BMJ Open

Microwave imaging for breast cancer screening: protocol for a multicentric, prospective study evaluating MammoWave system

SCHOLARONE™
Manuscripts

Microwave imaging for breast cancer screening: protocol for a multicentric, prospective study evaluating MammoWave system

Authors:

Daniel Álvarez Sánchez-Bayuela[1,2] (dalvarezs@sescam.jccm.es), Juan Fernández Martín[2] (jfernandezm@sescam.jccm.es), Gianluigi Tiberi[3,4*] (tiberig@lsbu.ac.uk), Navid Ghavami[3] (n.ghavami@ubt-tech.com), Rubén Giovanetti González[1,2] (rgiovanett@sescam.jccm.es), Lina Marcela Cruz Hernánez[1,2] (lmcruzh@sescam.jccm.es), Paul Martín Aguilar Angulo[1,2] (pmaa01@sescam.jccm.es), Aarón Darío Martínez Gómez[1,2] (aamartinezgomez@sescam.jccm.es), Ana Rodríguez Sánchez[1,2] (anarodriguezsanchez@sescam.jccm.es), Alessandra Bigotti[3] (a.bigotti@ubt-tech.com), Banafsheh Khalesi[3] (b.khalesi@ubt-tech.com), Letizia Pontoriero[5] (l.pontoriero@toscanalifesciences.org), Massimo Calabrese[6] (massimo.calabrese@hsanmartino.it), Alberto Tagliafico[6,7] (Alberto.Tagliafico@unige.it), Cristina Romero Castellano[1,2] (cromeroc@sescam.jccm.es)

[1] Hospital Universitario de Toledo (Servicio de Salud de Castilla - La Mancha, SESCAM), Toledo, Spain

[2] Grupo de Investigación Clínica Aplicada al Diagnóstico por Imagen, Instituto de Investigación Sanitaria de Castilla - La Mancha, Toledo, Spain

[3] UBT - Umbria Bioengineering Technologies, Perugia, Italy

[4] School of Engineering, London South Bank University, London, UK

[5] Fondazione Toscana Life Sciences, Siena, Italy

[6] IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[7] Department of Health Sciences, University of Genoa, Genoa, Italy

 # Corresponding Author:

Name: Gianluigi Tiberi

Affiliations: UBT - Umbria Bioengineering Technologies, Perugia, Italy

               School of Engineering, London South Bank University, London, UK

E-mails: tiberig@lsbu.ac.uk

               gianluigi@ubt-tech.com

Word count (main body): 4950

ABSTRACT

Introduction. Microwave imaging presents several potential advantages including its non-ionizing and harmless nature. This open, multicentric, interventional, prospective, non-randomized trial aims to validate MammoWave's AI-based classification algorithm, leveraging microwave imaging, to achieve a sensitivity exceeding 75% and a specificity exceeding 90% in breast screening.

Methods and analysis. 10,000 volunteers undergoing regular mammographic breast cancer screening will be recruited across nine European centers and invited to participate in the clinical study, involving MammoWave testing in both breasts. MammoWave results will be checked against the reference standard, to be intended as the output of conventional breast examination path. Anonymized clinical and MammoWave's results, including microwave images, associated features and a label provided by the AI-based classification algorithm, will be collected and stored in a dedicated electronic case report form. The prospective study will involve a comparative analysis between the output of conventional breast examination path (control intervention) and the labels provided by MammoWave's AI system (experimental intervention). These labels will categorize breasts into two groups: WSF (breast With Suspicious Finding), indicating the presence of a suspicious lesion, or NSF (No Suspicious Finding), indicating the absence of a lesion or the presence of a low-suspicion lesion. This trial aims to provide evidence regarding the novel MammoWave's AI system for detecting breast cancer in asymptomatic populations during screening.

Ethics and Dissemination. This study was approved by the Research Ethics Committee of the Liguria Region (CET), Italy (CET-Liguria: 524/2023 - DB id 13399), the Research Ethics Committee of Complejo Hospitalario de Toledo (CEIC), Spain (CEIC-1094), the National Ethics Committee for Clinical Research (CEIC), Portugal (CEIC-2311KC814), and the Bioethical Committee of Pomeranian Medical University in Szczecin, Poland (KB-006/23/2024). The findings of this study will be disseminated through academic and scientific conferences as well as peer-reviewed journals.

Trial registration number. ClinicalTrials.gov Identifier: NCT06291896

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first multicentric, prospective study to evaluate the screening efficacy of the MammoWave's AI solution within the framework of an asymptomatic population-based program for breast cancer detection.

- The MammoWave device will use an AI-powered clinical decision support system to automatically provide radiologists with a dedicated label indicating the presence or absence of suspicious findings in each breast.

- The study design will allow to investigate if MammoWave's AI solution reaches a sensitivity of over 75% and a specificity of over 90% in the detection of breast cancer within a screening population.

- The trial design will allow the comparative evaluation of both the conventional mammogram and MammoWave device in terms of cancer detection rate, number of recalls and positive predictive value, having as reference standard the 2-year follow-up of each volunteer.

- Study limitations include its non-randomized design. Moreover, the axillary region of the breast is not captured within MammoWave's cup. In addition, MammoWave's microwave images lack detailed morphological definition.

1.   INTRODUCTION

Breast cancer (BC) stands as the most prevalent cancer among women globally, with one in eight women experiencing its impact in their lifetime, rendering it a paramount challenge in public health (1–3). In response, many countries have instituted national or regional programs dedicated to early detection, exemplified by screening campaigns aimed at mitigating the burden of BC (4,5). At European level, the European Commission has always been committed to the fight against cancer, stimulating various initiatives such as the Europe's Beating Cancer Plan and the Mission Cancer, and acting by developing evidence-based recommendations. In fact, the European Commission Initiative on Breast Cancer (ECIBC) regularly updates a list of guidelines to perform and optimize breast screening practices, according to the existing level of evidence in used imaging technologies, age of screening, and frequency (6–8).

Full-field digital mammography, also called simply digital mammography (DM) and Digital Breast Tomosynthesis (DBT) serve as the gold standard technologies for mammographic screening, having demonstrated efficacy in reducing BC mortality through randomized controlled trials (5,9–12). However, these imaging modalities are not without limitations and potential adverse effects, including ionizing radiation exposure, breast compression discomfort, and inherent performance constraints associated with X-ray-based methods. Notably, dense breast tissue can diminish mammographic sensitivity, leading to reduced detection rates, and increased rates of false positives. To mitigate these challenges, recommendations such as double reading by expert radiologists and optimizing screening age and frequency have been proposed, considering the risk-benefit ratio of mammography (7,8,13). Indeed, risks associated with X-rays' cumulative effect, and low sensitivity in dense breasts, which may be reduced to 57.8% (14), limit the use of mammography in younger women or in reduced time intervals. In general, women are eligible for biennial screening only after the age of 45 according to ECIBC; nevertheless, recent studies estimate that 32.4% of new cancers in women aged under 50 are breast cancers (3,15). Moreover, emerging technologies like Computer Aided Detection (CAD) systems, based on deep learning algorithms (artificial intelligence) are aiding radiologists in interpretation and decision-making processes, offering potential improvements in screening efficacy (16–22).

Recognizing the imperative of early detection, attention has turned towards novel technologies such as Microwave Breast Imaging (MBI) as a promising avenue for overcoming the limitations of conventional X-ray-based approaches. MBI operates without ionizing radiation, utilizing radiofrequency (RF) signals to discern between healthy and malignant breast tissues based on their dielectric properties (23). Malignant cells, characterized by higher water and sodium accumulation, exhibit distinctive dielectric properties (conductivity and permittivity), allowing for microwave discrimination and cancer detection (24). Various MBI prototypes have been developed and clinically tested, among which MammoWave

(UBT - Umbria Bioengineering Technologies Srl, Italy) has garnered attention. MammoWave employs low-power microwaves and has demonstrated promising sensitivity for breast lesion detection in previous clinical trials (25–33), offering a non-compressive and safe imaging alternative that may be suitable for population-based mass BC screening.

Here, we introduce the approved clinical protocol (full title: A Clinical Investigation to Evaluate Microwave Imaging Via MammoWave in a Population-based Screening Program for Early Breast Cancer Detection, v. 1.0 of 04/09/2023) for an open, multicentric, interventional, prospective, and non-randomized trial aimed at evaluating, for the first time, MBI via MammoWave within the context of population-based BC screening. The study has been activated in the framework of the European co-funded project MammoScreen ("Innovative and safe microwave-based imaging technology to make BC screening more accurate, inclusive and female-friendly), under the programme Horizon Europe 2021-2027, grant ID 101097079. UBT - Umbria Bioengineering Technologies Srl is the sponsor of the study.

BOX 1 USE OF MAMMOWAVE'S AI SOLUTION IN BREAST SCREENING: ADVANTAGES AND LIMITATIONS

ADVANTAGES

- MammoWave's solution is based on harmless, non-ionizing microwave imaging which may allow more frequent examinations with no age restrictions.
- Dedicated facilities and sophisticated settings are not necessary.
- The scanning protocol, lasting 8 min per breast, is really simple: a technician will help the patient lie down, introducing the breast in a dedicated cup. Then, microwave images are reconstructed on an external server, and an AI-powered algorithm (machine learning approach) provides a label for each breast.
- MammoWave's AI is operator-free (no image interpretation is required).

LIMITATIONS

- Currently, there are no guidelines including the use of microwave imaging technologies in clinical practice.
- The cost-effectiveness and impact of implementing microwave imaging technologies have not been approached.
- The impact of hormonal changes in scattered radiofrequency signals and corresponding MammoWave microwave images during a woman's lifetime or menstrual cycle should be investigated.

2. METHODS AND ANALYSIS

2.1. MammoWave device and imaging algorithm

MammoWave (Fig. 1) is a new breast imaging device utilizing safe, non-ionizing low-power microwaves (radiofrequency signals), akin to those in mobile communications. It consists of two antennas emitting low-power (<1mW) radiofrequency signals in the microwave band (1-9 GHz) to illuminate the breast and measure corresponding scattered electromagnetic fields (denoted as S_{21}). The device's hardware comprises a cylindrical aluminum hub internally coated with an absorption cone structure, creating an anechoic chamber to absorb reflections of electromagnetic waves that could cause noise/artifacts during data acquisition. Two motorized arms support both antennas, rotating around the azimuth to irradiate the breast and capture scattered electromagnetic fields. Both transmitting (TX) and receiving (RX) antennas are connected to a Vector Network Analyzer (VNA) for precise signal transmission and measurement. The acquisition configuration involves 10 transmitting positions grouped into 5 doublet sections with centers at 0°, 72°, 144°, 216°, and 288°, with the receiving antenna collecting signals at 80 positions around the breast for each transmitting position. The VNA acquires the S_{21} parameter for 1601 frequencies from 1 to 9 GHz, in 5MHz increments. A Programming Logic Controller inside the hub controls all components, providing shield from external interferences and structural support. The examination bed, atop the hub, includes a plexiglass cup to accommodate the volunteer's breast without compression, with various cup sizes available for different breast sizes/types. The examination, lasting 8 minutes per breast, is performed with the woman lying face down.

MammoWave's software employs an imaging algorithm based on Huygens' principle (HP) to generate microwave images, which are intensity maps representing the homogeneity of breast tissues' dielectric properties (34,35). Images are maximum intensity projection coronal 2D maps of the entire breast volume. Specifically, after acquiring S_{21} data, the HP-based software produces microwave images and parameters describing them, such as the Max/Avg intensity ratio, used to assess images' non-homogeneity. MammoWave's output includes a label generated by a novel AI-based classification algorithm trained using previous clinical data (as described in the next sub-section).

2.1.1. MammoWave's artificial intelligence-powered clinical decision support system

MammoWave's novel software includes an artificial intelligence (machine learning-based) classification algorithm. This algorithm has been developed using the clinical data collected in a previous international, multicentric study (ClinicalTrials.gov Identifier: NCT04253366). In particular, the labels (reference standard, i.e. the output of conventional breast examination path) collected in such study were used for training and testing, with the aim of optimizing the AI-based classification algorithm (to be used, prospectively, within this clinical trial).

In particular, this AI-based classification algorithm works on the S_{21} data of each scanned breast, which is a matrix of complex electromagnetic signals derived from the measurement performed for multiple positions of the transmitting and receiving antennas and sampled in frequency. Principal Component Analysis (PCA) methods were used to reduce the matrix's dimensionality and fixing the number of components so that at least 95% of the variance in the data is accounted for. Various algorithms were tested (support vector machines (SVM), decision trees, random forests, logistic regression, k-nearest neighbors), using the cross-validation methodology and calculating the performances in terms of specificity and sensitivity (36). More specifically, the SVM-based algorithm will be used within this trial to categorize breasts into two groups: WSF (breast With Suspicious Finding), indicating the presence of a suspicious lesion, or NSF (No Suspicious Finding), indicating the absence of a lesion or the presence of a low-suspicion lesion.

As an examples, Fig. 2 shows MammoWave's output; reference standard output is also shown.

2.2. The clinical study

This study is entitled "A multicentric, prospective clinical investigation to evaluate microwave imaging via MammoWave in a population-based screening program for early breast cancer detection to make breast cancer screening more accurate, inclusive, and female-friendly" and has been activated in March 2024 (ClinicalTrials.gov Identifier: NCT06291896).

2.2.1. Hypothesis and objectives

The hypothesis underlying this clinical study aims to validate, prospectively, that MammoWave's AI-based classification algorithm achieves a sensitivity of over 75% and a specificity of over 90% in the detection of breast cancer within the screening process of asymptomatic individuals currently enrolled in population-based screening programmes.

The primary objective of this study is to generate evidence in the detection of BC by using MammoWave, evaluating its sensitivity and specificity, having as reference standard the output of conventional breast examination path (i.e. screening mammogram, integrated with other radiological/histological output when deemed necessary by the responsible Investigator). Additionally, there is a key safety objective to assess the safety and tolerability of MammoWave.

The secondary objectives of the study are as follows:

1. Evaluation of the sensitivity of MammoWave in detecting BC according to the ACR BI-RADS classification (37).
2. Evaluation of the effectiveness of MammoWave versus a conventional reading of digital mammographic images (either 2D or tomosynthesis) and analysis of whether they are equivalent in terms of detection rates of BC (sensitivity), number of recalls and positive predictive value (for the biopsies performed).
3. Evaluation of the detection rate (sensitivity) of each system according to the type of mammographic radiological finding (microcalcification, mass, asymmetry, or architectural distortion group).
4. Evaluation of the impact of breast density (according to the ACR BI-RADS classification (37) assigned by the radiologist, with or without automatic software if available) on the MammoWave detection rate of BC, number of recalls, and positive predictive value (of the biopsies performed).
5. Evaluation of the impact of breast density (according to BI-RADS classification assigned by the radiologist (37)) on the detection rate (sensitivity) of each system depending on the type of finding (microcalcification, mass, asymmetry, or architectural distortion group).

6. Comparison of radiological, histological, and stage characteristics between the BCs detected by each system.

7. Evaluation of the reproducibility of the AI-based MammoWave software's results.

8. Evaluation of the improvement in both sensitivity and specificity when retrospectively using AI algorithms to evaluate MammoWave data after its further optimization with all the data collected in the patients included in the study.

9. Volunteers' satisfaction related to MammoWave use, through a properly designed questionnaire collecting women's issues during the exam with MammoWave in the language spoken by the women.

Furthermore, an additional exploratory objective of the clinical study is to establish a predictive model capable of discriminating and classifying lesions in MammoWave outcomes for volunteers with breast lesions, if feasible.

2.2.2.   Study population, inclusion, and exclusion criteria

The study will include consecutive volunteers who are participants of the local, regional, or national breast cancer screening programs. These volunteers will fulfil all the prerequisites and inclusion criteria set forth by such programs, following the European guidelines on breast cancer screening and diagnosis (15): asymptomatic women aged between 45 and 74 years, with no indications of breast cancer suspicion, and not currently enrolled in other clinical imaging pathways (such as pathological, high-risk, or women with implants).

In more detail, participants fulfilling all the following inclusion criteria are eligible for the study: (1) women aged between 45 and 74 years old; (2) asymptomatic; (3) with signed informed consent form collected before starting any study activity; (4) with average risk of breast cancer (every woman except those with known BRCA1, 2, TP53, and/or previous breast cancer); (5) having a radiologist study output obtained using conventional mammographic exams, either 2D DM or 3D Digital Breast Tomosynthesis (DBT) (collecting oblique mediolateral projection [MLO] of the right breast, craniocaudal projection [CC] of the right breast, MLO projection of the left breast, CC projection of the left breast), performed within the past month with available results or planned to be performed in the same day of the MammoWave test or the subsequent days; and (6) with spontaneous willingness to comply with the Clinical Investigation Plan (CIP) and recommendations.

The presence of any one of the following criteria will lead to the exclusion of the participant: (1) women with breast prostheses; (2) women with symptoms or some sign of suspected breast cancer; (3) women with known BRCA 1, 2, TP53 or previous breast cancer; (4) pregnant women; (5) women who do not have a mammographic manifestation of the tumour (known occult breast cancer with only axillary manifestation); and (6) women with breast size larger than the largest MammoWave cup size.

2.2.3. Study design

This is an open, multicentric, interventional, prospective, non-randomized clinical investigation in which 10,000 volunteers undergoing conventional breast screening examination will also undergo the MammoWave exam. Recruitment of volunteers will be performed at nine centres in different European countries: two Italian hospitals (IRCCS Policlinico San Martino, Genova; and Ospedale San Giovanni Battista - USL Umbria 2, Foligno), one Polish hospital (Pomeranian Medical University Hospital, Szczecin), two Portuguese centres (Champalimaud Foundation, Lisbon; and Clínica Dr Passos Ângelo, Lisbon), three Spanish hospitals (Hospital Universitario de Toledo, Toledo; Hospital Universitario Reina Sofía, Córdoba; and Hospital General Universitario Morales Meseguer, Murcia), and one Swiss hospital (University Hospital, Zurich). The study (see Fig. 3) will be composed of two phases:

1) A preliminary phase is planned to validate and fine-tune the optimized MammoWave's AI classification algorithm. During this phase, the initial cohort will consist of 500 women recruited from all participating clinical sites. In this preliminary stage, all asymptomatic volunteers will undergo conventional mammography and ultrasound examinations at a minimum to ensure optimal diagnostic accuracy. Suspected cases will follow the standard site-specific pathways, which may include additional tests such as MRI and biopsy.

2) During the second phase, the remaining 9,500 women will be enrolled. If the MammoWave's AI label is positive, an ultrasound examination will be conducted (in addition to conventional mammography), particularly for women with dense breasts (recall, as per EUSOBI recommendations for screening in dense breasts (38)), unless such examination has already been performed. Suspected cases will follow the standard site-specific pathways, which may include additional tests such as MRI and biopsy. After the enrolment of 3,000 volunteers, an interim evaluation will be carried out.

Women attending the centres for their scheduled mammogram appointment (or those who have had a mammogram within the past month) will receive information about the study and will be invited to participate on a voluntary base. Women who agree to participate, meet the inclusion and exclusion criteria, and sign their Informed Consent Document (ICD) will undergo the MammoWave examination. The reason for non-participating in the study (fear of the new exam, lack of time, lack of information, lost-to-follow-up, breasts size larger than MammoWave's cup) will be recorded by the investigators.

Upon completion of MammoWave's scan of each breast, the data will undergo processing in a cloud platform to enable real-time and high-speed data processing. The output from MammoWave will primarily consist of microwave images (along with parameters that characterize these images) and will include the label generated by the novel AI-based classification algorithm; the label will be then used for final analysis by comparing it with conventional imaging results. Thus, the microwave images and

their associated features will not serve as a basis for diagnostic decisions made by radiologists or investigators.

Regarding intervention, if MammoWave's results (i.e., labels provided by its AI classification system) indicate WSF and there is disagreement between MammoWave output and conventional mammographic imaging, additional examinations may be warranted. These may include ultrasound, if not already conducted, particularly for dense breasts, aligning with EUSOBI recommendations due to the reduced sensitivity of conventional mammography in dense breasts (38). All output information, including MammoWave's results and conventional breast examination findings, will be collected and incorporated into this study. At each site, the investigators will prospectively compare MammoWave labels with the reference standard. Furthermore, upon the study's conclusion, the MammoWave labels will undergo centralized review by blinded specialists who will not have access to the reference standard. This review aims to validate the AI-produced data.

Following the study, a retrospective analysis will be conducted to refine an additional AI-generated algorithm using all acquired data. This algorithm will then be employed to re-evaluate the MammoWave data collected during the study, retrospectively reassessing the endpoints.

2.2.4. Choice of comparator/control intervention

MammoWave's results (labels provided by its AI-based classification algorithm), will undergo validation against a reference standard, which represents the output of the conventional breast examination pathway. This pathway includes screening mammograms conducted with digital mammography (DM) and digital breast tomosynthesis (DBT), integrated with other radiological/histological findings as required by the responsible investigator, following the site's ongoing procedures and clinical circuit. The reference standard's results will be categorized as "positive" when breast cancer (BC) presence is confirmed by histology (i.e., BI-RADS 6), otherwise labelled as "negative" (BI-RADS 1, 2, or 3).

Conventional mammogram studies (2D or tomosynthesis) will adhere to approved protocols and clinical practices for breast screening. Radiological reports and interpretations will align with international guidelines, particularly those set by the American College of Radiology (37). The radiologists involved in this study will have extensive experience in mammographic interpretation, serving as the benchmark during the study. Details such as single or double screening readings and the utilization of AI-assisted mammographic reading will be documented at each centre. Additionally, integration of conventional mammogram studies with other radiological/histological findings will occur when deemed necessary

by responsible investigators, who will record relevant variables in the electronic case report form (eCRF) following their usual clinical practice.

2.2.5. Collected variables

The following clinical variables will be collected per volunteer:

- Age (years).
- Mammographic breast density, rated according to the radiologist' BI-RADS assessment: A (breasts of fat density), B (breasts with areas of scattered fibroglandular tissue), C (heterogeneously dense breasts), D (extremely dense breasts).
- Breast (right/left) and quadrant (superior/inferior/lateral/medial) where the lesion is located (if present).
- BI-RADS score of the screening mammographic study for each breast (2D or tomosynthesis) according to the degree of suspicion (nominal qualitative variable).
- Breast type assigned by MammoWave (nominal qualitative variable): WSF, NSF.
- Radiological findings in the mammographic readings made by radiologists (none, nodule, microcalcifications, distortion, or asymmetric density).
- Additional tests (ultrasounds, MRI) performed, with correspondent outcomes (BI-RADS score, confirmed presence of BC, not conclusive, confirmed absence of BC).
- Biopsy performed, if any, with outcomes. When a biopsy is performed, the kind of method (Fine-needle aspiration biopsy or Core needle biopsy), histology of the lesion, and immunohistochemistry are recorded as:
    - Histopathological evaluation of BC according to typology (infiltrating ductal carcinoma, infiltrating lobular carcinoma, ductal carcinoma in situ, and other types).
    - Histopathological evaluation of BC according to tumour grade (I, II, III).
    - Molecular evaluation of BC (luminal A, luminal B, HER-2 positive, triple negative).
- Size of the confirmed lesion of BC (tumour), according to the tumour, node, and metastases (TNM) staging system (39) (T0: no evidence of primary tumour; T1mi: tumour less than or equal to 1mm; T1a: tumour between 1 and 5mm [included]; T1b: tumour between 5mm and 1cm [included]; T1c: tumour between 1 and 2cm [included]; T2: tumour between 2 and 5cm [included]; T3: tumour larger than 5cm; T4: tumour of any size with involvement in skin, chest wall or inflammatory BC).
- Lymph node involvement of BC, according to TNM staging system (N0: no evidence of BC in lymph nodes or areas of BC less than 0.2mm; N1: spread of BC in 1 to 3 internal axillary or mammary nodes; N2: spread of BC in 4 to 9 axillary nodes/spread of BC in internal mammary nodes, but not in axillary; N3: spread of BC to 10 or more nodes/spread of BC to supraclavicular or infraclavicular nodes).
- BC stage according to TNM staging system (0, IA, IIA, IIB, IIIB, IIIC).

- Suggested surgical treatment (conservative [quadrantectomy/lumpectomy]; radical).
- Women's satisfaction (a properly designed questionnaire collecting women's issues and plus during the exam with MammoWave in the language spoken by the women).
- Adverse events.

2.2.6. Study outcomes

The primary outcomes will be measured as follows:

- MammoWave's sensitivity (percentage of 'true positive' results) while using an optimized AI-based classification algorithm.
- MammoWave specificity (percentage of 'true negative' results) while using an optimized AI-based classification algorithm.

The secondary outcomes will be measured as follows:

- BC detection rates of each system by type of lesion (microcalcification, mass, asymmetry, or architectural distortion group).
- BC detection rates, recall, and positive predictive value (biopsy) of each system, also by breast density (types A and B being low-density breasts [fat], C and D high-density breasts [high content of fibroglandular tissue]).
- BC detection rates of each system by BI-RADS classification (37).
- BC detection rates of each system by type of lesion (microcalcification, mass, asymmetry, or architectural distortion group) and density (fat or high content of fibroglandular tissue).
- Program screening rate, calculated as the proportion of women diagnosed with BC in the study population.
- BC detection rates of each system by histological type and size of the BC, and BI-RADS classification (37).
- MammoWave's AI classification algorithm's sensitivity (frequency of 'true positive' results) and specificity (frequency of 'true negative' results) after a retrospective adjustment using the data at the end of the study.
- BC detection rate, recalls, and positive predictive value (biopsy), also by breast density (types A and B or C and D) after retrospective AI adjustment using the data at the end of the study.
- Program screening rate, calculated as the proportion of women diagnosed with BC in the study population after a retrospective adjustment using the data at the end of the study.
- Evaluation of the reproducibility of results comparing the lectures performed at the study centres and the centralized lectures.
- Volunteers' satisfaction through a properly designed questionnaire collecting women's issues during the exam with MammoWave in the language spoken by the women.

Regarding safety outcomes, all the events will be registered, and they will be identified as related or not to MammoWave.

2.2.7. Follow-up

The trial design will allow the comparative evaluation of both the conventional mammogram and MammoWave's AI solution in terms of cancer detection rate, number of recalls and positive predictive value, having as reference standard the 2-year follow-up of each volunteer. This follow-up allows to check retrospectively the possible rate of interval BC, and if this was reported as a false positive by MammoWave.

2.2.8. Study's ethical conduct

The study will be carried out following the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), in case of medical devices: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the European Law and the corresponding regulatory Competent Authorities (CA) requirements.

2.2.9. Patient privacy and confidentiality

The investigators will affirm and uphold the principle of the participant's right to privacy. Especially, the anonymity of the participants will be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

2.2.10. Patient and public involvement

This study will be carried out with patient involvement. Specifically, patients advocate and patient associations have been involved in the development of the study design, informed consent and satisfaction questionnaire. This involvement has been possible since: a) one patient association, i.e. Evita Cancro (Portugal), is a partner of the project MammoScreen, b) the MammoScreen project governance includes a dedicated Patient Advisory Group (PAG), i.e. an external board gathering the representatives of the major national/European patient organizations. PAG is periodically invited to support MammoScreen and provide guidance on clinical protocol, patients' continuous engagement tools, dissemination, and communication strategy.

2.3. Analysis

2.3.1. Number of Participants

The maximum number of participants will be 10,000 (for all the sites). The sample size was determined using the Buderer approach (40), considering that: (1) the primary objective of the study is to confirm that MammoWave reaches sensitivity > 75% and specificity > 90% in BC detection on 10,000 volunteers undergoing breast screening, (2) a 2-tailed 95% confidence interval (CI) for sensitivity and specificity (CI width = 10), and (3) a prevalence of female BC detected due to screening of 0.92%, according to the official English statistics of the NHS Breast Screening Programme (41). A minimum of 8,000 participants is required to reach the primary endpoint.

2.3.2. Datasets

For the analysis, the following datasets for specific populations have been defined: safety set (SAF), which corresponds to all study volunteers who undergo MammoWave examination; full analysis set (FAS), which includes all volunteers who undergo MammoWave examination and have an evaluable result for the primary endpoint; and per protocol set (PPS), which includes all volunteers who do not have significant CIP violations that regard inclusion/exclusion criteria or that can condition efficacy evaluations.

The primary analyses on both primary and secondary outcomes (except safety evaluation) will be performed on the FAS. The analyses on the PP population will be performed if the PP population differs from the FAS by at least 5% and will be considered supportive of the analyses on the FAS population (sensitivity analysis). The safety and tolerability analyses will be performed on the SAF.

2.3.3. Statistical considerations

Data from study participants will be analysed with descriptive statistics (mean, median, standard deviation, interquartile range, min/max for numerical variables, with frequency tables for categorical ones, percentages), 95% CIs as appropriate and graphical analysis on both the entire population and by strata (i.e. dense/no dense breast) at the interim analysis and the end of the study. All the methods adopted for the statistical analyses will be described in the Statistical Analysis Plan (SAP), to be issued before the interim analysis. The SAP will include a dedicated section in which the interim analyses are described. All analyses will be conducted using SAS (SAS Institute, Cary, NC) version 9.4.

2.3.4. Study period

The study commenced on March 15, 2024, with an anticipated conclusion on December 15, 2026. The enrolment period spans two years, from March 15, 2024, to March 15, 2026. The study completion, with the results report, is expected in November 2026.

Data collection, management, and monitoring

During each study visit, the study investigator (or designee) will first collect a written informed consent from the volunteer. All clinical data will be collected, anonymized, and properly identified with a dedicated study identification number, and stored in an Electronic Case Report Form (eCRF), secured by the Clinical Research Organization, CRO (JSB Solutions, Italy). The CRO will conduct all the monitoring activities at investigational sites. Data quality control measures will include queries. The eCRF system will record the date and time of any entry and/or correction and the user ID of the person making the entry/correction (audit trail). Only authorized investigators will be allowed to view and use the eCRF. The investigators will review all eCRFs and electronically sign and date them for each subject, verifying that the information is complete, true, and correct. All fields on the eCRF must be completed as applicable. Volunteers will be provided with a properly designed questionnaire collecting women's issues and thoughts during the exam with MammoWave, in the language spoken by the women. A copy of all questionnaires will be stored in the subject's folder as source document. It is the responsibility of the Investigator to correctly enter the data collected by the questionnaire in the relevant sections of the eCRF.

Data will not be shared with any outside person or organization and will not be used except for the development of this study.

eCRF pages will be reviewed both on-site, by the monitor of the centre, and remotely, by the Data Management staff of the CRO. Data Clarification Sheets (DCS) will be generated through the eCRF system, both automatically, through edit checks, and manually, by Clinical Research Associates (CRAs) and/or data managers; the investigator will have to check and solve them. The corresponding investigator is responsible for the review and approval of all query resolutions.

3.   ETHICS AND DISSEMINATION

This study was approved by the Research Ethics Committee of the Liguria Region (CET), Italy, on 13 November 2023 (approval number: CET - Liguria: 524/2023 - DB id 13399), the Research Ethics Committee of Complejo Hospitalario de Toledo (CEIC), Spain, on 29 November 2023 (approval number: CEIC - 1094), the National Ethics Committee for Clinical Research (CEIC), Portugal on 12 January 2024 (approval number: CEIC - 2311KC814), and the Bioethical Committee of Pomeranian Medical University in Szczecin, Poland (approval number: KB-006/23/2024) on 13 March 2024.

The findings of this study will be disseminated through academic and scientific conferences as well as peer-reviewed journals. Such publications will be planned and agreed upon with the investigators at each site.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
...

FIGURE CAPTIONS.

Figure 1. MammoWave system and its operability.

Figure 2. Left) Example of MammoWave output, which primarily consists of microwave image and includes the label generated by the novel AI-based classification algorithm, WSF for this breast; Right) reference standard output and details are given for the same breast.

Figure 3. Study design and recruitment process.

For peer review only

Author contributions

All authors met the criteria of authorship as outlined in the ICMJE and approved this manuscript for submission. Specific contributions were as follows.

Conceptualisation: D.Á.S.-B., J.F.M., G.T., N.G, L.P., M.C., AT., C.R.C.

MammoWave device and algorithm: D.Á.S.-B., G.T., N.G., A.B., B.K.

Methodology: all authors.

Drafting the work: R.G.G., L.M.C.H., P.M.A.A., A.D.M.G., A.R.S., A.B., B.K..

Revising it critically for important intellectual content: D.Á.S.-B., J.F.M., G.T., N.G., L.P., M.C., A.T., C.R.C.

Final approval of the version to be published: all authors.

Funding statement and disclaimer

Competing interests. Navid Ghavami, Gianluigi Tiberi, Banafsheh Khalesi and Alessandra Bigotti are employed by UBT - Umbria Bioengineering Technologies Srl. Navid Ghavami and Gianluigi Tiberi are shareholders of UBT - Umbria Bioengineering Technologies. UBT - Umbria Bioengineering Technologies Srl manufactured the microwave imaging device known as MammoWave. This does not alter our adherence to BMJOpen policies.

Patient and public involvement

This study will be carried out with patient involvement. Specifically, patients advocate and patient associations have been involved in the development of the study design, informed consent and satisfaction questionnaire. This involvement has been possible since: a) one patient association, i.e. Evita Cancro (Portugal), is a partner of the project MammoScreen, b) the MammoScreen project governance includes a dedicated Patient Advisory Group (PAG), i.e. an external board gathering the representatives of the major national/European patient organizations. PAG is periodically invited to support MammoScreen and provide guidance on clinical protocol, patients' continuous engagement tools, dissemination, and communication strategy.

References

1. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast Cancer Statistics, 2022. CA Cancer J Clin. 2022 Nov 3;72(6):524–41.

2. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. The Breast. 2022 Dec;66:15–23.

3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May 4;71(3):209–49.

4. Luo C, Wang L, Zhang Y, Lu M, Lu B, Cai J, et al. Advances in breast cancer screening modalities and status of global screening programs. Chronic Dis Transl Med. 2022 Jun 25;8(2):112–23.

5. Iwamoto Y, Kaucher S, Lorenz E, Bärnighausen T, Winkler V. Development of breast cancer mortality considering the implementation of mammography screening programs – a comparison of western European countries. BMC Public Health [Internet]. 2019 Dec;19(1):823. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-7166-6

6. Schünemann HJ, Lerda D, Dimitrova N, Alonso-Coello P, Gräwingholt A, Quinn C, et al. Methods for Development of the European Commission Initiative on Breast Cancer Guidelines. Ann Intern Med. 2019 Aug 20;171(4):273.

7. Canelo-Aybar C, Ferreira DS, Ballesteros M, Posso M, Montero N, Solà I, et al. Benefits and harms of breast cancer mammography screening for women at average risk of breast cancer: A systematic review for the European Commission Initiative on Breast Cancer. J Med Screen. 2021 Dec 25;28(4):389–404.

8. Canelo-Aybar C, Posso M, Montero N, Solà I, Saz-Parkinson Z, Duffy SW, et al. Benefits and harms of annual, biennial, or triennial breast cancer mammography screening for women at average risk of breast cancer: a systematic review for the European Commission Initiative on Breast Cancer (ECIBC). Br J Cancer. 2022 Mar 9;126(4):673–88.

9. Hanley JA, Hannigan A, O'Brien KM. Mortality reductions due to mammography screening: Contemporary population-based data. PLoS One. 2017;12(12):e0188947.

10. Romero Castellano C, Aguilar Angulo PM, Hernández LC, Sánchez-Camacho González-Carrato P, Giovanetti González R, Álvarez Martín J, et al. Breast cancer mortality after eight years of an improved screening program using digital breast tomosynthesis. J Med Screen [Internet]. 2021 Mar;096914132110025. Available from: http://journals.sagepub.com/doi/10.1177/09691413211002556

11. Broeders M, Moss S, Nyström L, Njor S, Jonsson H, Paap E, et al. The Impact of Mammographic Screening on Breast Cancer Mortality in Europe: A Review of Observational Studies. J Med Screen [Internet]. 2012 Sep;19(1_suppl):14–25. Available from: http://journals.sagepub.com/doi/10.1258/jms.2012.012078

12. Duffy SW, Vulkan D, Cuckle H, Parmar D, Sheikh S, Smith RA, et al. Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. Lancet Oncol. 2020 Sep;21(9):1165–72.

13. Siu AL. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016 Feb 16;164(4):279.

14. Tagliafico AS, Houssami N. Towards consensus on managing high mammographic density in population breast screening? The Breast. 2023 Jun;69:422–3.

15. European guidelines on breast cancer screening and diagnosis [Internet]. [cited 2023 May 20]. Available from: https://cancer-screening-and-care.jrc.ec.europa.eu/en/ecibc/european-breast-cancer-guidelines

16. Lång K, Hofvind S, Rodríguez-Ruiz A, Andersson I. Can artificial intelligence reduce the interval cancer rate in mammography screening? Eur Radiol. 2021 Aug 23;31(8):5940–7.

17. Lauritzen AD, Rodríguez-Ruiz A, von Euler-Chelpin MC, Lynge E, Vejborg I, Nielsen M, et al. An Artificial Intelligence–based Mammography Screening Protocol for Breast Cancer: Outcome and Radiologist Workload. Radiology. 2022 Jul;304(1):41–9.

18. Larsen M, Aglen CF, Lee CI, Hoff SR, Lund-Hanssen H, Lång K, et al. Artificial Intelligence Evaluation of 122 969 Mammography Examinations from a Population-based Screening Program. Radiology. 2022 Jun;303(3):502–11.

19. Romero-Martín S, Elías-Cabot E, Raya-Povedano JL, Gubern-Mérida A, Rodríguez-Ruiz A, Álvarez-Benito M. Stand-Alone Use of Artificial Intelligence for Digital Mammography and Digital Breast Tomosynthesis Screening: A Retrospective Evaluation. Radiology. 2022 Mar;302(3):535–42.

20. Larsen M, Aglen CF, Hoff SR, Lund-Hanssen H, Hofvind S. Possible strategies for use of artificial intelligence in screen-reading of mammograms, based on retrospective data from 122,969 screening examinations. Eur Radiol. 2022 Jun 15;32(12):8238–46.

21. van Winkel SL, Rodríguez-Ruiz A, Appelman L, Gubern-Mérida A, Karssemeijer N, Teuwen J, et al. Impact of artificial intelligence support on accuracy and reading time in breast tomosynthesis image interpretation: a multi-reader multi-case study. Eur Radiol. 2021 Nov 4;31(11):8682–91.

22. Pinto MC, Rodriguez-Ruiz A, Pedersen K, Hofvind S, Wicklein J, Kappler S, et al. Impact of Artificial Intelligence Decision Support Using Deep Learning on Breast Cancer Screening Interpretation with Single-View Wide-Angle Digital Breast Tomosynthesis. Radiology. 2021 Sep;300(3):529–36.

23. Nikolova N. Microwave Imaging for Breast Cancer. IEEE Microw Mag [Internet]. 2011 Dec;12(7):78–94. Available from: http://ieeexplore.ieee.org/document/6031961/

24. Lazebnik M, Popovic D, McCartney L, Watkins CB, Lindstrom MJ, Harter J, et al. A large-scale study of the ultrawideband microwave dielectric properties of normal, benign and malignant breast tissues obtained from cancer surgeries. Phys Med Biol. 2007 Oct 21;52(20):6093–115.

25. Sani L, Vispa A, Loretoni R, Duranti M, Ghavami N, Álvarez Sánchez-Bayuela D, et al. Breast lesion detection through MammoWave device: Empirical detection capability assessment of microwave images' parameters. Park CM, editor. PLoS One [Internet]. 2021 Apr;16(4):e0250005. Available from: https://dx.plos.org/10.1371/journal.pone.0250005

26. Álvarez Sánchez-Bayuela D, Ghavami N, Tiberi G, Sani L, Vispa A, Bigotti A, et al. A multicentric, single arm, prospective, stratified clinical investigation to evaluate MammoWave's ability in breast lesions detection. PLoS One. 2023 Jul 14;18(7):e0288312.

27. Álvarez Sánchez-Bayuela D, Giovanetti González R, Aguilar Angulo PM, Cruz Hernández LM, Sánchez-Camacho González-Carrato M del P, Rodríguez Sánchez A, et al. Integrating clinical research in an operative screening and diagnostic breast imaging department: First experience, results and perspectives using microwave imaging. Heliyon. 2023 Nov;9(11):e21904.

28. Álvarez Sánchez-Bayuela D, Giovanetti González R, Cruz Hernández LM, Aguilar Angulo PM, Sánchez-Camacho González-Carrato M del P, Rodríguez Sánchez A, et al. Introducing Microwave Breast Imaging via MammoWave into the clinical routine of a Reference Hospital. Results from a prospective, international clinical trial. In: European Congress of Radiology. EPOS; 2023.

29. Álvarez Sánchez-Bayuela D, Giovanetti González R, Cruz Hernández LM, Aguilar Angulo PM, Sánchez-Camacho González-Carrato M del P, Rodríguez Sánchez A, et al. Detection capabilities of the Microwave Breast Imaging system MammoWave on different malignant lesions. EPOS™; 2023.

30. Ghavami N, Sánchez-Bayuela DÁ, Sani L, Vispa A, Bigotti A, Badia M, et al. MammoWave Breast Imaging Device: An International and Multicentric Clinical Investigation. In: 2023 17th European Conference on Antennas and Propagation (EuCAP). IEEE; 2023. p. 1–5.

31. Sani L, Vispa A, Ghavami N, Loretoni R, Duranti M, Álvarez Sánchez-Bayuela D, et al. Empirical Assessment of Breast Lesion Detection Capability Through an Innovative Microwave Imaging Device. In: 2021 15th European Conference on Antennas and Propagation (EuCAP). IEEE; 2021. p. 1–5.

32. Sani L, Vispa A, Ghavami N, Sanchez-Bayuela DA, Badia M, Bigotti A, et al. MammoWave Breast Imaging Device: A Procedure for Device's Characterization Via Phantom Measurements and Subsequent Clinical Trials' Preliminary Results. In: 2021 IEEE Conference on Antenna Measurements & Applications (CAMA). IEEE; 2021. p. 483–6.

33. Romero Castellano C, Álvarez Sánchez-Bayuela D, Giovanetti González R, Cruz Hernández LM, Aguilar Angulo PM, Sánchez-Camacho González-Carrato M del P, et al. Microwave-Based Imaging for Breast Cancer Detection via MammoWave: Preliminary results of a Multicentric Trial in a Reference Hospital.

34. Ghavami N, Tiberi G, Craddock I, Probert Smith P, Edwards D. Non-iterative beamforming based on Huygens principle for multistatic ultrawide band radar: application to breast imaging. IET Microwaves, Antennas & Propagation [Internet]. 2015 Sep;9(12):1233–40. Available from: https://digital-library.theiet.org/content/journals/10.1049/iet-map.2014.0621

35. Tiberi G, Ghavami N, Edwards DJ, Monorchio A. Ultrawideband microwave imaging of cylindrical objects with inclusions. IET Microwaves, Antennas & Propagation [Internet]. 2011;5(12):1440. Available from: https://digital-library.theiet.org/content/journals/10.1049/iet-map.2011.0033

36. Papini L, Badia M, Sani L, Rana SP, Álvarez Sánchez-Bayuela D, Vispa A, et al. Breast Cancer Detection using Machine Learning Approaches on Microwave-based Data. In: 2023 17th European Conference on Antennas and Propagation (EuCAP). IEEE; 2023. p. 1–5.

37. D'Orsi C, Sickles E, Mendelson E, Morris E. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology; 2013.

38. Mann RM, Athanasiou A, Baltzer PAT, Camps-Herrero J, Clauser P, Fallenberg EM, et al. Breast cancer screening in women with extremely dense breasts recommendations of the European Society of Breast Imaging (EUSOBI). Eur Radiol. 2022 Jun 8;32(6):4036–45.

39. Koh J, Kim MJ. Introduction of a New Staging System of Breast Cancer for Radiologists: An Emphasis on the Prognostic Stage. Korean J Radiol. 2019;20(1):69.

40. Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med. 1996 Sep;3(9):895–900.

41. NHS Breast Screening Programme, England 2021-22 [Internet]. 2023 [cited 2024 Mar 18]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/breast-screening-programme/england---2021-22

Sketch of breast scan. Only for explanatory purposes. Note that whole breast is inserted into the cup and scanned.

2-port vector network analyser, i.e. the microwave signals generator & receptor, connected to Tx and Rx antennas

Cloud platform to allow real-time/high speed remote MammoWave data processing (anonymized)

MammoWave output will then be sent back to the PI

MammoWave output will be automatically recorded into eCRF

Figure 1. MammoWave system and its operability.

338x190mm (300 x 300 DPI)

MammoWave's output label: WSF

Female, 66 years old.
BI-RADS density: D
Microcalcifications
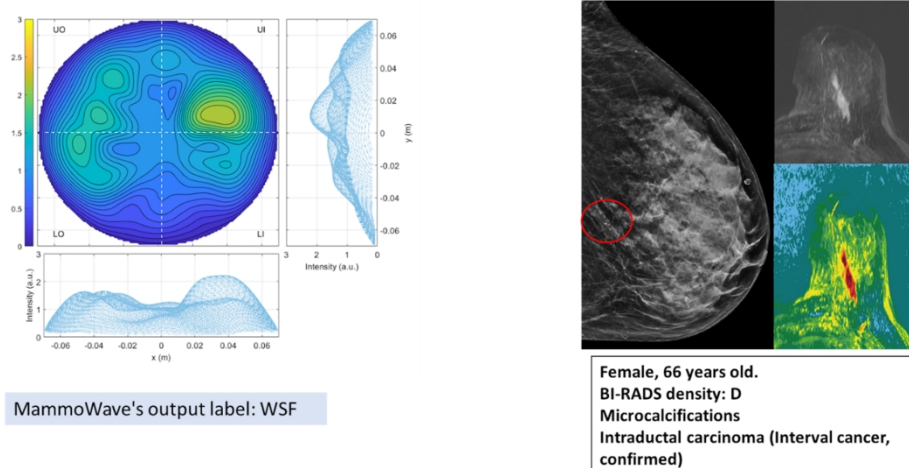Intraductal carcinoma (Interval cancer, confirmed)

Figure 2. Left) Example of MammoWave output, which primarily consists of microwave image and includes the label generated by the novel AI-based classification algorithm, WSF for this breast; Right) reference standard output and details are given for the same breast.
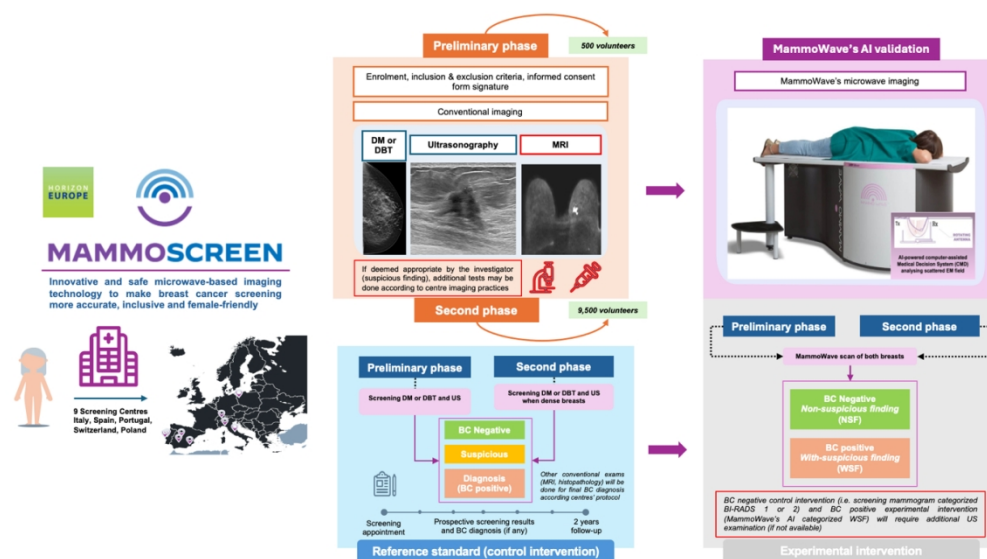
338x190mm (300 x 300 DPI)

Figure 3. Study design and recruitment process.

403x225mm (87 x 87 DPI)

BMJ Open

Microwave imaging for breast cancer screening: protocol for a multicentric, prospective study to evaluate cancer detection capabilities of MammoWave system on an asymptomatic population across multiple European countries

SCHOLARONE™
Manuscripts

Microwave imaging for breast cancer screening: protocol for an open, multicentric, interventional, prospective, nonrandomized clinical investigation to evaluate cancer detection capabilities of MammoWave system on an asymptomatic population across multiple European countries

Authors:

Daniel Álvarez Sánchez-Bayuela[1,2] (dalvarezs@sescam.jccm.es), Juan Fernández Martín[2] (jfernandezm@sescam.jccm.es), Gianluigi Tiberi[3,4*] (tiberig@lsbu.ac.uk), Navid Ghavami[3] (n.ghavami@ubt-tech.com), Rubén Giovanetti González[1,2] (rgiovanett@sescam.jccm.es), Lina Marcela Cruz Hernánez[1,2] (lmcruzh@sescam.jccm.es), Paul Martín Aguilar Angulo[1,2] (pmaa01@sescam.jccm.es), Aarón Darío Martínez Gómez[1,2] (aamartinezgomez@sescam.jccm.es), Ana Rodríguez Sánchez[1,2] (anarodriguezsanchez@sescam.jccm.es), Alessandra Bigotti[3] (a.bigotti@ubt-tech.com), Banafsheh Khalesi[3] (b.khalesi@ubt-tech.com), Letizia Pontoriero[5] (l.pontoriero@toscanalifesciences.org), Massimo Calabrese[6] (massimo.calabrese@hsanmartino.it), Alberto Tagliafico[6,7] (Alberto.Tagliafico@unige.it), Cristina Romero Castellano[1,2] (cromeroc@sescam.jccm.es)

[1] Hospital Universitario de Toledo (Servicio de Salud de Castilla - La Mancha, SESCAM), Toledo, Spain

[2] Grupo de Investigación Clínica Aplicada al Diagnóstico por Imagen, Instituto de Investigación Sanitaria de Castilla - La Mancha, Toledo, Spain

[3] UBT - Umbria Bioengineering Technologies, Perugia, Italy

[4] School of Engineering, London South Bank University, London, UK

[5] Fondazione Toscana Life Sciences, Siena, Italy

[6] IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[7] Department of Health Sciences, University of Genoa, Genoa, Italy

 # Corresponding Author:

Name: Gianluigi Tiberi

Affiliations: UBT - Umbria Bioengineering Technologies, Perugia, Italy

               School of Engineering, London South Bank University, London, UK

E-mails: tiberig@lsbu.ac.uk

               gianluigi@ubt-tech.com

Word count (main body): 4950

ABSTRACT

Introduction. Microwave imaging presents several potential advantages including its non-ionizing and harmless nature. This open, multicentric, interventional, prospective, non-randomized trial aims to validate MammoWave's AI-based classification algorithm, leveraging microwave imaging, to achieve a sensitivity exceeding 75% and a specificity exceeding 90% in breast screening.

Methods and analysis. 10,000 volunteers undergoing regular mammographic breast cancer screening will be recruited across nine European centres and invited to participate in the clinical study, involving MammoWave testing on both breasts. MammoWave results will be checked against the reference standard, to be intended as the output of conventional breast examination path (with histological confirmation of cancer cases) with 2 years follow up. Anonymized clinical and MammoWave's results, including microwave images, associated features and a label provided by the AI-based classification algorithm, will be collected and stored in a dedicated electronic case report form. The prospective study will involve a comparative analysis between the output of conventional breast examination path (control intervention) and the labels provided by MammoWave's AI system (experimental intervention). These labels will categorize breasts into two groups: WSF (breast With Suspicious Finding), indicating the presence of a suspicious lesion, or NSF (No Suspicious Finding), indicating the absence of a lesion or the presence of a low-suspicion lesion. This trial aims to provide evidence regarding the novel MammoWave's AI system for detecting breast cancer in asymptomatic populations during screening.

Ethics and Dissemination. This study was approved by the Research Ethics Committee of the Liguria Region (CET), Italy (CET-Liguria: 524/2023 - DB id 13399), the Research Ethics Committee of Complejo Hospitalario de Toledo (CEIC), Spain (CEIC-1094), the National Ethics Committee for Clinical Research (CEIC), Portugal (CEIC-2311KC814), the Bioethical Committee of Pomeranian Medical University in Szczecin, Poland (KB-006/23/2024) and the Zurich Cantonal Ethics Commission, Switzerland (BASEC 2023-D0101). The findings of this study will be disseminated through academic and scientific conferences as well as peer-reviewed journals.

Trial registration number. ClinicalTrials.gov Identifier: NCT06291896

STRENGTHS AND LIMITATIONS OF THIS STUDY

● This is the first multicentric, prospective study to evaluate the sensitivity and specificity of MammoWave's AI solution within the framework of an asymptomatic population-based program for breast cancer detection.

● The MammoWave device will use an AI-powered clinical decision support system to automatically provide radiologists with a dedicated label indicating the presence or absence of suspicious findings in each breast.

● As reference standard, the 2-year follow-up with histological confirmation of cancer cases will be used.

● Study limitations include its non-randomized design.

● The axillary region of the breast is not captured within MammoWave's cup.

1.   INTRODUCTION

Breast cancer (BC) stands as the most prevalent cancer among women globally, with one in eight women experiencing its impact in their lifetime, rendering it a paramount challenge in public health (1–3). In response, many countries have instituted national or regional programs dedicated to early detection, exemplified by screening campaigns aimed at mitigating the burden of BC (4,5). At European level, the European Commission has always been committed to the fight against cancer, stimulating various initiatives such as the Europe's Beating Cancer Plan and the Mission Cancer, and acting by developing evidence-based recommendations. In fact, the European Commission Initiative on Breast Cancer (ECIBC) regularly updates a list of guidelines to perform and optimize breast screening practices, according to the existing level of evidence in used imaging technologies, age of screening, and frequency (6–8).

Full-field digital mammography, also called simply digital mammography (DM) and Digital Breast Tomosynthesis (DBT) serve as the gold standard technologies for mammographic screening, having demonstrated efficacy in reducing BC mortality through randomized controlled trials (5,9–12). However, these imaging modalities are not without limitations and potential adverse effects, including ionizing radiation exposure, breast compression discomfort, and inherent performance constraints associated with X-ray-based methods. Notably, dense breast tissue can diminish mammographic sensitivity, leading to reduced detection rates, and increased rates of false positives. To mitigate these challenges, recommendations such as double reading by expert radiologists and optimizing screening age and frequency have been proposed, considering the risk-benefit ratio of mammography (7,8,13). Indeed, risks associated with X-rays' cumulative effect, and low sensitivity in dense breasts, which may be reduced to 57.8% (14), limit the use of mammography in younger women or in reduced time intervals. In general, women are eligible for biennial screening only after the age of 45 according to ECIBC; nevertheless, recent studies estimate that 32.4% of new cancers in women aged under 50 are breast cancers (3,15). Moreover, emerging technologies like Computer Aided Detection (CAD) systems, based on deep learning algorithms (artificial intelligence) are aiding radiologists in interpretation and decision-making processes, offering potential improvements in screening efficacy (16–22).

Recognizing the imperative of early detection, attention has turned towards novel technologies such as Microwave Breast Imaging (MBI) as a promising avenue for overcoming the limitations of conventional X-ray-based approaches. MBI operates without ionizing radiation, utilizing radiofrequency (RF) signals to discern between healthy and malignant breast tissues based on their dielectric properties (23). Malignant cells, characterized by higher water and sodium accumulation, exhibit distinctive dielectric properties (conductivity and permittivity), allowing for microwave discrimination and cancer detection (24). Various MBI prototypes have been developed and clinically tested, among which MammoWave

(UBT - Umbria Bioengineering Technologies Srl, Italy) has garnered attention. MammoWave employs low-power microwaves and has demonstrated promising sensitivity for breast lesion detection in previous clinical trials (25–33), offering a non-compressive and safe imaging alternative that may be suitable for population-based mass BC screening.

Here, we introduce the approved clinical protocol (full title: A Clinical Investigation to Evaluate Microwave Imaging Via MammoWave in a Population-based Screening Program for Early Breast Cancer Detection, v. 1.0 of 04/09/2023) for an open, multicentric, interventional, prospective, and non-randomized trial aimed at evaluating, for the first time, MBI via MammoWave within the context of population-based BC screening. The study has been activated in the framework of the European co-funded project MammoScreen ("Innovative and safe microwave-based imaging technology to make BC screening more accurate, inclusive and female-friendly"), under the programme Horizon Europe 2021-2027, grant ID 101097079. UBT - Umbria Bioengineering Technologies Srl is the sponsor of the study. Potential advantages and current limitation of MammoWave's solution are reported in box 1

BOX 1 USE OF MAMMOWAVE'S AI SOLUTION IN BREAST SCREENING: ADVANTAGES AND LIMITATIONS

ADVANTAGES

- MammoWave's solution is based on harmless, non-ionizing microwave imaging which may allow more frequent examinations with no age restrictions.

- Dedicated facilities and sophisticated settings are not necessary.

- The scanning protocol, lasting 8 min per breast, is simple: a technician will help the patient lie down, introducing the breast in a dedicated cup. Then, microwave images are reconstructed on an external server, and an AI-powered algorithm (machine learning approach) provides a label for each breast.

- MammoWave's AI is operator-free (no image interpretation is required).

LIMITATIONS

- Currently, there are no guidelines including the use of microwave imaging technologies in clinical practice.

- The cost-effectiveness and impact of implementing microwave imaging technologies have not been approached.

- The impact of hormonal changes in scattered radiofrequency signals and corresponding MammoWave microwave images during a woman's lifetime or menstrual cycle should be investigated.

2. METHODS AND ANALYSIS

2.1. MammoWave device and imaging algorithm

MammoWave (Fig. 1) is a new breast imaging device utilizing safe, non-ionizing low-power microwaves (radiofrequency signals), akin to those in mobile communications. It consists of two antennas emitting low-power (<1mW) radiofrequency signals in the microwave band (1-9 GHz) to illuminate the breast and measure corresponding scattered electromagnetic fields (denoted as S_{21}). The device's hardware comprises a cylindrical aluminium hub internally coated with an absorption cone structure, creating an anechoic chamber to absorb reflections of electromagnetic waves that could cause noise/artifacts during data acquisition. Two motorized arms support both antennas, rotating around the azimuth to irradiate the breast and capture scattered electromagnetic fields. Both transmitting (TX) and receiving (RX) antennas are connected to a Vector Network Analyzer (VNA) for precise signal transmission and measurement. The acquisition configuration involves 10 transmitting positions grouped into 5 doublet sections with centres at 0°, 72°, 144°, 216°, and 288°, with the receiving antenna collecting signals at 80 positions around the breast for each transmitting position. The VNA acquires the S_{21} parameter for 1601 frequencies from 1 to 9 GHz, in 5 MHz increments. A Programming Logic Controller inside the hub controls all components, providing shield from external interferences and structural support. The examination bed, atop the hub, includes a plexiglass cup to accommodate the volunteer's breast without compression, with various cup sizes available for different breast sizes/types. The examination, lasting 8 minutes per breast, is performed with the woman lying face down.

MammoWave's software employs an imaging algorithm based on Huygens' principle (HP) to generate microwave images, which are intensity maps representing the homogeneity of breast tissues' dielectric properties (34,35). Images are maximum intensity projection coronal 2D maps of the entire breast volume. Specifically, after acquiring S_{21} data, the HP-based software produces microwave images and parameters describing them, such as the Max/Avg intensity ratio, used to assess images' non-homogeneity. MammoWave's output includes a label generated by a novel AI-based classification algorithm trained using previous clinical data (as described in the next sub-section).

2.1.1. MammoWave's artificial intelligence-powered clinical decision support system

MammoWave's novel software includes an artificial intelligence (machine learning-based) classification algorithm. This algorithm has been developed using the clinical data collected in a previous international, multicentric study (ClinicalTrials.gov Identifier: NCT04253366). In particular, the labels (reference standard, i.e. the output of conventional breast examination path) collected in such

study were used for training and testing, with the aim of optimizing the AI-based classification algorithm (to be used, prospectively, within this clinical trial).

In particular, this AI-based classification algorithm works on the S_{21} data of each scanned breast, which is a matrix of complex electromagnetic signals derived from the measurement performed for multiple positions of the transmitting and receiving antennas and sampled in frequency. Principal Component Analysis (PCA) methods were used to reduce the matrix's dimensionality and fixing the number of components so that at least 95% of the variance in the data is accounted for. Various algorithms were tested (support vector machines (SVM), decision trees, random forests, logistic regression, k-nearest neighbours), using the cross-validation methodology and calculating the performances in terms of specificity and sensitivity (36). More specifically, the SVM-based algorithm will be used within this trial to categorize breasts into two groups: WSF (breast With Suspicious Finding), indicating the presence of a suspicious lesion, or NSF (No Suspicious Finding), indicating the absence of a lesion or the presence of a low-suspicion lesion. More details related to algorithm's validation methodology and performances in terms of specificity and sensitivity can be found in (36), where specificity of up to ~90% and sensitivity of up to ~85% have been reported.

As an examples, Fig. 2 shows MammoWave's output; reference standard output is also shown.

2.2. The clinical study

This study is entitled "A multicentric, prospective clinical investigation to evaluate microwave imaging via MammoWave in a population-based screening program for early breast cancer detection to make breast cancer screening more accurate, inclusive, and female-friendly" and has been activated in March 2024 (ClinicalTrials.gov Identifier: NCT06291896).

2.2.1. Hypothesis and objectives

The aim of this clinical study is to validate, prospectively, MammoWave's AI-based classification algorithm. The hypothesis underlying this clinical study is that MammoWave's AI-based classification algorithm achieves a sensitivity of over 75% and a specificity of over 90% in the detection of breast cancer within the screening process of asymptomatic individuals currently enrolled in population-based screening programmes.

The primary objective of this study is to generate evidence in the detection of BC by using MammoWave, evaluating its sensitivity and specificity, having as reference standard the output of conventional breast examination path (i.e. screening mammogram, integrated with other radiological/histological output when deemed necessary by the responsible Investigator).

The secondary objectives of the study are as follows:

1. Evaluation of the sensitivity of MammoWave in detecting BC according to the American College of Radiology (ACR) BI-RADS classification (37).
2. Evaluation of the effectiveness of MammoWave versus a conventional reading of digital mammographic images (either 2D or tomosynthesis) and analysis of whether they are equivalent in terms of detection rates of BC (sensitivity), number of recalls and positive predictive value (for the biopsies performed).
3. Evaluation of the detection rate (sensitivity) of each system according to the type of mammographic radiological finding (microcalcification, mass, asymmetry, or architectural distortion group).
4. Evaluation of the impact of breast density (according to the ACR BI-RADS classification (37) assigned by the radiologist, with or without automatic software if available) on the MammoWave detection rate of BC, number of recalls, and positive predictive value (of the biopsies performed).
5. Evaluation of the impact of breast density (according to BI-RADS classification assigned by the radiologist (37)) on the detection rate (sensitivity) of each system depending on the type of finding (microcalcification, mass, asymmetry, or architectural distortion group).

6. Comparison of radiological, histological, and stage characteristics between the BCs detected by each system.

7. Evaluation of the reproducibility of the AI-based MammoWave software's results.

8. Evaluation of the improvement in both sensitivity and specificity when retrospectively using AI algorithms to evaluate MammoWave data after its further optimization with all the data collected in the patients included in the study.

9. Volunteers' satisfaction related to MammoWave use, through a properly designed questionnaire (given here as supplementary material), collecting women's issues during the exam with MammoWave in the language spoken by the women.

Additionally, there is a secondary objective which is related to MammoWave safety and tolerability assessment. Furthermore, an additional exploratory objective of the clinical study is to establish a predictive model capable of discriminating and classifying lesions in MammoWave outcomes for volunteers with breast lesions, if feasible.

2.2.2. Study population, inclusion, and exclusion criteria

The study will include consecutive volunteers who are participants of the local, regional, or national breast cancer screening programs. These volunteers will fulfil all the prerequisites and inclusion criteria set forth by such programs, following the European guidelines on breast cancer screening and diagnosis (15): asymptomatic women aged between 45 and 74 years, with no indications of breast cancer suspicion, and not currently enrolled in other clinical imaging pathways (such as pathological, high-risk, or women with implants).

In more detail, participants fulfilling all the following inclusion criteria are eligible for the study: (1) women aged between 45 and 74 years old; (2) asymptomatic; (3) with signed informed consent form collected before starting any study activity; (4) with average risk of breast cancer (every woman except those with known BRCA1, 2, TP53, and/or previous breast cancer); (5) having a radiologist study output obtained using conventional mammographic exams, either 2D DM or 3D Digital Breast Tomosynthesis (DBT) (collecting oblique mediolateral projection [MLO] of the right breast, craniocaudal projection [CC] of the right breast, MLO projection of the left breast, CC projection of the left breast), performed within the past month with available results or planned to be performed in the same day of the MammoWave test or the subsequent days; and (6) with spontaneous willingness to comply with the Clinical Investigation Plan (CIP) and recommendations.

The presence of any one of the following criteria will lead to the exclusion of the participant: (1) women with breast prostheses; (2) women with symptoms or some sign of suspected breast cancer; (3) women with known BRCA 1, 2, TP53 or previous breast cancer; (4) pregnant women; (5) women who do not

have a mammographic manifestation of the tumour (known occult breast cancer with only axillary manifestation); and (6) women with breast size larger than the largest MammoWave cup size.

2.2.3. Study design

This is an open, multicentric, interventional, prospective, non-randomized clinical investigation in which 10,000 volunteers undergoing conventional breast screening examination will also undergo the MammoWave exam. Recruitment of volunteers will be performed at nine centres in different European countries: two Italian hospitals (IRCCS Policlinico San Martino, Genova; and Ospedale San Giovanni Battista - USL Umbria 2, Foligno), one Polish hospital (Pomeranian Medical University Hospital, Szczecin), two Portuguese centres (Champalimaud Foundation, Lisbon; and Clínica Dr Passos Ângelo, Lisbon), three Spanish hospitals (Hospital Universitario de Toledo, Toledo; Hospital Universitario Reina Sofía, Córdoba; and Hospital General Universitario Morales Meseguer, Murcia), and one Swiss hospital (University Hospital, Zurich). The study (see Fig. 3) will be composed of two phases:

1) A preliminary phase is planned to validate and fine-tune the optimised MammoWave's AI classification algorithm. During this phase, the initial cohort will consist of 500 women recruited from all participating clinical sites. In this preliminary stage, all asymptomatic volunteers will undergo conventional mammography and ultrasound (US) examinations at a minimum to ensure optimal diagnostic accuracy. Suspected cases will follow the standard site-specific pathways, which may include additional tests such as Magnetic Resonance Imaging (MRI) and biopsy.

2) During the second phase, the remaining 9,500 women will be enrolled. If the MammoWave's AI label is positive, an ultrasound examination will be conducted (in addition to conventional mammography), particularly for women with dense breasts (recall, as per the European Society of Breast Imaging, EUSOBI, recommendations for screening in dense breasts (38)), unless such examination has already been performed. Suspected cases will follow the standard site-specific pathways, which may include additional tests such as MRI and biopsy. After the enrolment of 3,000 volunteers, an interim evaluation will be carried out.

Women attending the centres for their scheduled mammogram appointment (or those who have had a mammogram within the past month) will receive information about the study and will be invited to participate on a voluntary base. Women who agree to participate, meet the inclusion and exclusion criteria, and sign their Informed Consent Document (ICD) will undergo the MammoWave examination. All the eligible women will be enrolled consecutively. The reason for non-participating in the study (fear of the new exam, lack of time, lack of information, lost-to-follow-up, breasts size larger than MammoWave's cup) will be recorded by the investigators.

Upon completion of MammoWave's scan of each breast, the data will undergo processing in a cloud platform to enable real-time and high-speed data processing. The output from MammoWave will primarily consist of microwave images (along with parameters that characterize these images) and will include the label generated by the novel AI-based classification algorithm; the label will be then used for final analysis by comparing it with conventional imaging results. Thus, the microwave images (which lack detailed morphological definition) and their associated features will not serve as a basis for diagnostic decisions made by radiologists or investigators.

Regarding intervention, if MammoWave's results (i.e., labels provided by its AI classification system) indicate WSF and there is disagreement between MammoWave output and conventional mammographic imaging, additional examinations may be warranted. These may include ultrasound, if not already conducted, particularly for dense breasts, aligning with EUSOBI recommendations due to the reduced sensitivity of conventional mammography in dense breasts (38). All output information, including MammoWave's results and conventional breast examination findings, will be collected and incorporated into this study. At each site, the investigators will prospectively compare MammoWave labels with the reference standard. Furthermore, upon the study's conclusion, the MammoWave labels will undergo centralized review by blinded specialists who will not have access to the reference standard. This review aims to validate the AI-produced data.

Following the study, a retrospective analysis will be conducted to refine an additional AI-generated algorithm using all acquired data. This algorithm will then be employed to re-evaluate the MammoWave data collected during the study, retrospectively reassessing the endpoints.

Regarding blinding strategies, the study will proceed as follows: first, each mammogram (either full-field digital mammography or digital breast tomosynthesis) will be independently double-read by two radiologists, with consensus or arbitration for any discordant interpretations, in accordance with European breast screening guidelines (European Guidelines on Breast Cancer Screening and Diagnosis, European Commission Initiative on Breast Cancer). Following this, all the eligible women will be enrolled consecutively, as detailed above. Blinding will be in place for the participants within the study. The output from MammoWave will be automatically transmitted to the responsible Investigator; blinding will be in place for MammoWave analysis.

2.2.4. Study period

Recruitment started in February 2024; recruitment of the last participant is planned on February 2026. The deadline for first evaluation of the results in planned on December 2026.

2.2.5. Choice of comparator/control intervention

MammoWave's results (labels provided by its AI-based classification algorithm), will undergo validation against a reference standard, which represents the output of the conventional breast examination pathway. This pathway includes screening mammograms conducted with DM or DBT, integrated with other radiological/histological findings as required by the responsible investigator, following the site's ongoing procedures and clinical circuit. The reference standard's results will be categorized as "positive" when BC presence is confirmed by histology (i.e., BI-RADS 6), otherwise labelled as "negative" (BI-RADS 1, 2, or 3). Specifically, within this study BI-RADS 4 and BI-RADS 5 are only image suspicion criteria: when a biopsy is performed, they will be categorized as "positive" when BC presence is confirmed by histology (i.e., BI-RADS 6), otherwise labelled as "negative" (BI-RADS 1, 2, or 3).

Conventional mammogram studies (2D or tomosynthesis) will adhere to approved protocols and clinical practices for breast screening. Radiological reports and interpretations will align with international guidelines, particularly those set by the American College of Radiology (37). The radiologists involved in this study will have extensive experience in mammographic interpretation, serving as the benchmark during the study. Details such as single or double screening readings and the utilization of AI-assisted mammographic reading will be documented at each centre. Additionally, integration of conventional mammogram studies with other radiological/histological findings will occur when deemed necessary by responsible investigators, who will record relevant variables in the electronic case report form (eCRF) following their usual clinical practice.

2.2.6. Collected variables

The following clinical variables will be collected per volunteer:

- Age (years).
- Mammographic breast density, rated according to the radiologist' BI-RADS assessment: A (breasts of fat density), B (breasts with areas of scattered fibroglandular tissue), C (heterogeneously dense breasts), D (extremely dense breasts).
- Breast (right/left) and quadrant (superior/inferior/lateral/medial) where the lesion is located (if present).
- BI-RADS score of the screening mammographic study for each breast (2D or tomosynthesis) according to the degree of suspicion (nominal qualitative variable).
- Breast type assigned by MammoWave (nominal qualitative variable): WSF, NSF.
- Radiological findings in the mammographic readings made by radiologists (none, nodule, microcalcifications, distortion, or asymmetric density).

- Additional tests (ultrasounds, MRI) performed, with correspondent outcomes (BI-RADS score, confirmed presence of BC, not conclusive, confirmed absence of BC).
- Biopsy performed, if any, with outcomes. When a biopsy is performed, the kind of method (Fine-needle aspiration biopsy or Core needle biopsy), histology of the lesion, and immunohistochemistry are recorded as:
  - Histopathological evaluation of BC according to typology (infiltrating ductal carcinoma, infiltrating lobular carcinoma, ductal carcinoma in situ, and other types).
  - Histopathological evaluation of BC according to tumour grade (I, II, III).
  - Molecular evaluation of BC (luminal A, luminal B, HER-2 positive, triple negative).
- Size of the confirmed lesion of BC (tumour), according to the tumour, node, and metastases (TNM) staging system (39) (T0: no evidence of primary tumour; T1mi: tumour less than or equal to 1mm; T1a: tumour between 1 and 5mm [included]; T1b: tumour between 5mm and 1cm [included]; T1c: tumour between 1 and 2cm [included]; T2: tumour between 2 and 5cm [included]; T3: tumour larger than 5cm; T4: tumour of any size with involvement in skin, chest wall or inflammatory BC).
- Lymph node involvement of BC, according to TNM staging system (N0: no evidence of BC in lymph nodes or areas of BC less than 0.2mm; N1: spread of BC in 1 to 3 internal axillary or mammary nodes; N2: spread of BC in 4 to 9 axillary nodes/spread of BC in internal mammary nodes, but not in axillary; N3: spread of BC to 10 or more nodes/spread of BC to supraclavicular or infraclavicular nodes).
- BC stage according to TNM staging system (0, IA, IIA, IIB, IIIB, IIIC).
- Suggested surgical treatment (conservative [quadrantectomy/lumpectomy]; radical).
- Women's satisfaction (a properly designed questionnaire collecting women's issues and plus during the exam with MammoWave in the language spoken by the women).
- Adverse events (AE).

2.2.7. Study outcomes

The primary outcomes will be measured as follows:
- MammoWave's sensitivity (percentage of 'true positive' results) while using an optimized AI-based classification algorithm.
- MammoWave specificity (percentage of 'true negative' results) while using an optimized AI-based classification algorithm.

The secondary outcomes will be measured as follows:
- BC detection rates of each system by type of lesion (microcalcification, mass, asymmetry, or architectural distortion group).

- BC detection rates, recall, and positive predictive value (biopsy) of each system, also by breast density (types A and B being low-density breasts [fat], C and D high-density breasts [high content of fibroglandular tissue]).
- BC detection rates of each system by BI-RADS classification (37).
- BC detection rates of each system by type of lesion (microcalcification, mass, asymmetry, or architectural distortion group) and density (fat or high content of fibroglandular tissue).
- Program screening rate, calculated as the proportion of women diagnosed with BC in the study population.
- BC detection rates of each system by histological type and size of the BC, and BI-RADS classification (37).
- MammoWave's AI classification algorithm's sensitivity (frequency of 'true positive' results) and specificity (frequency of 'true negative' results) after a retrospective adjustment using the data at the end of the study.
- BC detection rate, recalls, and positive predictive value (biopsy), also by breast density (types A and B or C and D) after retrospective AI adjustment using the data at the end of the study.
- Program screening rate, calculated as the proportion of women diagnosed with BC in the study population after a retrospective adjustment using the data at the end of the study.
- Evaluation of the reproducibility of results comparing the lectures performed at the study centres and the centralized lectures.
- Volunteers' satisfaction through a properly designed questionnaire collecting women's issues during the exam with MammoWave in the language spoken by the women.

Regarding safety outcomes, all the events will be registered, and they will be identified as related or not to MammoWave.

2.2.8. Follow-up

The trial design will allow the comparative evaluation of both the conventional mammogram and MammoWave's AI solution in terms of cancer detection rate, number of recalls and positive predictive value, having as reference standard the 2-year follow-up of each volunteer. This follow-up allows to check retrospectively the possible rate of interval BC, and if this was reported as a false positive by MammoWave.

2.2.9. Study's ethical conduct

The study will be carried out following the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), in case of medical devices: the European Directive on medical devices 93/42/EEC and the

ISO Norm 14155 and ISO 14971, the European Law and the corresponding regulatory Competent Authorities (CA) requirements.

2.2.10.   Patient privacy and confidentiality

The investigators will affirm and uphold the principle of the participant's right to privacy. Especially, the anonymity of the participants will be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

2.2.11.   Patient and public involvement

This study will be carried out with patient involvement. Specifically, patient advocates and patient associations have been involved in the development of the study design, informed consent and satisfaction questionnaire. For example, within the development of the study design, patient advocates and patient associations highlighted the importance of EUSOBI recommendations for screening in dense breasts. This involvement has been possible since: a) one patient association, i.e. Evita Cancro (Portugal), is a partner of the project MammoScreen, b) the MammoScreen project governance includes a dedicated Patient Advisory Group (PAG), i.e. an external board gathering the representatives of the major national/European patient organizations. PAG is periodically invited to support MammoScreen and provide guidance on clinical protocol, patients' continuous engagement tools, dissemination, and communication strategy.

2.3. Analysis

2.3.1. Number of Participants

The maximum number of participants will be 10,000 (for all the sites). The sample size was determined using the Buderer approach (40), considering that: (1) the primary objective of the study is to confirm that MammoWave reaches sensitivity > 75% and specificity > 90% in BC detection on 10,000 volunteers undergoing breast screening, (2) a 2-tailed 95% confidence interval (CI) for sensitivity and specificity (CI width = 10), and (3) a prevalence of female BC detected due to screening of 0.92%, according to the official English statistics of the NHS Breast Screening Programme (41). A minimum of 8,000 participants is required to reach the primary endpoint.

2.3.2. Datasets

For the analysis, the following datasets for specific populations have been defined: safety set (SAF), which corresponds to all study volunteers who undergo MammoWave examination; full analysis set (FAS), which includes all volunteers who undergo MammoWave examination and have an evaluable result for the primary endpoint; and per protocol set (PPS), which includes all volunteers who do not have significant CIP violations that regard inclusion/exclusion criteria or that can condition efficacy evaluations.

The primary analyses on both primary and secondary outcomes (except safety evaluation) will be performed on the FAS. The analyses on the PP population will be performed if the PP population differs from the FAS by at least 5% and will be considered supportive of the analyses on the FAS population (sensitivity analysis). The safety and tolerability analyses will be performed on the SAF.

2.3.3. Statistical considerations

Data from study participants will be analysed with descriptive statistics (mean, median, standard deviation, interquartile range, min/max for numerical variables, with frequency tables for categorical ones, percentages), 95% CIs as appropriate and graphical analysis on both the entire population and by strata (i.e. dense/no dense breast) at the interim analysis and the end of the study. All the methods adopted for the statistical analyses will be described in the Statistical Analysis Plan (SAP), to be issued before the interim analysis. The SAP will include a dedicated section in which the interim analyses are described. We anticipate that, within the interim analysis, sensitivity and specificity will be evaluated. In case the lower limit of the 95% CI is lower than 60% for the sensitivity or 70% for the specificity, the classification algorithm will be updated; otherwise, the study will continue without any modification.

All analyses will be conducted using SAS (SAS Institute, Cary, NC) version 9.4.

2.3.4. Data collection, management, and monitoring

During each study visit, the study investigator (or designee) will first collect a written informed consent from the volunteer. All clinical data will be collected, anonymized, and properly identified with a dedicated study identification number, and stored in an Electronic Case Report Form (eCRF), secured by the Clinical Research Organization, CRO (JSB Solutions, Italy). The Investigator is responsible for ensuring the accuracy, completeness and consistency of the data entered in the eCRF. The data entered in the eCRF (in English language) must be present in the source documents of the volunteers at the investigational centre.

The Investigator and the designated person from his/her staff will be trained by CRO for the use of the eCRF and will be responsible for the data entry into the eCRF in accordance with the relevant user guidelines. During the study, the medical records related to the participating volunteer will be kept in the centre. Source data must be available at the site to document the existence of the study participants.

The eCRF system will record the date and time of any entry and/or correction and the user ID of the person making the entry/correction (audit trail). Only authorized investigators will be allowed to view and use the eCRF. The investigators will review all eCRFs and electronically sign and date them for each subject, verifying that the information is complete, true, and correct. All fields on the eCRF must be completed as applicable. Volunteers will be provided with a properly designed questionnaire collecting women's issues and thoughts during the exam with MammoWave, in the language spoken by the women. A copy of all questionnaires will be stored in the subject's folder as source document. It is the responsibility of the Investigator to correctly enter the data collected by the questionnaire in the relevant sections of the eCRF.

The collection of AEs will start after the time that the informed consent is signed and continue until the volunteer completes the data acquisition. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the Sponsor. All reported AEs will be documented on source documents and then reported on the eCRF and will include the event description, date of onset date, resolution, seriousness, severity, relatedness, cause, action taken, and outcome. The investigator or an authorized designee must assess the causality, severity, and relatedness for all the AEs.

Data will not be shared with any outside person or organization and will not be used except for the development of this study.

The monitoring activities will be conducted by the CRO according to a monitoring plan agreed with the Sponsor. The eCRF pages will be reviewed both on-site, by the monitor of the centre, and remotely, by the Data Management staff of the CRO. Data Clarification Sheets (DCS) will be generated through the eCRF system, both automatically, through edit checks, and manually, by Clinical Research Associates

(CRAs) and/or data managers; the investigator will have to check and solve them. The CRAs will be permitted to inspect all study documentation provided that subject confidentiality is respected; to verify the patients' informed consent forms, to verify the data reported in eCRF vs the source data and in case of any discrepancies, they will issue the queries. The corresponding investigator is responsible for the review and approval of all query resolutions. The CRAs will be responsible to verify the proper management of study documentation at the site.

3. ETHICS AND DISSEMINATION

This study was approved by the Research Ethics Committee of the Liguria Region (CET), Italy, on 13 November 2023 (approval number: CET - Liguria: 524/2023 - DB id 13399), the Research Ethics Committee of Complejo Hospitalario de Toledo (CEIC), Spain, on 29 November 2023 (approval number: CEIC - 1094), the National Ethics Committee for Clinical Research (CEIC), Portugal on 12 January 2024 (approval number: CEIC - 2311KC814), the Bioethical Committee of Pomeranian Medical University in Szczecin, Poland (approval number: KB-006/23/2024) on 13 March 2024, and the Zurich Cantonal Ethics Commission, Switzerland (BASEC 2023-D0101) on 7 June 2024.

The findings of this study will be disseminated through academic and scientific conferences as well as peer-reviewed journals. Such publications will be planned and agreed upon with the investigators at each site.

FIGURE CAPTIONS.

Figure 1. MammoWave system and its operability.

Figure 2. Left) Example of MammoWave output, which primarily consists of microwave image and includes the label generated by the novel AI-based classification algorithm, WSF for this breast; Right) reference standard output and details are given for the same breast.

Figure 3. Study design and recruitment process.

Author contributions

All authors met the criteria of authorship as outlined in the ICMJE and approved this manuscript for submission. Specific contributions were as follows.

Conceptualisation: D.Á.S.-B., J.F.M., G.T., N.G, L.P., M.C., AT., C.R.C.

MammoWave device and algorithm: D.Á.S.-B., G.T., N.G., A.B., B.K.

Methodology: all authors.

Drafting the work: R.G.G., L.M.C.H., P.M.A.A., A.D.M.G., A.R.S., A.B., B.K.

Revising it critically for important intellectual content: D.Á.S.-B., J.F.M., G.T., N.G., L.P., M.C., A.T., C.R.C.

Final approval of the version to be published: all authors.

The guarantor of the study is G.T.: he accepts full responsibility for the finished work and controlled the decision to publish.

Competing interests.

Navid Ghavami, Gianluigi Tiberi, Banafsheh Khalesi and Alessandra Bigotti are employed by UBT - Umbria Bioengineering Technologies Srl. Navid Ghavami and Gianluigi Tiberi are shareholders of UBT - Umbria Bioengineering Technologies. UBT - Umbria Bioengineering Technologies Srl manufactured the microwave imaging device known as MammoWave. This does not alter our adherence to BMJ Open policies.

Patient and public involvement

This study will be carried out with patient involvement. Specifically, patient advocates and patient associations have been involved in the development of the study design, informed consent and satisfaction questionnaire. This involvement has been possible since: a) one patient association, i.e. Evita Cancro (Portugal), is a partner of the project MammoScreen, b) the MammoScreen project governance includes a dedicated Patient Advisory Group (PAG), i.e. an external board gathering the representatives of the major national/European patient organizations. PAG is periodically invited to support MammoScreen and provide guidance on clinical protocol, patients' continuous engagement tools, dissemination, and communication strategy.

References

1. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast Cancer Statistics, 2022. CA Cancer J Clin. 2022 Nov 3;72(6):524–41.

2. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. The Breast. 2022 Dec;66:15–23.

3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May 4;71(3):209–49.

4. Luo C, Wang L, Zhang Y, Lu M, Lu B, Cai J, et al. Advances in breast cancer screening modalities and status of global screening programs. Chronic Dis Transl Med. 2022 Jun 25;8(2):112–23.

5. Iwamoto Y, Kaucher S, Lorenz E, Bärnighausen T, Winkler V. Development of breast cancer mortality considering the implementation of mammography screening programs – a comparison of western European countries. BMC Public Health [Internet]. 2019 Dec;19(1):823. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-7166-6

6. Schünemann HJ, Lerda D, Dimitrova N, Alonso-Coello P, Gräwingholt A, Quinn C, et al. Methods for Development of the European Commission Initiative on Breast Cancer Guidelines. Ann Intern Med. 2019 Aug 20;171(4):273.

7. Canelo-Aybar C, Ferreira DS, Ballesteros M, Posso M, Montero N, Solà I, et al. Benefits and harms of breast cancer mammography screening for women at average risk of breast cancer: A systematic review for the European Commission Initiative on Breast Cancer. J Med Screen. 2021 Dec 25;28(4):389–404.

8. Canelo-Aybar C, Posso M, Montero N, Solà I, Saz-Parkinson Z, Duffy SW, et al. Benefits and harms of annual, biennial, or triennial breast cancer mammography screening for women at average risk of breast cancer: a systematic review for the European Commission Initiative on Breast Cancer (ECIBC). Br J Cancer. 2022 Mar 9;126(4):673–88.

9. Hanley JA, Hannigan A, O'Brien KM. Mortality reductions due to mammography screening: Contemporary population-based data. PLoS One. 2017;12(12):e0188947.

10. Romero Castellano C, Aguilar Angulo PM, Hernández LC, Sánchez-Camacho González-Carrato P, Giovanetti González R, Álvarez Martín J, et al. Breast cancer mortality after eight years of an improved screening program using digital breast tomosynthesis. J Med Screen [Internet]. 2021 Mar;096914132110025. Available from: http://journals.sagepub.com/doi/10.1177/09691413211002556

11. Broeders M, Moss S, Nyström L, Njor S, Jonsson H, Paap E, et al. The Impact of Mammographic Screening on Breast Cancer Mortality in Europe: A Review of Observational Studies. J Med Screen [Internet]. 2012 Sep;19(1_suppl):14–25. Available from: http://journals.sagepub.com/doi/10.1258/jms.2012.012078

12. Duffy SW, Vulkan D, Cuckle H, Parmar D, Sheikh S, Smith RA, et al. Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. Lancet Oncol. 2020 Sep;21(9):1165–72.

13. Siu AL. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016 Feb 16;164(4):279.

14. Tagliafico AS, Houssami N. Towards consensus on managing high mammographic density in population breast screening? The Breast. 2023 Jun;69:422–3.

15. European guidelines on breast cancer screening and diagnosis [Internet]. [cited 2023 May 20]. Available from: https://cancer-screening-and-care.jrc.ec.europa.eu/en/ecibc/european-breast-cancer-guidelines

16. Lång K, Hofvind S, Rodríguez-Ruiz A, Andersson I. Can artificial intelligence reduce the interval cancer rate in mammography screening? Eur Radiol. 2021 Aug 23;31(8):5940–7.

17. Lauritzen AD, Rodríguez-Ruiz A, von Euler-Chelpin MC, Lynge E, Vejborg I, Nielsen M, et al. An Artificial Intelligence–based Mammography Screening Protocol for Breast Cancer: Outcome and Radiologist Workload. Radiology. 2022 Jul;304(1):41–9.

18. Larsen M, Aglen CF, Lee CI, Hoff SR, Lund-Hanssen H, Lång K, et al. Artificial Intelligence Evaluation of 122 969 Mammography Examinations from a Population-based Screening Program. Radiology. 2022 Jun;303(3):502–11.

19. Romero-Martín S, Elías-Cabot E, Raya-Povedano JL, Gubern-Mérida A, Rodríguez-Ruiz A, Álvarez-Benito M. Stand-Alone Use of Artificial Intelligence for Digital Mammography and Digital Breast Tomosynthesis Screening: A Retrospective Evaluation. Radiology. 2022 Mar;302(3):535–42.

20. Larsen M, Aglen CF, Hoff SR, Lund-Hanssen H, Hofvind S. Possible strategies for use of artificial intelligence in screen-reading of mammograms, based on retrospective data from 122,969 screening examinations. Eur Radiol. 2022 Jun 15;32(12):8238–46.

21. van Winkel SL, Rodríguez-Ruiz A, Appelman L, Gubern-Mérida A, Karssemeijer N, Teuwen J, et al. Impact of artificial intelligence support on accuracy and reading time in breast tomosynthesis image interpretation: a multi-reader multi-case study. Eur Radiol. 2021 Nov 4;31(11):8682–91.

22. Pinto MC, Rodriguez-Ruiz A, Pedersen K, Hofvind S, Wicklein J, Kappler S, et al. Impact of Artificial Intelligence Decision Support Using Deep Learning on Breast Cancer Screening Interpretation with Single-View Wide-Angle Digital Breast Tomosynthesis. Radiology. 2021 Sep;300(3):529–36.

23. Nikolova N. Microwave Imaging for Breast Cancer. IEEE Microw Mag [Internet]. 2011 Dec;12(7):78–94. Available from: http://ieeexplore.ieee.org/document/6031961/

24. Lazebnik M, Popovic D, McCartney L, Watkins CB, Lindstrom MJ, Harter J, et al. A large-scale study of the ultrawideband microwave dielectric properties of normal, benign and malignant breast tissues obtained from cancer surgeries. Phys Med Biol. 2007 Oct 21;52(20):6093–115.

25. Sani L, Vispa A, Loretoni R, Duranti M, Ghavami N, Álvarez Sánchez-Bayuela D, et al. Breast lesion detection through MammoWave device: Empirical detection capability assessment of microwave images' parameters. Park CM, editor. PLoS One [Internet]. 2021 Apr;16(4):e0250005. Available from: https://dx.plos.org/10.1371/journal.pone.0250005

26. Álvarez Sánchez-Bayuela D, Ghavami N, Tiberi G, Sani L, Vispa A, Bigotti A, et al. A multicentric, single arm, prospective, stratified clinical investigation to evaluate MammoWave's ability in breast lesions detection. PLoS One. 2023 Jul 14;18(7):e0288312.

27. Álvarez Sánchez-Bayuela D, Giovanetti González R, Aguilar Angulo PM, Cruz Hernández LM, Sánchez-Camacho González-Carrato M del P, Rodríguez Sánchez A, et al. Integrating clinical research in an operative screening and diagnostic breast imaging department: First experience, results and perspectives using microwave imaging. Heliyon. 2023 Nov;9(11):e21904.

28. Álvarez Sánchez-Bayuela D, Giovanetti González R, Cruz Hernández LM, Aguilar Angulo PM, Sánchez-Camacho González-Carrato M del P, Rodríguez Sánchez A, et al. Introducing Microwave Breast Imaging via MammoWave into the clinical routine of a Reference Hospital. Results from a prospective, international clinical trial. In: European Congress of Radiology. EPOS; 2023.

29. Álvarez Sánchez-Bayuela D, Giovanetti González R, Cruz Hernández LM, Aguilar Angulo PM, Sánchez-Camacho González-Carrato M del P, Rodríguez Sánchez A, et al. Detection capabilities of the Microwave Breast Imaging system MammoWave on different malignant lesions. EPOS™; 2023.

30. Ghavami N, Sánchez-Bayuela DÁ, Sani L, Vispa A, Bigotti A, Badia M, et al. MammoWave Breast Imaging Device: An International and Multicentric Clinical Investigation. In: 2023 17th European Conference on Antennas and Propagation (EuCAP). IEEE; 2023. p. 1–5.

31. Sani L, Vispa A, Ghavami N, Loretoni R, Duranti M, Álvarez Sánchez-Bayuela D, et al. Empirical Assessment of Breast Lesion Detection Capability Through an Innovative Microwave Imaging Device. In: 2021 15th European Conference on Antennas and Propagation (EuCAP). IEEE; 2021. p. 1–5.

32. Sani L, Vispa A, Ghavami N, Sanchez-Bayuela DA, Badia M, Bigotti A, et al. MammoWave Breast Imaging Device: A Procedure for Device's Characterization Via Phantom Measurements and Subsequent Clinical Trials' Preliminary Results. In: 2021 IEEE Conference on Antenna Measurements & Applications (CAMA). IEEE; 2021. p. 483–6.

33. Romero Castellano C, Álvarez Sánchez-Bayuela D, Giovanetti González R, Cruz Hernández LM, Aguilar Angulo PM, Sánchez-Camacho González-Carrato M del P, et al. Microwave-Based Imaging for Breast Cancer Detection via MammoWave: Preliminary results of a Multicentric Trial in a Reference Hospital.

34. Ghavami N, Tiberi G, Craddock I, Probert Smith P, Edwards D. Non-iterative beamforming based on Huygens principle for multistatic ultrawide band radar: application to breast imaging. IET Microwaves, Antennas & Propagation [Internet]. 2015 Sep;9(12):1233–40. Available from: https://digital-library.theiet.org/content/journals/10.1049/iet-map.2014.0621

35. Tiberi G, Ghavami N, Edwards DJ, Monorchio A. Ultrawideband microwave imaging of cylindrical objects with inclusions. IET Microwaves, Antennas & Propagation [Internet]. 2011;5(12):1440. Available from: https://digital-library.theiet.org/content/journals/10.1049/iet-map.2011.0033

36. Papini L, Badia M, Sani L, Rana SP, Álvarez Sánchez-Bayuela D, Vispa A, et al. Breast Cancer Detection using Machine Learning Approaches on Microwave-based Data. In: 2023 17th European Conference on Antennas and Propagation (EuCAP). IEEE; 2023. p. 1–5.

37. D'Orsi C, Sickles E, Mendelson E, Morris E. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology; 2013.

38. Mann RM, Athanasiou A, Baltzer PAT, Camps-Herrero J, Clauser P, Fallenberg EM, et al. Breast cancer screening in women with extremely dense breasts recommendations of the European Society of Breast Imaging (EUSOBI). Eur Radiol. 2022 Jun 8;32(6):4036–45.

39. Koh J, Kim MJ. Introduction of a New Staging System of Breast Cancer for Radiologists: An Emphasis on the Prognostic Stage. Korean J Radiol. 2019;20(1):69.

40. Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med. 1996 Sep;3(9):895–900.

41. NHS Breast Screening Programme, England 2021-22 [Internet]. 2023 [cited 2024 Mar 18]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/breast-screening-programme/england---2021-22
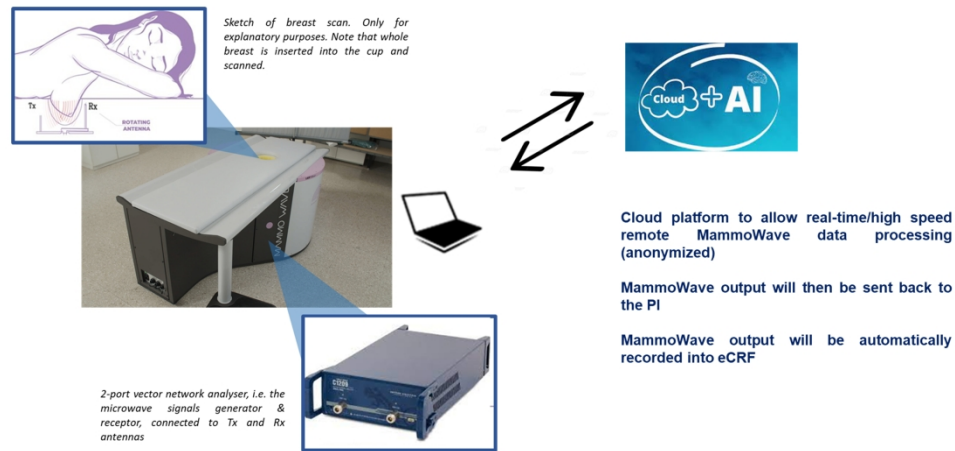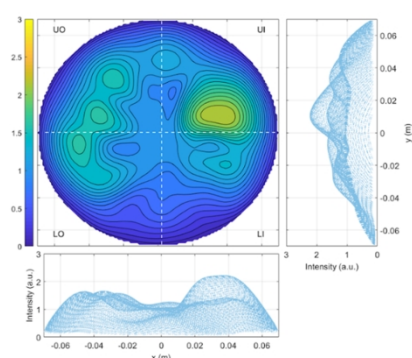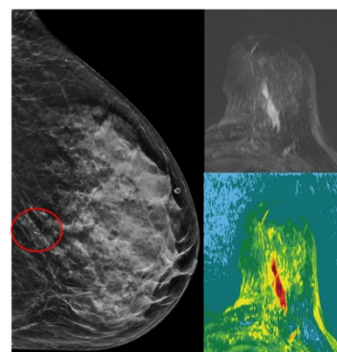
Sketch of breast scan. Only for explanatory purposes. Note that whole breast is inserted into the cup and scanned.

2-port vector network analyser, i.e. the microwave signals generator & receptor, connected to Tx and Rx antennas

Cloud platform to allow real-time/high speed remote MammoWave data processing (anonymized)

MammoWave output will then be sent back to the PI

MammoWave output will be automatically recorded into eCRF

Figure 1. MammoWave system and its operability.

338x190mm (300 x 300 DPI)

Figure 2. Left) Example of MammoWave output, which primarily consists of microwave image and includes the label generated by the novel AI-based classification algorithm, WSF for this breast; Right) reference standard output and details are given for the same breast.
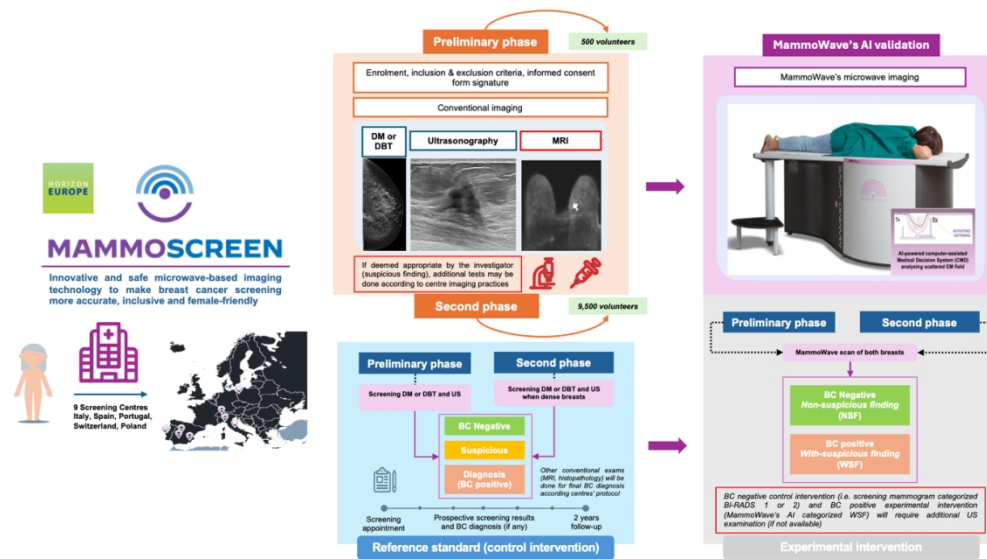
338x190mm (300 x 300 DPI)

Figure 3. Study design and recruitment process.

403x225mm (87 x 87 DPI)

SPONSOR : UBT Srl	STUDY CODE : UBT 2023-01

WOMEN'S SATISFACTION QUESTIONNAIRE

ID number: |__|__|__|__|

Clinical center number: |__|__|

Date: |__|__|-|__|__|- |__|__|__|__|
             mm   dd   yyyy

1. Has the examination been interrupted?   ☐ **YES** ☐ **NO**

If **YES**, explain why:

_____

_____

_____

2. Did you find the microwave examination tedious?

Please answer the question by indicating your opinion on a scale of 1 to 3

☐ **3** = yes, very much

☐ **2** = a little

☐ **1** = absolutely not

3. Did you find the microwave examination painful?

Please answer the question by indicating your opinion on a scale of 1 to 3

☐ **3** = yes, very much

☐ **2** = a little

☐ **1** = absolutely not

4. Did you find the microwave examination uncomfortable?

Please answer the question by indicating your opinion on a scale of 1 to 3

☐ **3** = yes, very much

☐ **2** = a little

☐ **1** = absolutely not

5. Did you find the examination long-lasting?

Please answer the question by indicating your opinion on a scale of 1 to 3

☐ **3** = yes, very much

☐ **2** = a little

☐ **1** = absolutely not

6. Did you feel adequately informed about the microwave examination?

Please answer the question by indicating your opinion on a scale of 1 to 3

☐ **3** = yes, very much

☐ **2** = a little

☐ **1** = absolutely not

7. Would you recommend the microwave examination?   ☐ **YES** ☐ **NO**

If **NO**, explain why:

_____

_____

_____