A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PATIENT PREFERENCE AND SATISFACTION OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER

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Main Information

Primary registry identifying number
LBCTR2019030205

Protocol number
MO40628

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
28/02/2019

Primary sponsor
F. HOFFMANN-LA ROCHE LTD

Primary sponsor: Country of origin
Switzerland

Date of registration in primary registry
28/01/2020

Date of registration in national regulatory agency
28/02/2019

Public title
A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PATIENT PREFERENCE AND SATISFACTION OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER

Acronym
PhranceSCa

Scientific title
A RANDOMIZED, MULTICENTER, OPEN-LABEL CROSS-OVER STUDY TO EVALUATE PATIENT PREFERENCE AND SATISFACTION OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER_ EUDRACT NUMBER: 2018-002153-30

Acronym
PhranceSCa

Brief summary of the study: English

The main purpose of this study is to assess patient preferences for a new, combined preparation of pertuzumab and trastuzumab that can be given as a single injection into the tissue just under the skin (called subcutaneous, or SC, administration). Perjeta (also called pertuzumab) and Herceptin (also called trastuzumab) are two drugs that are given together as standard treatment for HER2-positive breast cancer. Perjeta IV and Herceptin IV are given, one after another, by intravenous (IV) infusion (by drip through a needle into a vein, usually in the arm, or into a central venous catheter [a tube inserted into a vein so that IV drugs can be administered]). The time to give each Perjeta IV or Herceptin IV infusion is between approximately 60 to 30 minutes. The new preparation, called “pertuzumab and trastuzumab fixed-dose combination for subcutaneous use” (pertuzumab and trastuzumab FDC SC), contains both drugs (the same drugs as in Perjeta IV and Herceptin IV) and is given as a single injection under the skin of the thigh. This single SC injection usually takes less than 10 minutes. Perjeta IV and Herceptin IV are each approved by health authorities for the treatment of HER2-positive early and advanced breast cancer. Pertuzumab and trastuzumab FDC SC contains the same drugs as Perjeta IV and Herceptin IV, but combines both drugs in a single mixture and includes another ingredient called rHuPH20 that helps pertuzumab and trastuzumab spread following SC injection. rHuPH20 is a man-made protein that is approved by health authorities in the United States as Hylenex® where it is used to help drugs spread following SC injection. rHuPH20 is included in a preparation of Herceptin (called Herceptin SC) that is approved by health authorities for SC administration. Pertuzumab and trastuzumab FDC SC is an experimental drug, meaning it is not currently approved by any health authority for breast cancer treatment.
About 140 people will take part in this study.

Brief summary of the study: Arabic

إن الهدف الرئيسي من هذه الدراسة هو تقييم تفضيلات المريض في تناول مركب جديد من البيرتوزوماب والتراستوزوماب الذي يمكن استخدامه كحقنة واحدة في الأنسجة الموجودة تحت الجلد مباشرة (يُطلق عليها الحقن تحت الجلد). إن بيرجيتا (لمعروف كذلك باسم بيرتوزوماب) وهيرسبتن (المعروف كذلك باسم تراستوزوماب) هما نوعان من العقاقير التي تُحقن معًا كعلاج معياري لسرطان الثدي من النوع إيجابي مستقبلات هير (HER2)
حيث حُقن كل من بيرجيتا وهيرسبتن عن طريق الوريد واحدًا تلو الآخر عبر ، التسريب الوريدي (بالتقطير بغرز إبرة في الوريد، عادة ما تكون في الذراع، أو في قسطرة في الوريد المركزي)أنبوب 60يُدخل في وريد من خلاله تُحقن العقاقير). تتراوح مدة اعطاء كل حقنة من بيرجيتا وهيرسبتن عن طريق الوريد بين 30و دقيقة، وتحتوي التركيبة الجديدة المسماة (توليفة بيرتوزوماب وتراستوزوماب محددة الجرعة للحقن تحت الجلد) على كلا النوعين من العقاقير (نفس العقاقير الموجودة في بيرجيتا وهيرسبتن عن طريق الوريد) وتُعطى كحقنة واحدة تحت الجلد في منطقة الفخذ، وعادة ما يستغرق ذلك الحقن تحت الجلد ما يقل عن 10دقائق .
إن حقن بيرجيتا وهيرسبتن عن طريق الوريد معتمدة من هيئات الصحة لعلاج سرطان الثدي من النوع إيجابي مستقبلات هير2 (HER2)
في مرحلتيه المبكرة و المتقدمة . وتحتوي توليفة بيرتوزوماب وتراستوزوماب محددة الجرعة للحقن تحت الجلد على نفس العقاقير التي تحتويها حقن بيرجيتا وهيرسبتن عن طريق الوريد، إلا أنها تدمج كلا النوعين في مزيج واحد بالإضافة إلى مادة أخرى تسمى rHuPH20
التي تساعد البيرتوزوماب والتراستوزوماب على الانتشار بعد الحقن تحت الجلد .إن مادة rHuPH20 هي بروتين من صنع الإنسان معتمد من هيئات الصحة الأمريكية تحت مسمى هيلينيكس حيث تُستخدم لمساعدة العقاقير على rHuPH20 . الانتشار بعد الحقن تحت الجلد. كما أن مادة
جودة في مركب هيرسبتن (حقن
هيرسبتن تحت الجلد) معتمدة من هيئات الصحة المعنية بالحقن تحت الجلد. إن توليفة بيرتوزوماب وتراستوزوماب محددة الجرعة للحقن تحت الجلد هي عقاقير تجريبية، بمعنى أنها لم تُعتمد من أي هيئة صحية لعلاج سرطان الثدي حتى الآن
شخص في هذه الدراسة140سيشارك حوالي

Health conditions/problem studied: Specify

This study will evaluate patient preference for a subcutaneously administered fixed-dose combination formulation (FDC SC) of pertuzumab and trastuzumab compared with intravenously (IV) administered Perjeta® and Herceptin® formulations (P+H IV) in patients with HER2-positive (HER2+) early breast cancer (EBC). The study will also evaluate patient reported satisfaction with pertuzumab and trastuzumab FDC SC and health-related quality of life (HRQoL) outcomes; Healthcare professionals (HCPs) perception of time/resource use and convenience of pertuzumab and trastuzumab FDC SC and P+H IV; as well as the safety and efficacy of each study regimen.

Interventions: Specify

The investigational medicinal products (IMPs) for this study are pertuzumab and trastuzumab Fixed Dose Combination SC, Perjeta IV, and Herceptin IV.

Key inclusion and exclusion criteria: Inclusion criteria

Inclusion Criteria:
Patients must meet the following criteria for study entry:

1-Disease-specific criteria:
-Female or male with histologically confirmed, HER2+ inflammatory, locally advanced or early stage breast cancer who have received neoadjuvant Perjeta + Herceptin and have completed neoadjuvant chemotherapy and subsequently undergone surgery for their breast cancer.
-HER2+ breast cancer assessed at the local laboratory prior to initiation of neoadjuvant therapy. HER2+ status must be determined based on breast biopsy material obtained prior to neoadjuvant treatment and is defined as 3+ by immunohistochemistry (IHC) and/or positive by HER2 amplification by in situ hybridization (ISH) with a ratio of ≥ 2 for the number of HER2 gene copies to the number of chromosome 17 copies
-Hormone receptor status of the primary tumour determined by local assessment. Hormone receptor-positive status may be either positive (i.e. ER-positive and/or PgR-positive) or negative (i.e. ER-negative and PgR-negative)
-Completed all neoadjuvant chemotherapy and surgery. Adjuvant radiotherapy may be planned or ongoing at study entry and adjuvant hormone therapy is allowed during the study. Note that study treatment cannot be initiated within < 2 weeks of surgery but must be initiated ≤ 9 weeks from the last administration of systemic neoadjuvant therapy.
-No evidence of residual, locally recurrent or metastatic disease after completion of surgery. Patients with clinical suspicion of metastases must undergo radiological assessments per institutional practice to rule out distant disease.
-Wound healing after breast cancer surgery adequate per investigator's assessment to allow initiation of study treatment within ≤ 9 weeks of last systemic neoadjuvant therapy
-No adjuvant chemotherapy planned. Note that adjuvant hormonal treatment is allowed during the study.
2- General criteria:
 Signed Informed Consent Form
 Age ≥ 18 years at time of signing Informed Consent Form
 Ability to comply with the study protocol, in the investigator's judgment
 Eastern Cooperative Oncology Group performance status 0 or 1
 Intact skin at planned site of subcutaneous (SC) injections (thigh)
 LVEF ≥ 55% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) within 28 days of study randomization
 No major surgical procedure unrelated to breast cancer within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
 For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs.
 For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom,and agreement to refrain from donating sperm.
 A negative serum pregnancy test must be available prior to randomization for women of childbearing potential (defined as post-menarchal, has not had ≥ 12 continuous months of amenorrhea with no identified cause other than menopause, and has not undergone surgical sterilization [removal of ovaries and/or uterus])
There is no age limited mentioned in inclusion exclusion and it is added in the Age maximum as it is a mandatory field, and as advised by MOH representative

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

100

Key inclusion and exclusion criteria: Exclusion criteria

Exclusion Criteria:
Patients who meet any of the following criteria will be excluded from study entry:
1-Cancer-specific criteria:
 Stage IV (metastatic) breast cancer
 Current or prior history of active malignancy (other than current breast cancer) within the last five years. Appropriately treated non-melanoma skin cancer; in situ carcinomas, including cervix, colon, or skin; or Stage I uterine cancer within the last five years are allowed. A patient with previous invasive non-breast cancer is eligible provided he/she has been disease free for more than five years.
 Previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy [selective oestrogen receptor modulators, aromatase inhibitors], and antitumor vaccines) for treatment or prevention of breast cancer, except neoadjuvant Perjeta, Herceptin and chemotherapy for current breast cancer
2-General criteria:
 Investigational treatment within four weeks of enrolment
 Serious cardiac illness or medical conditions including, but not confined to, the following:
− History of NCI CTCAE v4.0 Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) Class ≥ II
− High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate ≥ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz II] or third-degree AV-block)
− Serious cardiac arrhythmia or severe conduction abnormality not controlled by adequate medication
− Angina pectoris requiring anti-angina medication
− Clinically significant valvular heart disease
− Evidence of transmural infarction on electrocardiogram (ECG)
− Evidence of myocardial infarction within 12 months prior to randomization
− Poorly controlled hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg)
 History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalaemia, hypomagnesemia, hypocalcaemia), or family history of sudden unexplained death or long QT syndrome
 Inadequate bone marrow function, defined by any of:
− Absolute neutrophil count < 1.5 x 109/L
− Platelet count < 100 x 109/L
− Haemoglobin < 9 g/dL

 Impaired liver function, defined by any of:
− Serum (total) bilirubin > 1.25 x upper limit of normal (ULN). In case of Gilbert's syndrome: a total bilirubin of 2 x ULN is permitted.
− Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 1.25 x ULN
− Albumin < 25 g/L
 Inadequate renal function with serum creatinine > 1.5 x ULN
 Current severe, uncontrolled systemic disease that may interfere with planned treatment (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders)
 Pregnant or breastfeeding, or intending to become pregnant during the study or within seven months after the last dose of study treatment. Women of childbearing potential must have a negative serum pregnancy test result within seven days prior to initiation of study treatment
 Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in, and completion of, the study
 Known active liver disease, for example, active viral hepatitis infection (i.e., hepatitis B or hepatitis C), autoimmune hepatic disorders, or sclerosing cholangitis
 Concurrent, serious, uncontrolled infections, or known infection with human immunodeficiency virus (HIV)
 Known hypersensitivity to any of the study drugs, excipients, and/or murine proteins
 Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Other

Trial scope: Specify scope

Study design: Allocation

Randomized controlled trial

Study design: Masking

Open (masking not used)

Study design: Control

Active

Study phase

2

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Crossover

Study design: Specify assignment

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

The investigational medicinal products (IMPs) for this study are pertuzumab and trastuzumab FDC SC, Perjeta IV, and Herceptin IV. Test Product (Investigational Drug) Pertuzumab and trastuzumab FDC SC

Year of authorization

Month of authorization

Type of IMP

Others

Pharmaceutical class

The investigational medicinal products (IMPs) for this study are pertuzumab and trastuzumab FDC SC, Perjeta IV, and Herceptin IV.
Test Product (Investigational Drug)
Pertuzumab and trastuzumab FDC SC (no market authorization)
The investigational medicinal products (IMPs) for this study are pertuzumab and trastuzumab FDC SC, Perjeta IV, and Herceptin IV. Test Product (Investigational Drug) Pertuzumab and trastuzumab FDC SC Comparator
(Active Control)
Pertuzumab IV and (has market authorization)
Trastuzumab IV (has market authorization)

1- Pertuzumab: (rhuMAb 2C4 [Perjeta]) is a recombinant, humanized immunoglobulin (Ig)G1κ monoclonal antibody, which targets the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab is the first in a class of targeted cancer treatments called HER2 dimerization inhibitors. By binding to the subdomain 2 epitope of the extracellular domain of HER2, it prevents heterodimerization of HER2 with other members of the HER family (HER1, HER3 and HER4). As a result, ligand-activated downstream signaling is blocked by pertuzumab. Pertuzumab is also capable of mediating antibodydependent cell-mediated cytotoxicity (ADCC) in cell-based assays.
Pertuzumab and trastuzumab (Herceptin□) bind to distinct epitopes on the HER2 receptor without competing with each other, and have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity in vitro and in vivo when pertuzumab and trastuzumab are given in combination.

2- Trastuzumab: is produced by a genetically engineered Chinese hamster ovary (CHO) cell line, grown in large scale, which secretes trastuzumab into the culture medium. The antibody is then purified extensively using standard chromatographic and filtration methods.
--Intravenous Formulation (Herceptin IV):
Herceptin (trastuzumab) powder for concentrate for solution for injection (IV administration), also referred to as Herceptin IV, is supplied commercially as a
lyophilized formulation in either single-dose (150 mg) or multi-dose (440 mg) vials. A single-dose lyophilized 60-mg vial formulation is also available for use in Australia and Japan only. Herceptin is formulated in histidine/histidine-HCl monohydrate (buffer), -trehalose dihydrate (tonicity adjuster), and polysorbate 20 (stabilizer/emulsifier).
Following reconstitution in either sterile water for injection (SWFI) for the single dose preparation or bacteriostatic water for injection (BWFI) for the multi-dose preparation, Herceptin is further diluted in 250 mL 0.9% sodium chloride solution for administration.
--Subcutaneous Formulation (Herceptin SC):
Herceptin(trastuzumab) solution for injection (for SC administration), also referred to as Herceptin SC, is supplied as a ready-to-use liquid formulation with a nominal
trastuzumab content of 600 mg/5 mL, recombinant human PH20 hyaluronidase (rHuPH20) 2000 U/mL (recombinant protein manufactured in a CHO cell line, a permeation enhancer to allow SC administration of higher volumes), histidine/histidine-HCl monohydrate (buffer), □,□-trehalose dihydrate (tonicity adjuster), methionine (stabilizer), and polysorbate 20 (stabilizer/emulsifier) in water for injection at a pH of 5.5 +/-0.3.
Two presentations of Herceptin SC have been used in clinical trials: a 6-mL vial and a single-use injection device (SID), both containing 600 mg/5 mL of Herceptin SC. The SID is a self-contained automated delivery system in which a cartridge containing the drug solution is integrated.

3-The pertuzumab (Perjeta®) and trastuzumab (Herceptin®) fixed dose combination (FDC) is a ready-to-use formulation of pertuzumab and trastuzumab with recombinant human hyaluronidase (rHuPH20) for subcutaneous (SC) administration (the product is referred to as “PH FDC SC” throughout the document). The active ingredients (monoclonal antibodies: pertuzumab and trastuzumab) in PH FDC SC are identical to the active ingredients in the Perjeta and Herceptin intravenous (IV) formulations. PH FDC SC has been developed to offer patients a less invasive, faster, and more convenient administration of pertuzumab and trastuzumab compared to IV infusions, while also offering treatment facilities improved time and resource utilization.
Pertuzumab and trastuzumab are recombinant humanized immunoglobulin (Ig)G1κ monoclonal antibodies, which target the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab and trastuzumab bind to distinct HER2 epitopes without competing and have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity in vitro and in vivo when pertuzumab and trastuzumab are given in combination.

Two clinical trial formulations of pertuzumab and trastuzumab for SC administration (loading and maintenance dose) are being used for PH FDC SC. These formulations of PH FDC SC are provided in a single dose of either 15 mL (loading dose) or 10 mL (maintenance dose) per vial of buffered L-histidine hydrochloride buffer (pH 5.5) containing trehalose, sucrose, polysorbate 20, methionine and rHuPH20. The drug products are formulated as 1200 mg pertuzumab +600 mg trastuzumab (15.0 mL/vial) for the loading dose and as 600 mg pertuzumab +600 mg trastuzumab (10.0 mL/vial) for the maintenance dose.

Therapeutic indication

HER2-positive Early Breast Cancer

Therapeutic benefit

The safety and efficacy of Herceptin SC has been shown to be consistent with Herceptin IV with no safety issues attributable to the route of administration or to formulation with rHuPH20. Pertuzumab dosing in the FDC SC formulation has been
selected to provide similar PK as approved Perjeta IV dosing. No new safety issues have been seen in clinical evaluation of co-infused Perjeta IV and Herceptin IV preparations. Ongoing clinical evaluation of co-administered and co-formulated SC
preparations conducted by the Sponsor has also found no safety issues that would not be expected with sequential IV administrations.
This study is being conducted in HER2+ EBC patients for whom combined treatment with Perjeta IV and Herceptin is indicated. As summarized above, the benefit-risk of incorporating pertuzumab and trastuzumab FDC SC into study participants' anti-HER2 regimen is based on the demonstrated non-inferiority of Herceptin SC PK profile and efficacy (as assessed by pCR rate) with respect to Herceptin IV, the equivalent bioavailability of pertuzumab SC and IV formulations and the consistency of safety profiles among IV, SC, and FDC SC formulations.

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

N/A

Time perspective

N/A

Time perspective: Explain time perspective

N/A

Time perspective: Specify perspective

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

None retained

Biospecimen description

NA

Target sample size

140

Actual enrollment target size

140

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

01/04/2019

Date of study closure: Type

Anticipated

Date of study closure: Date

31/01/2023

Recruitment status

Recruiting

Recruitment status: Specify

Date of completion

01/10/2019

IPD sharing statement plan

Yes

IPD sharing statement description

During this study, health and personal information about subjects will be collected. This section describes the protection, use, and sharing of information, which consists of the following:
• Information in the medical record, which is held by Sites.
• Information that is collected or produced during this study ("study data"), which is held by sites, Roche, Roche affiliates, and Roche's representatives.
Subject privacy is very important, and Roche uses many safeguards to protect privacy, in accordance with applicable data privacy laws and laws related to the conduct of clinical trials.
Subject study data and samples will be labelled with a patient identification (ID) number that is unique and not related to or derived from information that identifies subject (such as name, picture, or any other personally identifying information). Roche, Roche affiliates, and Roche's representatives will only have access to study data and samples labelled with a patient ID number, except as described below. Subjects medical record, which includes personal information that can identify subjects, will not be accessed for the purposes of this study, except as described below:
Information (which includes information in medical record that can identify subjects) may need to be reviewed to make sure the study is being done properly or to check the quality of the information. This information will be kept private. The following people and groups of people may and/or copy this information:
• Study monitors of Roche and/or CRO, a company hired by Roche to perform certain study activities
• The Institutional Review Board or Ethics Committee
• Regulatory authorities

Roche, Roche affiliates, and Roche's collaborators and licensees (people and companies who partner with Roche) may use study data labelled with patient ID number for research purposes or to advance science and public health.
Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. These data will not include information that identifies subjects, and extra steps will be taken to safeguard privacy.
Subject information will not be given to insurance company or employer, unless required by law. If the results from this study are published in a medical journal or presented at a scientific meeting, subjects will not be identified.
Information from this study will be retained by Sites for 15 years after the end of the study. In addition, Roche will retain the study data for up to 25 years after the end of the study.

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

No Numbers

Sources of Monetary or Material Support

No Sources

Secondary Sponsors

No Sponsors

Contact for Public/Scientific Queries

No Contacts

Centers/Hospitals Involved in the Study

No Centers/Hospitals

Ethics Review

No Reviews

Countries of Recruitment

No Countries

Health Conditions or Problems Studied

No Problems Studied

Interventions

No Interventions

Primary Outcomes

No Outcomes

Key Secondary Outcomes

No Outcomes

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files