheduled IP dose, the IP dose will be considered a missed dose. The next dose is to be given on the next scheduled visit date (based on study day 1). Under no circumstances IP should be administered twice within 3 months.

11.3 Investigational Product (IP)-Denosumab/ Placebo

11.3.1 Formulation, Packaging and Labeling

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line by recombinant DNA technology and will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical trial drug distribution procedures.
Denosumab (XGEVA®) will be provided in single use vials, as a solution for injection.

Each vial contains 120 mg of denosumab. Placebo will be supplied in matched containers and the formulation will be identical to denosumab with the exception of the protein content.

11.3.2 Treatment Assignment

This is a double-blind study. Participant treatment assignments will remain blinded to investigator, participants and study sponsors, except for dedicated ABCSG safety personnel for regulatory purposes, in order to reduce bias.
Unique boxes will be assigned for each dose the subject will receive while on study.
The box number of investigational product is to be recorded on each participant's investigational product administration eCRF.
A participant's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the participant (refer to section 7.4).

11.3.3 Storage, Handling and Processing

The boxes containing denosumab/placebo will be stored at the investigational site at 2°C to 8°C. Vials are to be kept in the outer carton until the time of use in order to protect from light and should not be frozen.
dDenosumab/placebo may be stored at room temperature (up to 25°C) for up to 30 days in the original container. Once removed from the refrigerator, denosumab/ placebo must be used within this 30 day period.

Actual storage conditions records during the period of the study must be maintained and include the date, time and initials of the person checking on the "working day" temperatures of the refrigerator used for the storage of trial supplies. Continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording shall also be maintained.

11.3.4 Special precautions for disposal and other handling

Before administration, the denosumab/placebo solution should be inspected visually. The solution may contain trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is cloudy or discoloured. Do not shake

excessively. To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25ºC) before injecting and inject slowly. A 27 gauge needle is recommended for the administration of denosumab/placebo. Do not re-enter the vial.

11.3.5 Supply and Return of Drug

Investigational product (denosumab or placebo) will be shipped to the responsible person (e.g. a pharmacist) at the investigator's institution, who will check the amount and condition of the drug and confirm receipt as outlined in specific guidance documents.

It is recommended that sites destroy used and unused product if local capabilities and regulations permit. If this is not permissible, at the end of the study, or as directed, unused containers, will be returned according to guidance documents.

11.3.6 Investigational Product Accountability

An Investigational Product Accountability Record for the investigational products is mandated by the protocol, must be kept current and should contain:

- The dates and quantities of denosumab/placebo received from Amgen
- Packaging lot number for product received
- Participant's identification (subject number)
- Date denosumab/placebo dispensed
- The initials of the dispenser

These inventories must be made available for inspection by an authorized national sponsor representative or designee and regulatory agency inspectors. The investigator is responsible for the accountability of all used and unused trial supplies.

11.4 Dose and Treatment Modifications

No dose modification will be done.

11.5 Permitted Ancillary Medications/ Supplements

Daily supplements, containing 500 mg elemental calcium and at least 400 I.U. vitamin D are highly recommended throughout study treatment.

11.6 Prohibited Concomitant Medications

Commercially available denosumab (ie, XGEVA® or Prolia®) is not to be administered during the treatment phase.

The following medications should not be administered during the treatment phase: fluoride (for osteoporosis), strontium ranelate, selective estrogen receptor modulators (eg, tamoxifen, raloxifene), tibolone, calcitonin, anabolic steroids, parathyroid hormone (or a derivative), aromatase inhibitor therapy, bisphosphonates (IV or over 30 days oral) and any other medication that is known or suspected to have activity on bone metabolism (except calcium and vitamin D), as well as any anti-angiogenic agent.

Use of any other investigational product is not permitted until EOT (current or prior Aspirin or NSAIDs are permitted).

Participants who receive medication mentioned above during the treatment phase will be withdrawn from investigational product (early EOT).

12. STATISTICAL COSIDERATION AND METHODOLOGY

12.1 Analysis Sample Size Estimation

Based on breast cancer incidence estimates presented in Table 1, we have calculated an annual breast cancer risk of 1.84% in the placebo control population. We have also assumed a reduction in breast cancer risk by 35%, which corresponds to a hazard ratio of 0.65 in women who receive denosumab q6m compared to women who do not receive denosumab. Our sample size calculation is also based on a very conservative drop out rate, since it is difficult to assess whether women who initially do not intend to undergo prophylactic mastectomy change their mind during the subsequent 5 to 7 years. Also, women with intact ovaries might decide to become pregnant during the trial period. We have therefore assumed a drop-out rate of 50% of randomized mutation carriers at 5 years to account for women who decide to either become pregnant, undergo prophylactic bilateral mastectomy (PBM), chose an alternative prevention strategy (tamoxifen etc.), or drop out from the trial for another reason. Under these assumptions, a 35% reduction in breast cancer risk would be detected with an 80% power and a two-sided significance level of 5 % if 167 breast cancer cases are observed. We expect to observe the number of events needed if 1459 subjects per group (2,918 in total) are randomized.

It is important to note that the sample size calculation is also based on the assumption

that PBSO does not decrease the risk to develop breast cancer in BRCA mutation carriers. Although several publications and one meta-analysis have previously suggested that PBSO is associated with a 50% reduction in breast cancer risk,[53,54] more recent data suggest that these estimates were affected by considerable bias, and are thus not correct, at least in the case of *BRCA1* mutation carriers where PBSO may not affect breast cancer risk ([7] and personal communication, Steven Narod). We have therefore not corrected for PBSO rates in our sample size estimate.

The data monitoring committee (DMC) will, however perform a blinded sample size re-estimation in order to check whether our assumptions (drop out rates for PBM, alternative chemoprevention, etc., lack of preventive effect of PBSO), which have been used to calculate the power of the study are indeed correct, and would correct the sample size if needed.

12.2 Description of analysis population sets

ITT Population:

Efficacy analysis will be evaluated in the Intent-to-treat (ITT) population which is defined as all randomized subjects including those who did not start any treatment. Subjects will be analyzed according to the treatment to which they were randomized. Randomized subjects consist of all participants who have given their written informed consent and for whom there is confirmation of successful allocation of a randomization number through the IxRS (Interactive Voice and/or Web Response System).

Safety Population (SP):

For the purpose of evaluating adverse events, the safety population (SP) is defined as all randomized subjects excluding those who did not start treatment. In the SP, participants will be analyzed according to the treatment, which they actually received.

12.3 Methods of statistical analyses

Descriptive tables are summarized in demographic characteristics. For metric variables, descriptive statistics are chosen according to the distribution of the respective variables (number of observations, mean, median, standard deviation,

minimum, maximum, 25%- and 75%-quartiles). For qualitative variables (categorical or ordinal), absolute and relative frequencies are given.

12.3.1 Evaluation of the primary endpoint

The primary endpoint is the time from randomization to the occurrence of breast cancer (invasive or DCIS). Women without breast cancer will be censored at the date of last disease assessment, withdrawal of informed consent or death, whatever occurs first.

The null and alternative hypotheses to be tested in terms of hazard ratio (HR) of the group receiving denosumab to the group receiving placebo are defined as:

H0: There is no difference with respect to time to occurrence of breast cancer (invasive or DCIS) between subjects with and without denosumab (HR = 1)

H1: There is a difference with respect to time to occurrence of breast cancer (invasive or DCIS) between subjects with and without denosumab (HR ≠ 1)

Data analysis for the primary endpoint is based on the ITT-population. Time to breast cancer (invasive or DCIS) will be compared between the two treatment arms using a stratified Cox proportional hazards regression model.

Additional sensitivity analyses of covariates that may modify the primary outcome may be conducted using additional multivariate Cox regression model (e.g. menopausal status, PBSO, OC and HRT as time-dependent covariates). Analyses may include each covariate individually and furthermore, an analysis adding all potential covariates may be used to obtain the covariate-adjusted estimate of the treatment effect and its p-value. Covariates of multivariate models and possible subgroup analyses (i.e. in pre- vs postmenopausal women, etc.) will be defined in the Statistical Analysis Plan.
Although there is growing evidence suggesting that the protective effect of PBSO on breast cancer risk is limited to young mutation carriers, it cannot be excluded that there is indeed some effect of PBSO on breast cancer incidence in denosumab-treated and non-treated *BRCA1* carriers which could impact the sample size calculation. We therefore plan to follow breast cancer incidence in the respective groups by a data monitoring committee which will be blinded to the treatment arm, and will adjust sample

sizes accordingly in a pre-planned analysis which will be scheduled in year 2 of the trial.

12.3.2 Evaluation of the secondary endpoints

The methods used for the evaluation of the primary endpoint also apply to the analysis of the secondary time-to-event endpoints. Analyses of the secondary endpoints are also based on the ITT. There will be no multiplicity adjustment for the secondary endpoints but endpoints are to be analyzed in a hierarchical order. The primary null hypothesis will be tested first at a significance level of 0.05. If the primary null hypothesis is rejected, the secondary null hypotheses will be tested in a stepwise fashion over 5 steps at a significance level of 0.05. In case any one of the hypotheses is not rejected at a previous step, all subsequent endpoints will be analysed in an exploratory manner only. Time to ovarian cancer will be analyzed in the overall group and in different strata (OC use, HRT use, and menopausal status). Further details on the secondary endpoints will be defined in the Statistical Analysis Plan.

12.3.3 Safety evaluation

Safety evaluation will be based on the safety population (SP). Adverse event incidences including clinical fractures, ONJ and AFF and their frequencies will be collected during each subject visit (i.e. before every denosumab/placebo dosing [i.e. q6m], until 30 days after the last denosumab/placebo dose) and will be evaluated and adjudicated per arm. During the follow up phase only clinical fractures and AEs of special interest (ONJ and AFF) will be reported in the eCRF.

No formal testing will be performed other than descriptive testing. Women of childbearing potential will be required to undergo a pregnancy test before every denosumab/placebo dosing (i.e. q6m).

12.3.4 Evaluation of exploratory endpoint

Exploratory endpoints will be analyzed according to a separate analyses plans provided within the translational research program.

12.4 Time-points of analyses

The primary analysis (including all endpoints) will be performed when 167 primary endpoint events will have occurred.

An update analysis – including, but not limited to, the clinical fracture and cancer event endpoints – will be conducted after end of study. The purpose of this analysis is to estimate the longterm treatment effect. All details and main statistical analyses will be described in the SAP.

13. SAFETY INSTRUCTIONS AND GUIDANCE

13.1 Adverse Events – General Overview

For each adverse event recorded on an Adverse Event eCRF page, the investigator will make an assessment of seriousness (see Section 13.4. for seriousness criteria), severity (see section 13.5), and causality (see Section 13.6).

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by applicable regulations.

13.2 Adverse and Serious Adverse Event Reporting

Safety and tolerability will be assessed by physical examinations, lab tests or other means as indicated.

Adverse events will be collected in a cumulative manner, with duration (start and stop) dates and using CTCAE v.0 Adverse Event Severity Grading Scale.

For this trial, eCRFs are used for routine AE reporting in MACRO.

Note: All AEs during the defined AE Reporting Period require reporting regardless of causality. Attribution to treatment or other cause should be provided.

13.3 Safety Reporting Period

(Serious) Adverse event (Safety) reporting is mandatory from the date of informed consent form signature (i.e. baseline) until 6 months after last administration of investigational product (denosumab or placebo). In case of re-initiation of denosumab/placebo after pregnancy, SAE reporting will be resumed with the day of

administration of denosumab/placebo until 6 months after last administration of investigational product (denosumab or placebo).

During the Baseline Assessment Phase, only AEs deemed to be serious (SAEs) **and** related to any protocol mandated and not routinely performed procedure have to be reported.

During the follow up period only SAEs that are considered as related to IP have to be reported. Additionally, AEs of special interest (ONJ and AFF) will be documented in the eCRF.

13.4 Adverse Events

According to the ICH guideline for Good Clinical Practice an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Information concerning the AE, provided by the participant herself, discovered by the querying investigator, or by means of a physical examination, laboratory tests, or other means should be recorded in the eCRF at the latest at the end of each visit.

Pre-existing medical conditions should be considered adverse events if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Laboratory values out of range without associated clinical symptoms are not considered as Adverse Events. Laboratory values out of range and considered to be of clinical significance will be considered as Adverse Events. Clinical significance is defined as meeting one or more of the following conditions:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. interruption or permanent discontinuation)

- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

Any laboratory abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

Planned medical or surgical procedures are not considered adverse events.

All AEs occuring after the participant had signed the Informed Consent until 6 months after last administration of investigational product (denosumab or placebo) are reported in the AE section of the eCRF.
During the follow up phase only clinical fractures and AEs of special interest (ONJ and AFF) will be documented in the eCRF.
To the extent possible, each AE should be described according to the following properties:

- its duration (start and end date)
- its seriousness
- its intensity (mild, moderate, severe, life threatening, death)
- its outcome
- and its relationship to denosumab/placebo

13.5 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that results in any of the following outcomes:

- Fatal (i.e., the adverse event actually causes or leads to death)
- A life threatening experience (NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)
- Hospitalisation or prolongation of existing hospitalisation (at least one overnight stay)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

or are considered to be a

- Significant medical event in the investigator's judgment (e.g. may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following hospitalization scenarios are not considered to be adverse events:

- ✓ Hospitalisation for respite care, cosmetic surgery, for social reasons or in a rehabilitation center
- ✓ Hospitalisation for a preexisting condition provided that all of the following criteria are met:
  - The hospitalisation was planned prior to the study
  - The patient has not suffered an adverse event

13.6 Assessment of Severity / Intensity of Adverse Events

The degree of severity of an adverse event provides a qualitative determination of the extent or the intensity of an AE as determined by the investigator or reported by the participant. The severity does not reflect the clinical danger of the event, but merely the degree or extent of the suffering or of the event (for example, severe nausea, mild attack).

Intensity of all AEs will be graded according to the NCI CTCAE v4.0 on a five-point scale (grade 1 to 5) and reported in detail in the eCRF. AEs not listed in the NCI CTCAE v4.0 should be graded according to the five-point scale shown in the following table.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Table 4 : NCI CTCAE v4.0 (grades 1 to 5)

A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

13.7 Relationship between Adverse Events and IP

The relationship between the administration of the IP and the occurrence of an AE is described as being either "Related" by the investigator or not "Not Related".

0 = Not related	Based on the chronological relationship between the clinical event and the administration of the IP, a causal relationship is improbable, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
1 = Related	Based on the chronological relationship between the clinical event and the administration of the IP, a causal relationship is possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event

All serious unexpected adverse events judged by either the investigator or ABCSG as having a reasonable suspected causal relationship to the investigational product qualify as suspected unexpected serious adverse reactions (SUSARs).

13.8 Expedited Adverse Event Reporting

Certain events require immediate reporting:

- SAEs (Serious adverse events)
- AESIs (Adverse Events of Special Interest)
    - ONJ (Osteonecrosis of Jaw)
    - AFF (Atypical Femur Fracture)

During the reporting period, the investigator must report such events to the national study sponsor and the ABCSG safety department, who holds the safety database and is responsible for SUSAR evaluation, immediately (i.e., no more than 24 hours after becoming aware of the information). The study specific SAE reporting form and the study specific reporting pathway have to be used.

The investigator must report new significant follow-up information for these events to the respective national study sponsor and ABCSG immediately.
After the end of the safety reporting period only SAEs that are considered as related to the IP have to be reported.

13.9 Pregnancies

Pregancies have to be reported to the respective national study sponsor and ABCSG safety department immediately.
All pregnancies reported during the study should be followed until pregnancy outcome.

14. REGULATORY OBLIGATIONS

14.1 Regulatory and Ethical Compliance

By signing the protocol the investigator agrees to treat all of the information that is provided with the strictest confidentiality and to require the same of his personnel as well as the IRB/IEC/REC. Study documents (protocols, investigator`s brochures, eCRFs, etc.) provided by the respective national study sponsor / ABCSG / Amgen will be stored in an appropriate manner in order to ensure confidentiality. The information provided to the investigator must not be made available to other parties without a direct written authorization by the aforesaid parties, with the exception of the extent to which disclosure is necessary in order to obtain informed consent from the women who wish to participate in the study.

14.2 Ethics and Good Clinical Practice

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulation and applicable local, state and federal laws.

Studies conducted in the European Union/European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC including 2005/28/EC) until the E.U. Directive 2001/20/EC will be repealed and the E.U. regulation 536/2014 will enter into force by the publication of E.U. or EMA.

By signing the study protocol, the investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of good clinical practice, which these instructions and procedures reflect.

14.3 Independent Ethics Committee/Institutional Review Board/Research Ethics Committee

A copy of the protocol, proposed informed consent form, other written participantinformation, and any proposed advertising material must be submitted to the respective national IEC/IRB/REC for written approval. For each participating site, the respective national study sponsor must receive a copy of the written approval of the protocol and informed consent form before recruitment of participants into the study and shipment of investigational product.

The national study sponsor or if applicable the investigator must submit and, where necessary, obtain approval from the IEC/IRB/REC for all subsequent protocol amendments and changes to the informed consent document. The national study sponsor or if applicable the investigator should notify the IEC/IRB/REC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the national sponsor, in accordance with local procedures.

The national study sponsor or if applicable the investigator will be responsible for obtaining annual IEC/IRB/REC renewal (if applicable according to national legislation) throughout the duration of the study as applicable. Copies of IEC/IRB/REC approval of the protocol, consent form, and participant information sheet and the IEC/IRB/REC continuance of approval must be filed in the study files.

14.4 Prestudy Documentation Requirements

The investigator is responsible for forwarding the following documents to the national study sponsor for review before any investigational product is shipped:

- Signed and dated protocol signature page (Investigator's Agreement)
- Up-to-date curricula vitae of principal investigator and all co/subinvestigators
- Signed study contract
- Completed Financial Disclosure Form
- Completed Confidential Disclosure Forms

  Other country-specific forms, as defined in the country-specific requirements

The national study sponsor will provide following documents to the investigator, or otherwise, the investigator to the national study sponsor, as applicable:

- Copy of the IEC/IRB/REC approval of the protocol, consent form, and participant information sheet
- IEC/IRB/REC composition and/or written statement that IEC/IRB/REC is in compliance with regulations

14.5 Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On the case report forms or other documents submitted to the national study sponsor and to ABCSG, participants should be identified by the study specific ID only. Documents that are not for submission to the national study sponsor (e.g. signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with local regulatory requirements and ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of national study sponsor, of the regulatory agency(s), and the IEC/IRB/REC direct access to review the participant'soriginal medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the participant to permit named representatives to have access to her study-related records without violating the confidentiality of the participant.

14.6 Informed Consent

The written informed consent document should be prepared in the languages of the potential participant population. ABCSG will provide an English Master IC template which will be disseminated to the national study sponsors for adaptation, translation, regulatory submission, and use in their respective countries. Before a woman's participation in the clinical study, the investigator is responsible for obtaining written informed consent from her or a legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent on behalf of a prospective participant, to the participant's participation in the clinical study. The acquisition of informed consent and the participant'sagreement or refusal of his/her notification of the primary care physician should be documented in the participant'smedical records, and the informed consent form should be signed and personally dated by the participantor a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily an investigator, if acceptable according to respective national legislation). The originally signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the participantor legally acceptable representative.

If a potential participantis illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the participantand must allow for questions (if acceptable according to national legislation). Thereafter, both the participantor legally acceptable representative and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

15. ADMINISTRATIVE AND LEGAL OBLIGATIONS

15.1 Protocol Amendments and Study Termination

Any modifications to the protocol or the Informed Consent Form which may impact on the conduct of the study, potential benefit of the study, or may affect participantsafety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by the study steering

committee and the respective national study sponsors, agreed by the investigator(s) and approved by relevant IRBs/IECs/REC/CA prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs/IECs/REC/CA must be provided to the national study sponsors before the study is initiated.
Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by national study sponsors, agreed by the investigator(s) and notified to the IRB/IEC(s)/REC/CA.

The national study sponsor and the investigator (at the repective study site) reserve the right to terminate the study according to the study contract. The investigator or the national study sponsor, if applicable, should notify the IRB/IEC/REC/CA in writing of the study's completion or early termination and send a copy of the notification to the national study sponsor, if applicable, and inform ABCSG.

15.2 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Delegation of Authority Form. Source documents are original documents, data, and records from which the participants case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from applicable national or international regulatory authorities. If required by national legislation, all original source documents supporting entries in the case report forms must be maintained and be readily available.
Any records and documents relating to the conduct of this study and the distribution of IP, including ICFs, eCRFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for a minimum of 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the

documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the national study sponsor. Written notification should be provided to the national study sponsor prior to transferring any records to another party or moving them to another location.

15.3 Data Collection

The site will be supplied with the following data collection tool: a web browser address for an Electronic Data Capture (EDC) system database that has been fully validated and conforms to 21 CFR Part 11 and the Guidance for Industry on Computerized Systems Used in Clinical Trials requirements. The EDC system provided by ABCSG, DATAPORT (software MACRO, provided byElsevier Ltd), enables the investigator to work on a web-based online documentation (e-CRF).
MACRO provides communication tools which will help users to manage discrepancies electronically, to conduct source data verification and to improve communication within the study team.

The trained Investigator site staff will enter the data required by the protocol into the eCRFs from source documents (e.g. medical records and study-specific data capture forms as needed) into the EDC system. All information on the eCRFs must be traceable to these source documents. Data recorded directly on the eCRFs will be defined before study start. eCRFs will be completed for all participants randomized to study treatment. eCRFs for subjects who are randomized but not treated will be completed with all data collected at the time of participantstudy discontinuation. A Clinical Monitor will review the eCRFs entered by investigational staff for completeness and accuracy according to respective national trial monitoring plan.

Automatic validation programs or manual checks for data discrepancies in the eCRFs may result in data queries generated for resolution by the investigational site. Designated investigator site staff is required to respond to these data queries and to perform/provide any necessary changes/clarifications to the data.

All treatment-emergent AEs (events occurring from the first dose of IP until 6 months after last administration of investigational product (denosumab or placebo) will be recorded. AEs will be coded using the MedDRA dictionary.

Clinical fractures and AESIs (ONJ and AFF) will be collected in the eCRF until EOS.

- To ensure the quality of clinical data across all participants and sites, a clinical data management review will be performed on participants data received at ABCSG. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be raised via EDC for site completion.
- The principal investigators/delegates will only sign the Investigator Verification Form and sign and date the indicated places on the CRF. These signatures will indicate that the principal investigator inspected or reviewed the CRF, the data queries, and the site notifications, and agrees with the content. Paper output of the CRF is available in case that the investigator or the IRB require hard copy output. At the end of the study ABCSG CDM will provide documented site data on an electronic storage device for the purpose of archiving.

15.4 Study Monitoring

The study will be monitored according to GCP by regular site visits and calls. National study sponsor is responsible for Monitoring activities in the respective country.

The responsible and adequately trained monitor (Clinical Research Associate, CRA) or his/her designee will contact and visit the study sites as defined in the study specific Monitoring Plan. The monitor will be permitted to inspect the various records of the study participants (e.g. source documents) on request provided that the participantconfidentiality is maintained in accordance with local regulations.

The monitor is responsible for eCRF inspection on a regular basis throughout the study according to the study specific Monitoring Plan in order to verify adherence to the study protocol and in order to verify completeness, consistency and accuracy of the entered data. Furthermore, the monitor follows the progress of participantenrollment and ensures that IP is stored, dispensed and accounted for according to defined specifications. The monitor will access participantrecords needed for verification of eCRF entries. The investigator or designee agrees to cooperate with the monitor to ensure resolution of problems and other issues identified during study monitoring.

The monitor is responsible for verifying the case report forms eCRF at regular intervals throughout the study to verify adherence to the protocol;, completeness, accuracy, and consistency of the data and adherence to local regulations on the conduct of clinical research.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

15.5 Quality Control/ Audits

The investigational site must also allow inspections by applicable health authorities and the respective national study sponsor in accordance with ICH GCP.

The national study sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, case report forms and other pertinent data) provided that subject confidentiality is respected. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

15.6 Important Protocol Deviations

The investigator is responsible to document and explain any important deviations from the approved protocol. The investigator should promptly report any deviations that might impact participantsafety and data integrity to the respective study sponsor, to ABCSG and if applicable, to the respective IRB/IEC/REC in accordance with local IRB/IEC/REC policies and procedures.

16. PUBLICATION STRATEGY

The Coordinating Investigators and ABCSG will comply with recognized ethical standards concerning publications and authorship, including Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors. Furthermore, publications and oral presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with any specific policy developed for the study.

A Publication Committee will be established from participating centers which will determine the writing committee and the appropriate number and position of authorships for all papers associated with the trial. It will be co-chaired by M Gnant (ABCSG) and the Chair of the Trial Steering Committee. Details and/or changes will be regulated by a dedicated presentation and publication charter.

17. TRIAL GOVERNANCE STRUCTURE

17.1 Translational Committee

A Translational Committee will be established from participating centers and will be originally be led by G Lindeman and J Penninger. The aim of this translational committee will be to define additional translational projects and to review study proposals relevant to the trial. Details and/or changes will be regulated by a dedicated translational research charter.

17.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be established to provide the overall supervision of the trial and will be chaired by J Garber. The TSC will monitor trial progress and conduct and advises on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Independent Data Monitoring Committee (IDMC) and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. Details and/or changes will be regulated by a dedicated TSC charter.

17.3 Independent Data Monitoring Committee (IDMC)

An independent Data Monitoring Committee (IDMC) will monitor accumulating participant safety data and evaluate important protocol deviations (IPDs) at specified frequencies until the last participant has completed study treatment.

The external IDMC will have access to participant treatment assignments. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or participants. This IDMC will review unblinded safety data. Safety analyses provided to the IDMC will be descriptive in nature.

Additional details and/or changes (e.g. IDMC members, communication, affiliations) will be provided in the IDMC charter.

18. TRANSLATIONAL RESEARCH PROGRAM

The following translational research questions may be addressed in this trial, if agreed upon by the respective national study sponsor:

- Measurement of serum markers of bone turnover at baseline, after 1 year (in centers in which annual serum collection is SoC), and within 1 year of study completion (in centers in which annual serum collection is SoC) in order to evaluate the effect of denosumab/placebo on bone turnover in both pre- and postmenopausal („postmenopausal“ includes premenopausal women who have undergone PBSO).
- Measurement of bone density at baseline and at yearly visits until treatmentcompletion in order to evaluate the effect of denosumab/placebo on bone density in both pre- and postmenopausal women („postmenopausal“ includes premenopausal women who have undergone PBSO) in centers in which this is SoC or locally funded.
- Measurement of serum RANK, RANKL, OPG, as well as E2, progesterone, LH and FSH, at baseline; and at yearly visits until treatment completion in order to evaluate the effect of denosumab/placebo on bone density in both pre- and postmenopausal women („postmenopausal“ includes premenopausal women who have undergone PBSO) in centers in which serum collection is SoC or locally funded.
- Collection of leucocyte DNA and cell-free DNA from plasma and whole cell blood at baseline and at treatment completion in all subjects (in centers in which blood collection is SoC or locally funded). Establishment of an NGS-based genomic signature in women who develop breast cancer or ovarian cancer - during the trial.
- Collection of tumor samples from patients who develop breast cancer or ovarian cancer during the trial for histology, immunophenotyping, gene expression and epigenetic / proteomic profiling in centers in which this procedure is SoC or locally funded.
- Serial collection of digital images (or plain films) to study breast mammographic

density (or breast background parenchymal enhancement on MRI using a BIRADs score).

- Profile germline SNPs that have been associated with altered breast cancer risk, mammographic density, bone mineral density and study their relationship to the effects of denosumab/placebo therapy.
- Analyze distal fallopian tubes collected at RRSO (Risk-reducing salpingo-oophorectomy) to determine the incidence of serous tubal in situ carcinoma (STIC), other precursor lesions and occult neoplasia .Study additional research questions / to perform additional analyses from biological material and / or clinical data that are to be collected within this trial (upon decision of the steering committee and in alignment with the national study sponsors).
- Measurement of Quality of Life in all participating women, as well as menopausal symptoms in participating perimenopausal/postmenopausal women by analysing QoL questionnaires completed by participants: (1) SF-12[48], a generic quality of life measure, (2) Cancer Worry Scale[49], (3) Impact of Events Scale (IES)[50] and (4) the Greene Climacteric Scale[51]).

19. INSURANCE AND INDEMNITY

The NHS indemnity scheme will apply to this study to ensure it meets the potential legal liability of the sponsor, equipment, employer and investigators/collaborators for harm to participants arising from the management, design and conduct of the research. No arrangements will be made for the payment of compensation in the unlikely event of harm.

21. APPENDICES

Appendix A: Classification Eastern Cooperative Oncology Group (ECOG) Performance Scale

0 - Fully active, able to carry out all pre-disease performance without restriction.

1 - Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, (eg, light housework, office work).

2 - Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 - Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.

5 - Dead.

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