PROTOCOL NAME:

EVALUATING THE USE OF ADVANRX IN A RANDOMIZED CONTROLLED TRIAL OF ADULTS TREATED FOR HYPERTENSION (EARLY)

PROTOCOL IDENTIFYING NUMBER:
AD-NA-001

PROTOCOL VERSION DATE:
Version 01- 15 January 2016

GENERAL INFORMATION

Name and address of the sponsor of the study

Advantage Clinical
100 Advantage Way
Toronto, Ontario
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Name and address of the person authorized to sign the protocol and amendments

Fraser Gibson
Advantage Clinical
100 Advantage Way
Toronto, Ontario
N1N 1N1

Name and address of study monitor

John Doe
Advantage Clinical
100 Advantage Way
Toronto, Ontario
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Name, title, address and telephone number(s) of the medical expert for the trial

Dr. Jane Doe
Medical Monitor
Advantage Clinical
100 Advantage Way
Toronto, Ontario
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Name and addresses of the clinical laboratories and/or other institutions involved in the trial

Fergus Laboratories
200 Advantage Way
Toronto, Ontario
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Study Summary

Title	**Evaluating the Use of AdvanRx in a Randomized Controlled Trial of Adults Treated for Hypertension**
Short Title	*EARLY*
Protocol Number	*AD-NA-001*
Phase	*3*
Methodology	*Randomized, double blind, placebo controlled*
Study Duration	*2 years*
Study Center(s)	*Multicenter (10 centers)*
Objectives	*To compare the safety and efficacy of AdvanRx based on mean reduction of systolic blood pressure at 90-days in subjects with diagnosed hypertension.*
Number of Subjects	*100*
Diagnosis and Main Inclusion Criteria	*Diagnosed hypertension, treatment naive*
Study Product, Dose, Route, Regimen	*AdvanRx 1mg oral administration, taken once per day*
Duration of administration	*90 days*
Reference therapy	*Placebo*
Statistical Methodology	*The primary efficacy endpoint if the mean reduction in systolic blood pressure in patients treated with AdvanRx.* *Primary safety endpoints are the adverse events, laboratory chemistry, vital signs, and ECGs.* *Endpoints will be evaluated with an intent to treat analysis.*

Principal Investigator Signature Page

PROTOCOL ID: AD-NA-001
SPONSOR: Advantage Clinical
STUDY TITLE: Evaluating the Use of AdvanRx in a Randomized Controlled Trial of Adults Treated for Hypertension

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I understand the contents and intend to comply fully with all requirements and the applicable current local regulations and guidelines. I will conduct this study as outlined herein, including all statements regarding confidentiality. No changes will be made without formal authorization by Advantage Clinical in the form of a protocol amendment.

I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the subjects in the study.

I agree to conduct this study in full accordance with all applicable regulations and ICH/Good Clinical Practice (GCP).

Investigator's Signature	Date
Principal Investigator's Name (PRINT)	

Sponsor Signature Page

PROTOCOL ID: AD-NA-001
SPONSOR: Advantage Clinical
STUDY TITLE: Evaluating the Use of AdvanRx in a Randomized Controlled Trial of Adults Treated for Hypertension

I have read the protocol and the appendices and agree that it contains all necessary details for carrying out the study as described. I understand the contents and intend to have Advantage Clinical comply fully with all requirements and the applicable current local regulations and guidelines. Any changes in the protocol will only be implemented after with formal authorization and approval of appropriate ethic committees and by Advantage Clinical in the form of a protocol amendment.

Sponsor's Signature	Date
Sponsor's Name (PRINT)	

Table of Contents

List of Abbreviations

(e.g.)

ICH	International Conference on Harmonisation
CRF	Case Report Form
GCP	Good Clinical Practice
IRB/IEC	Institutional Review Board or Ethics Committee
BP	Blood Pressure
ACE	Angiotensin Converting Enzyme

1 Background

Angiotensin Converting Enzyme or "ACE" is a central component of the renin-angiotensin system, which controls blood pressure by regulating the volume of fluids in the body. It converts the hormone angiotensin I to the active vasoconstrictor angiotensin II. Therefore, ACE indirectly increases blood pressure by causing blood vessels to constrict.

AdvanRx is a member of the drug class, Angiotensin Converting Enzyme (ACE) inhibitors. This group of drugs cause relaxation of blood vessels, as well as a decreased blood volume, which leads to lower blood pressure and decreased oxygen demand from the heart. They inhibit the angiotensin-converting enzyme, an important component of the renin-angiotensin-aldosterone system.

1.1 Preclinical and Clinical Experience

An accumulation of medical evidence in animals and humans has demonstrated a high degree of safety with AdvanRx therapy as well as its efficacy in reducing mean systolic blood pressure at 90 days.

Pre-clinical data in canines demonstrated a safety profile congruent with marketed ACE inhibitors and a mean reduction in blood pressure of 15mmhg at 90 days.

Name of Test	Test Category	Results overview
Cytotoxicity	In Vitro Tests AdvanRX with Murine Fibroblasts	Negative
Sensitization	Animal Tests AdvanRX with Guinea Pigs	Negative reaction at 24 and 48 hours
Acute systemic toxicity	Animal Tests AdvanRX With Mice	Passed:
Pyrogenicity	Animal Tests AdvanRX With Rabbits	Passed: 3/9 rabbits had mild reaction
Mutagenesis	Ames Test	Passed

150 humans have been treated in phase 1 and 2 studies with AdvanRx. The safety profile is congruent with marketed ACE inhibitors and demonstrated a mean reduction in systolic blood pressure of 18mmhg at 90 days.

1.2 Dose Rationale

Pre-clinical data suggests a maximum dose of 15mg orally administered per day before hypotension resulting in multiple organ failure is experienced as a result of reduced hemoperfusion.

Dose escalation studies in human subjects have demonstrated an acceptable safety profile for 1mg oral administration per day.

1.3 Trial Conduct

This study will be conducted in compliance with the approved protocol, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the oversight IRB/IEC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB/IEC as soon as possible.

1.4 Population

Subjects recently diagnosed with hypertension who are treatment naive

1.5 Literature

References to published articles on AdvanRX would be listed here. AdvanRx is a fictional compound and no literature exists to reference in this section.

2 Trial Objectives

The primary objective is to compare the safety and efficacy of AdvanRx, vs placebo, based on mean reduction of systolic blood pressure at 90-days in subjects with diagnosed hypertension.

The secondary trial objectives are as follows:

- To compare the mean change in diastolic blood pressure at 90 days
- To compare the mean time to diastolic pressure <100mmhg
- To compare the mean time to systolic pressure <140mmhg

3 Trial Design

3.1 Study Design/Type

EARLY is a randomized, double blind, placebo controlled study.

3.2 Randomization

Subjects will be randomized via pre-determined randomization schedule accessed via the internet based randomization program located at:

www.advantage-clinical.com/EARLYRandomizationLogin

A username and password login will be provided to the principal investigator and study coordinator at each site upon site initiation.

For each study site, the pharmacy (or delegated individual) will dispense the 'treatment packages.' An independent statistician will generate the randomization schemes for the entire study. For each study site, subjects will be randomized in a 1:1 ratio to the two treatment groups (AdvanRX or placebo). A blocked randomization scheme with mixed randomized block sizes of 2 and 4 will be used to provide approximately balanced allocation to the two treatment groups for each investigative site during the study.

3.3 Maintenance

Randomization codes containing treatment assignment will be stored on the Advantage Clinical Server.

In the event that the blind must be broken, the treatment assignment can be obtained by logging into the server or calling the 24-hour help line at 1-800-UNB-LIND.

The server is located at www.advantage-clinical.com/emergencyunblinding
You will require the site and subject ID as well as your assigned login details.

3.4 Trial Treatment

Subjects will be randomized to receive either:

- AdvanRx 1mg Oral tablet taken once daily for 90 days
- Placebo oral tablet taken once daily for 90 days

Investigational product will be labelled with a treatment assignment number which will correspond to either AdvanRx or placebo.

Subject's will be dispensed one bottle of 90 tablets with the treatment assignment number determined by the randomization system linked with each subject.

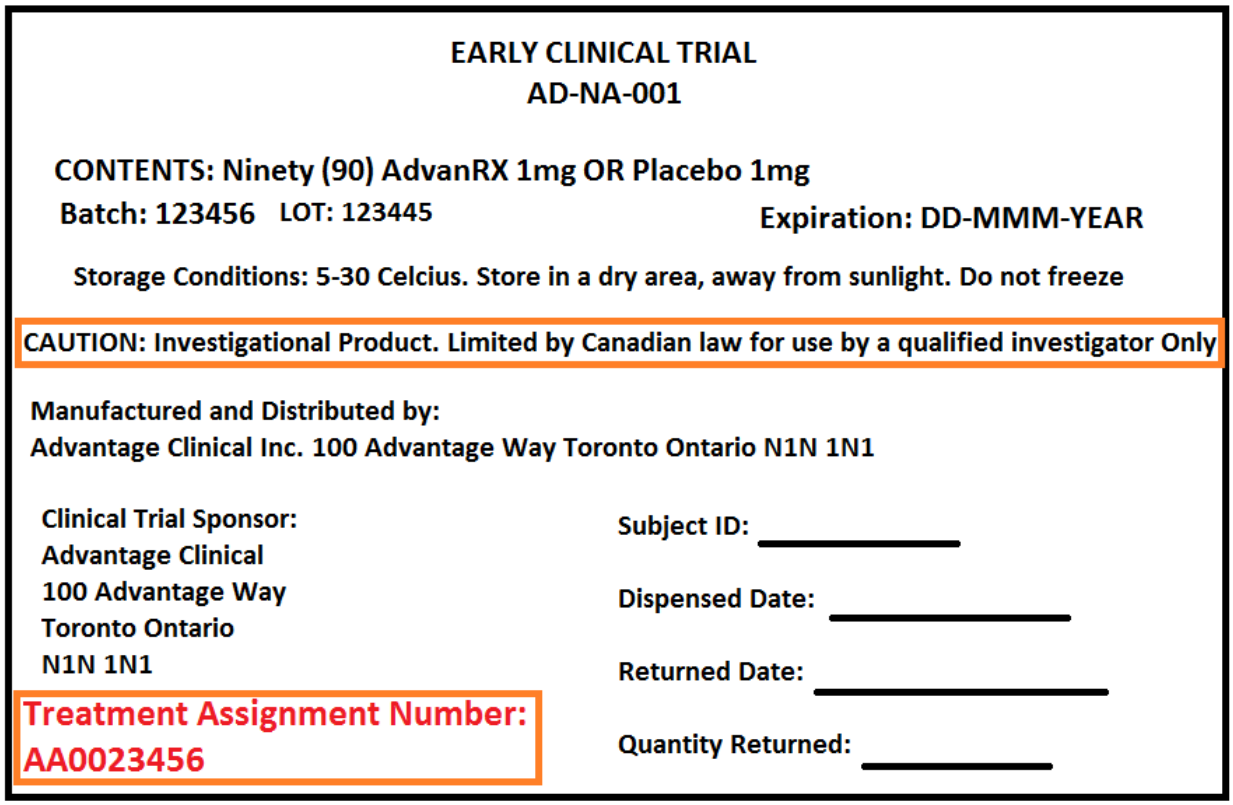

Figure 1- Investigational Product Label- AdvanRX / Placebo EARLY Trial

3.5 Duration

Subjects will be followed every thirty days for a total of ninety days. Any ongoing serious adverse events will require follow up to resolution beyond 90 days from randomization.

3.6 Discontinuation

Subjects will be discontinued at the discretion of the principal investigator.

A data safety monitoring board (DSMB) has been established for the EARLY trial. The DSMB will meet quarterly to review unblended safety data. The DSMB will make recommendations to Advantage Clinical as follows:

- Continue the trial as is
- Continue the trial with modifications
- Continue the trial as is with an increase in frequency of DSMB review
- Premature discontinuation due to concerns for patient safety

4 Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

The subject, or an acceptable surrogate health related decision maker, will be asked to sign an informed consent form. The subject (or surrogate) must understand, sign, and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures being performed.

Subjects who meet the following criteria (and have a signed informed consent) will be allowed into the study:

1. Current diagnosis of hypertension defined as
    a. Systolic Pressure >140mmhg and diastolic pressure >90mmg for two consecutive office visits
    OR
    b. Ambulatory Blood Pressure Monitoring (24hour) mean systolic pressure of >140mmhg and mean diastolic pressure > 90mmhg
2. Age >18 years old

4.2 Exclusion Criteria

Subjects who meet the following criteria will NOT be allowed into the study:

1. Inability to obtain an informed consent from the subject
2. Received treatment with any of the following anti-hypertensive therapies
    a. Thiazide Diuretics
    b. Calcium channel blockers
    c. ACE inhibitors
    d. Angiotensin II receptor antagonists
    e. Beta Blockers
3. Acute myocardial infarction (MI) in the past year
4. Body weight < 40kg
5. Currently enrolled in another investigational drug trial
6. Any other condition that in the opinion of the investigator, would preclude the subject from being a suitable candidate for enrollment.

4.3 Subject Withdrawal

Every effort within the bounds of safety, and subject choice, should be made to have each subject complete the study. The investigator may terminate a subject's participation at any time for reasons such as adverse events, intercurrent illness, noncompliance with study procedures, serious eligibility or on-study protocol violations, or in the best interests of the subject, in the opinion of the investigator. Subjects are also free to withdraw their consent at any time during the study.

At the time of withdrawal the investigator will complete the End of Study/Early Termination Assessments if possible.

4.4 Concomitant Medications

During the course of this study, subjects should not receive any other anti-hypertensive therapy (except in the case of medical emergencies), including the following classes of anti-hypertensives:

a. Thiazide Diuretics
b. Calcium channel blockers
c. ACE inhibitors
d. Angiotensin II receptor antagonists
e. Beta Blockers

4.5 Monitoring for subject compliance

Subjects will complete a medication diary where they will note the date and time of each dose of AdvanRx / placebo (Appendix 1)

5 Assessment of Efficacy and Safety

5.1 Parameters

The primary efficacy endpoint if the mean reduction in systolic blood pressure in patients treated with AdvanRx.

Primary safety endpoints are the adverse events, laboratory chemistry, vital signs, and ECGs.

5.2 Schedule of Assessments

Table 1- Schedule of Assessments

Assessment	Screening	Day 0 Baseline	Day 30 (+-5days)	Day 60 (+-5days)	Day 90 (+-5days) / Early Termination
Informed Consent	X				
Inclusion /Exclusion Review	X				
Demographics		X			
Medical History		X			
Physical Exam		X			X
Vital Signs		X	X	X	X
12 Lead ECG		X			X
Seated BP Measurements		X	X	X	X
Laboratory Assessments*		X	X	X	X
Randomization		X			
Concomitant Medications		X	X	X	X
Adverse Events Assessment		X	X	X	X

* CBC, ALT, AST, CK, Creatinine performed by local lab

Screening:

Subjects will be assessed against inclusion / exclusion criteria for EARLY. Once these criteria have been reviewed, the subject will be asked to sign an informed consent to permit randomization into the study.

Baseline Assessments (Day 0):

After the subject has been randomized, the following assessments and procedures to determine baseline values will be recorded in the subject's record (source documentation and CRF). The timeline for recording baseline assessments + 5 days from randomization. Laboratory assessments made per standard of care may be abstracted from the source records for up to 5 days prior to randomization.

1. Demographics
2. Significant medical history
3. Physical Exam
4. Vital Signs
    a. Respiration rate
    b. Heart Rate
    c. Temperature
5. 12 Lead ECG
    a. Performed locally
6. Seated blood pressure measurements
    a. Subject seated for 5 minutes before first measurement

   b. 3 consecutive measurements taken manually every 5 minutes (+/-1 minute)
7. Laboratory Assessments performed locally as follows:
   a. CBC
   b. ALT
   c. AST
   d. CK
   e. Creatinine
8. Concomitant medication assessment
9. Adverse event assessment

Day 30 & 60:

The following assessments and procedures to determine will be recorded in the subject's record (source documentation and CRF). The timeline for recording day 30 & 60 assessments is +/- 5 days.

1. Vital Signs
   a. Respiration rate
   b. Heart Rate
   c. Temperature
2. Seated blood pressure measurements
   a. Subject seated for 5 minutes before first measurement
   b. 3 consecutive measurements taken manually every 5 minutes (+/-1 minute)
3. Laboratory Assessments performed locally as follows:
   a. CBC
   b. ALT
   c. AST
   d. CK
   e. Creatinine
4. Concomitant medication assessment
5. Adverse event assessment

End of Study (Day 90) or Early Termination:

The following assessments and procedures will be recorded in the subject's record (source documentation and CRF). The timeline for recording end of study assessments is +/- 5 days from day 90. The following procedures are to be performed in the event of subject withdrawal or early termination. All serious adverse events ongoing at this visit must be followed through to resolution. Any subject diaries and unused study medication will be collected at this visit.

1. Physical Exam
2. Vital Signs
   a. Respiration rate
   b. Heart Rate
   c. Temperature
3. 12 Lead ECG

   a. Performed locally
4. Seated blood pressure measurements
   a. Subject seated for 5 minutes before first measurement
   b. 3 consecutive measurements taken manually every 5 minutes (+/-1 minute)
5. Laboratory Assessments performed locally as follows:
   a. CBC
   b. ALT
   c. AST
   d. CK
   e. Creatinine
6. Concomitant medication assessment
7. Adverse event assessment

5.3 Adverse Event Reporting

The safety event collection period begins at randomization and ends after completion of the End of Study (Day 90) visit. Any ongoing SAEs at the Day 90 visit must be followed through to resolution.

Any AE or SAE that occurs during the study must be documented in the subject's medical record (source document), in accordance with the investigator's normal clinical practice, and on the appropriate CRFs. The investigator will be asked to define the AE using the Common Terminology Criteria for Adverse Events (CTCAE) and assess the severity of the AE using the following categories: Grade 1, Grade 2, Grade 3, Grade 4 and Grade 5 based on the common terminology criteria (CTCAE available online at http://safetyprofiler-ctep.nci.nih.gov/ctc/ctc.aspx).

The investigator is responsible for ensuring that follow-up includes any necessary supplemental investigations to elucidate the nature and/or causality of the event. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

All Serious Adverse Events (SAEs) must be promptly reported to the Advantage Clinical Safety Department within 24 hours of the Investigator's first knowledge of the event (or at the latest, on the following working day), even if the event does not appear to be related to the investigational product.

Complete Safety Event Form and fax to:
Fax: 555-555-5555

The investigator is responsible for reporting all serious adverse events to their local ethics committee per local reporting requirements.

5.4 Definitions

Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a subject receiving an investigational product, which does not necessarily imply a causal relationship with treatment. An AE includes any unfavorable and unintended sign that could include a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of the study product, whether or not considered related to the study product.

Serious Adverse Event

A Serious Adverse Event (SAE) is an adverse event that results in any of the following outcomes:

- Death
- A life-threatening condition (with immediate risk of dying)
- Prolongation of existing hospitalization, or subsequent inpatient hospitalization
- Requiring intervention to prevent permanent impairment/damage
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect in the offspring of a subject

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Unanticipated Serious Adverse Event

An Unanticipated Serious Adverse Event (USAE) is any SAE not previously identified in nature, severity or degree of incidence in the protocol, Investigator Brochure, Summary of Previous Studies Document, or other sources of information for AdvanRx. Additionally, a USAE is any other unanticipated serious problem associated with the investigational product that relates to the rights, safety, or welfare of subjects.

6 Statistical Plan

Note: A statistical plan was not developed for this mock protocol. Sample headings are contained below for reference only.

6.1 Statistical Methods

6.2 Subject Population(s) for Analysis

6.3 Significance

6.4 Termination Criteria

6.5 Accountability Procedure

6.6 Deviation Reporting

7 Direct Access to Source Data/Documentation

It should be specified in the protocol or other written agreement the investigator(s)/institution(s) will permit trial-related monitoring, audits, IHREB review and regulatory inspection(s) by providing direct access to source data/documentation.

8 Ethical Considerations

This study will be conducted according to Canadian and international standards of Good Clinical Practice for all studies. Applicable government regulations and local research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the local IRB/IEC for formal approval to conduct the study. The decision of the IRB/IEC concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the local IRB/IEC. The formal consent of a subject, using the IRB/IEC-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

9 Records Retention

The investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including but not limited to those documents defined by GCP as essential documents, for the longer of: (i) 2 years after the last marketing authorization for the study device has been approved or the Sponsor has discontinued its research with respect to such investigational product or (ii) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify in writing the Sponsor of its intent to destroy all such material. The Sponsor shall have 30 days to respond to the investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

10 Review of Source Records

The investigator agrees that qualified representatives of the Sponsor, or its designee and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Subjects will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the subject will be maintained unless disclosure is required by regulations. Accordingly, the following statement (or similar statement) will be included in the ICF:

"Representatives of regulatory agencies, IRBs, the Sponsor, and your personal physician may review your medical records and all information related to this study as permitted by law. Identifying information will not appear on any record received by the Sponsor. Your identity will remain confidential unless disclosure is required by law."

Appendix 1

EVALUATING THE USE OF ADVANRX IN A RANDOMIZED CONTROLLED TRIAL OF ADULTS TREATED FOR HYPERTENSION (EARLY)

Subject Medication Diary

Instructions: Please complete this diary for each day of participation in the EARLY clinical trial.

Please bring this diary with you to each study visit.

Example:

Date	Time	Tablets Taken	Adverse Effects	Comments
01-Jan-2015	13:27	1	Dizzy	None

Subject ID:_____
Treatment Assignment Number:_____

Principal Investigator and Study Coordinator Contact Information:

Names
Address
Address
Phone Number

Start of Diary

Date	Time	Tablets Taken	Adverse Effects	Comments