Appendix 1: Informed consent materials

Informed Consent Form

Study title: A PHASE III, RANDOMIZED, TWO ARMED PATIENT-OUTCOME ASSESSOR-DATA ANALYZER BLINDED, PARALLEL ACTIVE CONTROLLED NON-INFERIORITY CLINICAL TRIAL STUDY OF ARYOTRUST (ARYOGEN PHARMED TRASTUZUMAB) EFFICACY AND SAFETY IN HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2–POSITIVE BREAST CANCER IN COMPARISON TO HERCEPTIN® (GENENTECH/ROCHE) CONTROL.

Mr./Mrs. ……

We invite you to participate in the above-mentioned clinical study. Information about this research is provided in this sheet, and you are free to join this research or not.

You do not have to make an immediate decision and you are given a deadline to announce your opinion after consulting the research team and anyone you desire, about participation and your involvement in this research is entirely voluntarily. Before signing this consent, make sure that you understand all the information in this form and all of your questions are answered.
Researcher: Dr. Seyed Reza Safaie Nodehi

1- I know that purposes of this research are: the evaluation of the efficacy and safety of trastuzumab of AryoGen Pharmed company in comparison with trastuzumab of Genentech/Roche company.
2- I know that my participation in this study is completely voluntary and I am not obligated to participate in this research. I was assured that if I were not willing to participate in this research, I would not be deprived of routine diagnostic and therapeutic care and my therapeutic relationship with the health center and my physician will not get affected.
3- I know that even after agreeing to participate in the research, I can resign freely at any time after informing the researcher, without giving any reason and my withdrawal from the research will not deprive me of the usual treatment services.
4- This is how my participation is in this study:
   After the diagnosis of doctors about the need for using trastuzumab to treat my illness, and after agreeing to participate in the study, I will randomly be assigned to one of the two groups receiving trastuzumab of an Iranian company AryoGen Pharmed or trastuzumab of Genentech/Roche company.

I know that the other treatments and prescribed medications are similar between the two groups, and the randomization between the two groups is completely accidental and no one predetermines it. During the study, I must receive the prescribed medication and refer to the doctor's instructions for the tests and related visits on a regular basis. I know that the procedures in each visit are as follows: At the first session (visit 0), my health status is evaluated by the physician, and previous laboratory data and imaging results are monitored and recorded. Next, a blood sample of me is taken to assess the physical condition and health indicators. Then an echocardiographic test and a breast sonography will be done. If I have done a sonography, MRI or mammography within the last week, there is no need to do it again. If the results of the tests, imaging and evaluation of the physician were not inconsistent with my presence in the study, I will be included in the study and will receive the first dose of cyclophosphamide and adriamycin. My participation in the study includes two stages of treatment, in the first stage of 4 cycles (including visits one, two, three, and four), I go to the health center every two weeks and receive cyclophosphamide and adriamycin as treatment, except for the first session (visit 1), which is in the same time as I present the results of my previous laboratory test. In the next three sessions of this stage, a blood sample will be taken from me every time to evaluate my health and my ability to continue the study. At the end of these four sessions, an echocardiography and sonography will be done for me again, these results and the result of blood tests will be presented to my doctor for review and record in the next visit (visit 5). In visit 6, the second stage of treatment, which consists of 4 cycles, every 3 weeks, starts for me. In each session, I will receive docetaxel (100 mg per square meter of body surface area) and one of the two AryoTrust or Herceptin® (the first course is 8 mg per kilogram, and in the next 3 courses, 6 mg per kilogram). I know that AryoTrust is the trastuzumab drug which is produced by AryoGen Pharmed company in Iran, and the Herceptin® drug is the brand trastuzumab drug which is produced by Genentech/Roche Company. I will receive AryoTrust, If I am in the first group, and I will receive Herceptin® and if I am in the second group. I know that it's totally coincidental that I am selected for which group and I will not be aware of my group until the end of the study. My doctor explained to me that the process of choosing a therapeutic group unknowingly is completely scientific and is because of evaluating the drugs properly. My doctor also assured me that regardless of in which group of treatments I am, all the necessary procedures for appropriate treatment will be done for me, and wherever participation in this study is considered to be dangerous for my health, I will be excluded from the study and I will receive the appropriate treatment according to my health condition. I know that all medications in the two treatment groups are similar and the difference between the two groups is due to the difference in the company that makes the drug trastuzumab. At each of the treatment sessions, my health status is evaluated by the medical staff of the study, and in order to fully control my health conditions, in addition to the blood tests performed in each session (8 times total), in the first visit, the 5th visit and before the surgery (9th visit), echocardiography of the heart (3 times total)

and sonography (3 times total) will be done for me. The total number of visits is 10 sessions and the duration of the treatment is 21 or 23 weeks. In every visit, questions about my health conditions from the previous visit until now, are asked. At the end of the course of drug therapy, regardless of the treatment group, I will be referred for surgery. I know that after the end of the study (if I need to continue treatment), given the fact that the trastuzumab of both types (Iranian and brand) is available in the pharmaceutical market of the country, and given the insurance coverage of this drug, I can provide this drug from reputable pharmacies. I know that according to the principles of conducting clinical trials of AryoGen Pharmed company, the cost of trastuzumab will be paid up to the end of the study, and after the completion of the study, it will be my responsibility, like other patients.

5- The possible benefits of my participation in this research are as follows:

I receive free treatment for 23 weeks. Also, in each of the study groups, during this study, I will be examined and evaluated by the physicians with greater precision and sensitivity regarding my condition and the side effects of drugs. Also, the effects of my treatment will be carefully evaluated. After surgery, I will be informed of the outcome of my treatment, and the treatment outcomes will fully be explained to me, and my questions about my health status and the continuation of treatment will completely be answered. The contact number of the researcher or his authorized representative is available to me so that if I had a question during the study or if a health problem occurred to me, I can have immediate access to him.

6- The possible harms and adverse events of my participation in this research are as follows:

I have been informed that previous studies on AryoTrust have shown similar side effects as Herceptin®, and there is no evidence that AryoTrust has more adverse effects than Herceptin®. I know that receiving trastuzumab (AryoTrust or Herceptin®) in the first cycle may cause fever and chills and flu-like symptoms and there is only a small chance that these symptoms are severe and associated with nausea and skin rashes.

These complications will usually get milder in subsequent visits. Less likely, trastuzumab may cause cardiomyopathy and reduce heart's ability to transfer blood to organs, although in most cases it is not seen, or it is so insignificant that it does not cause a symptom, or only it causes symptoms such as transient shortness of breath, but in some cases it may also lead to congestive heart failure or cerebral stroke. During the study and after each session I receive medical treatment, health examinations and diagnostic laboratory tests will be done for me, as well as three times echocardiography in the first, fourth (the end of the first stage treatment) and the ninth visit (The end of the second stage of treatment and before surgery) will be done for me, and if the continuation of the study is dangerous for my health, I will be excluded from this treatment. In the case of mild flu-like syndromes, I will receive treatments for reducing the symptoms. If these complications cause disability for me, with the doctor's diagnosis, the interval between treatment cycles may get longer, or even the treatment can be discontinued for a

while. In the case of cardiac complications, temporary or permanent cessation of treatment, my heart status will be consulted with the help of a cardiologist. In the case of any complication that occurs for me in this study, the investigator will report them to the responsible authorities in accordance with the relevant laws. Also, me or my family should inform my doctor of any adverse event occurrence during the study (including events leading to hospitalization and death) as soon as possible. This undesirable event may not be due to the drug being studied, but in any case, I should inform my doctor as soon as possible. I know that if any complication occurs for me in this study, the investigator will report them to the responsible authorities in accordance with the relevant laws, and I will regularly be monitored by the treatment team for the incidence of these complications.

7- In the case of unwillingness to participate in the research, the usual services (therapeutic, diagnostic, etc.) for me will be provided which the benefits and harms are as follows:
In case of unwillingness to participate in the research, the usual services (therapeutic, diagnostic, etc.), for me will be provided which is the same treatment described in the second group of study (the Herceptin® group, trastuzumab of Roche company). A routine visit will be performed by the doctor and the usual care will be provided. My drugs will be prescribed to me by my physician diagnosis. The cost of laboratory testing and drugs will be paid by myself according to my insurance coverage, and I will be referred for surgery at the end of the treatment cycles. Also, because the treatment is routinely similar to that used in the study, the complications and drug adverse events are similar to the research.

8- I know that the researchers of this study will keep all of my information confidential and are only allowed to publish the overall and collective results of this research without mentioning my name and my profile.

9- I know that the Ethics Committee in my study is allowed to have access to my information to monitor my rights.

10- I know that I should not pay any of the costs below:
1-Trastuzumab drug cost (Iranian or brand), 2-Costs related to diminishing the complications related to the study drug, 3-Costs of diagnostic procedures related to the company in the study and related to the side effects of the drug studied, including laboratory tests, imaging, echocardiography and pathology, 4-The cost of the patient's share of other medications (after deducting the share of insurance) during the study in 26 weeks (about 6 months). In the case of no need for more diagnostic procedures, the number of diagnostic procedures is as follows: Total blood tests 8 times, Echocardiography (total 3 times) and Sonography (total 3 times).

11- I know that if during and after the research any physical and mental problems arose because of my participation in this research, it will be the responsibility of the researcher to treat the complications and the related damages.

I know that if I become hospitalized due to participation in this study, or a disability or any other unpleasant consequence occurs to me in this study, that if I did not attend this study, it would not have happened for me, the relevant compensation is AryoGen Pharmed company responsibility and I am insured by the AryoGen Pharmed company concerning the adverse events occurring for me because of my participation in the study.

12- Mrs. Elham Farhang has been introduced to me for answering my questions, and I was told that during the study any time a health problem occurred to me or if I had a question regarding participation in this research, I can share with her and ask for guidance. Her following address and phone number were given to me:
Address: Fifth floor, No 74, Near faculty of Nutrition, Hafezi Street, Shahrak Gharb, Tehran, Iran.
Telephone: 00982188078848
Cell phone: 00989129592162

13- I know that if I have a problem or objection to executors of the research or the research process, I can contact the Ethics Committee of the Tehran University of Medical Sciences at the address of: Room 605, 6th Floor, Central headquarters of Tehran University of Medical Sciences, Qods Street, Keshavarz Blvd., Tehran, Iran. Telephone: 009821-81633626 or Vice-Chancellor for Research in Isfahan Province with the telephone number of 031-36682407, and present my problem either verbally or in writing.

This form of information and informed consent is provided in two copies and will be signed by the researcher and me. A signed copy will be given to me and a signed copy will be given to the researcher.

I have read and understood the explanations mentioned above, and based on that, I declare my informed consent to participate in this research.

Participant signature:

I consider myself bound to comply with the obligations of the executor in the above provisions, and I undertake to work on the rights and safety of people participating in this research.

Researcher signature: