CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20420

PHARMACOLOGY REVIEW(S)

Arbutamine Safety Review
NDA No. 20-420
Submission date: December 20, 1993
Sponsor: Gensia Inc., San Diego, CA 92121-1207
Type of Submission: Original New Medical Entity
Pharmacologic class: synthetic catecholamine, β_1- and β_2-adrenergic agonist with little α-adrenergic agonist activity. Other drugs in this class include dobutamine, dopamine, norepinephrine, epinephrine and neosynephrine
Generic Name: Arbutamine
Brand Name: GenESA System, comprised of proprietary drug delivery device (the GenESA Device) and the pharmacologic stress agent (arbutamine)
Formulation: Solution for intravenous injection
0.05 mg/ml in 20 ml pre-filled syringes
Reviewer: Karen A. Frank, M.D.
Statistical Reviewer: Kooros Mahjoob, Ph.D. (consultation for access to CANDA data and SAS programming for calculation of p-values.)
Date of First Review Draft: October 21, 1994
Date of Final Review Revision: November 1, 1994

TABLE OF CONTENTS

INTRODUCTION

Arbutamine (NDA 20-420) is submitted for use as a diagnostic adjunct for the imaging of myocardial ischemia, using ECG, ECHO, and SPECT detection methods. The drug is a synthetic catecholamine, and the proposed use is to increase myocardial oxygen demand by utilizing its positive chronotropic and inotropic effects. The final revision of the closed loop algorithm allowed for administration of arbutamine in infusion rates ranging up to 0.8 µg/kg/min, and total doses of 10 µg/kg. Safety data have been collected and analyzed for anticipated events (clinical endpoints in diagnostic stress testing), adverse events, arrhythmias, clinical pathology/laboratory data, ECG intervals, drug-drug interactions, and drug-disease interactions. Where available, analyses based on subgroups and dose range are included in the review. The **DCRDP medical efficacy reviewer, Dr. Steven Rodin,** provided guidance throughout the course of this review. The **DCRDP statistical reviewer, Dr. Kooros Mahjoob,** assisted in access to the CANDA database and wrote SAS programming to allow for the

calculation of p-values in cases where the descriptive statistics suggested a difference in signal between ESA and ETT or between subgroups. While p-values arising from post-hoc analyses cannot be considered truly quantitative, they can be taken as an extension of the descriptive statistics when looking at comparative incidence of adverse events between treatment groups and between subgroups. The **DCRDP biopharmaceutics reviewers, Dr. Olaf Borga and Dr. Ameeta Parekh,** provided advise on metabolism and analysis of adverse events by dose-range in a non-steady state system. Brief synopses of the pharmacology and pharmacokinetics are included below. The issues of device safety are deferred to the CDRH reviewer.

SUMMARY OF PHARMACOLOGY

Arbutamine is a synthetic catecholamine with both β_1- and β_2-adrenergic receptor blocking properties. There is little α-adrenergic blocking activity.

Arbutamine increases heart rate, cardiac contractility, cardiac output in a dose dependent manner. In most cases, there is a corresponding increase in systolic blood pressure secondary to cardiac effects, but there is also β_2-mediated vasodilatation that can lead to decrease in systemic arterial pressure. This $\beta 2$-agonism may also induce coronary vasodilation creating concomitant flow maldistribution.

SUMMARY OF PHARMACOKINETICS

Arbutamine is intended for administration as a single dose, titrated, intravenous infusion. The pharmacokinetic half-life is approximately 8 minutes, and the pharmacodynamic half-life (the time for heart rate to fall 50% after discontinuation of the infusion) is 15 minutes. Arbutamine undergoes degradation by extra-hepatic catechol-methyl transferase to inactive metabolite(s), which are then renally excreted. Renal insufficiency would thus increase the half-life of the metabolites, but would not increase the half-life of the parent compound. Arbutamine does not cross the blood-brain barrier.

OUTLINE BY STUDY

Phase I (Studies in Normal Volunteers)

Open-Loop Studies

0102 Pharmacokinetics/Pharmacodynamics (IV vs. transdermal)

Completed, open-label, single-blind, crossover, PCO controlled, dose-ranging study to determine the dosage to achieve 85% maximal heart rate. 34 normal males 19-33 y/o given (a) 16 min PCO run in, then ARB at constant infusion rate of 0.0007 µg/kg/min to 0.1792 µg/kg/min IV gtt for entire test period or (b) 32 min pco run in, then 32 min TD ARB **Mean total iv dose:** 0.02±0.00 - 5.71±0.01 µg/kg/min **Mean duration:** 31.40±0.50 -31.96±0.04 min (intravenous), 31.69±0.11 - 32.14±0.18 min (transdermal) **AE:** tachycardia 35-48%, Headache 12-15% **SAE:** none **Lab AE**: none

0103 Transdermal administration with propranolol and occluder cuff

Completed, open-label single-blind administration of transdermal arbutamine. 6 normal males 19-28 y/o received 0.6 mA/cm^2 TD ARB x 20 minutes followed by observation, with propranolol 0.075 mg/kg or

occluder cuff to assess efficacy in reversing ARB-induced tachycardia. **Mean duration:** 20.0±0.0 min **AE**: application site reaction 100%, tachycardia 83%, palpitations 83%. **SAE:** none **Lab AE**: none

0104 Pharmacokinetics/Pharmacodynamics (IV vs. transdermal)

Completed, open-label, single-blind, PCO-controlled, dose-ranging study comparing intravenous and transdermal administration of arbutamine. 6 normal males 21-31 y/o given open-loop IV ARB 0.3 µg/kg/min to 85% maximum HR or 20 minutes maximum duration, then crossed-over after a 24 hour hiatus to transdermal ARB 70 Mm/1.0 Ma/cm^2 to 80% maximal predicted HR or 10 minutes maximum duration. **Mean Total dose:** 5.10±0.73 µg/kg (intravenous) **Mean duration:** 16.99±2.42 min (intravenous), 9.83±0.03 min (transdermal)**AE:** none **SAE:** none **Lab:** serum K^+ fell by 21% following IV and 4% following transdermal administration.

0105 Pharmacodynamics multiple intermittent IV and TD dosing

Completed, randomized, cross-over, open-label, single-blind, dose-ranging study comparing intravenous to transdermal administration of arbutamine. 8 normal males given 0.05, 0.1, 0.2 µg/kg/min then TD 1.0 mA/cm^2 load and 0.8, 1.0 and 1.2 mA/cm^2 in random order. **Mean total dose:** 1.75±0.01µg/kg (intravenous) **Mean duration:** 15.02±0.07 min (intravenous), 23.59±2.32 min (transdermal) **AE**: palpitations 100%, headache 38%, flushing 25% **SAE:** none **Lab**: no decrease K^+.

0106 Transdermal administration.

Completed, randomized, single-blind, open-label, three-way crossover study to investigate the effects of thermal or pharmacologic vasodilation on the delivery of transdermal arbutamine. Eight subjects each underwent three successive treatments of transdermal ARB, each separated by 24 hours. In four subjects the duration of each treatment was 14 minutes, and in the other four subjects the duration of treatment was 32 minutes. The rate of delivery of all treatments was set at 1 electrode/0.6 mA/cm_2. The pretreatment schedule consisted of: (1) ARB alone (2) heat pretreatment or (3) Rubriment pretreatment. **Mean duration:** 14.00±0.00 min (4 patients on 14 min schedule) and 28.50±2.36 - 32.25±0.63 minutes (4 patients on 32 min schedule) and **AE:** application site irritation 95%, tachycardia 63% **SAE:** none **Lab**: no AE.

0110 Drug-drug pharmacodynamic interaction (propranolol, metoprolol)

Completed, open-label, randomized, three-way crossover study to investigate the effects of cardioselective and non-cardioselective beta-blockade on the dose-response relationship of intravenous arbutamine. 7 normal males 19-39 y/o given ARB at 0.05, 0.1, 0.2, 0.4, 0.6, 0.8 and 1.1 µg/mg/kg for 3 min each until target HR achieved, SBP 220 mmhg, max infusion rate 0.8 µg/kg/min or 10 µg/kg max total dose. Pretreatment with propranolol 0.075 mg/kg IVB (4 subjects) or 3 doses of metoprolol 5 mg IVP (4 subjects) or placebo (4 subjects). In two subjects the placebo infusion was terminated at 0.4 and 0.6 µg/kg/min, respectively. **Mean total dose:** 9.80±0.04 µg/kg (2 subjects on placebo with ARB to full 1.1 µg/kg/min), 9.84±0.00 µg/kg (propranolol), 9.84±0.01 µg/kg (metoprolol) **Mean total duration:** 21.08±0.00 min (2 placebo on ARB to 1.1 µg/kg/min), 21.08±0.00 min (propranolol), 21.08±0.00 min (metoprolol) **AE**: paradoxical decrease in BP in 3/4 patients. **SAE**: none **Lab AE**: decrease in plasma K^+ by 30% from baseline in placebo treated subjects, 30% from baseline in metoprolol treated subjects, and 8% from baseline in propranolol treated subjects.

0116 Drug-drug pharmacodynamic interaction (propranolol, atenolol)

Completed, open-label, randomized, crossover, dose-ranging at trough of propranolol, or atenolol. 6 normal males 20-36 y/o given ARB at 0.2-0.8 µg/kg/min 23 hours after pretreatment with propranolol (160 mg po qd x 4 days) or atenolol (100 mg po qd x 3 days). **Mean total dose:** 15.40±2.20 µg/kg (propranolol), 2.73-12.40 µg/kg (atenolol), 0.95 µg/kg (placebo). **AE**: three subjects withdrawn because of PVCs, tremors **SAE:** none **Lab:** serum K^+ decreased in 5/6 subjects

0125 Pharmacokinetics and Metabolism of single-dose ^{14}C-Arbutamine

Completed, open-label, single dose study of the distribution, metabolism and elimination of intravenous arbutamine. 4 healthy male volunteers 26-41 y/o given 0.2 µg/kg/min for 20 min. **Mean total dose:** 4.00±0.00 µ/kg **AE:**none **SAE:** none

0118 Drug-drug pharmacodynamic interaction (atropine)

Completed, randomized, dose-ranging study with incomplete block design. 21 normal volunteers (50-61 y/o, M/F 14/70 received pretreatment with atropine 6, 8, 11, 15 µg/kg or PCO and were then given IV ARB in forced titration 0.05, 0.1, and 0.2 µg/kg/min for 10 min each dose. **Mean total dose:** 3.48±0.00 µg/kg (placebo), 3.34±0.08 µg/kg (atropine).**AE:** arrhythmias (PVC and PSVT) and hypotension in atropine group. hypokalemia 0,30,60 min--baseline at 120 min post. **SAE:** none **Lab**: none.

Closed-loop studies

0111 Pharmacodynamics/ Testing of ESA System
Completed three-way crossover to test the ability of the closed-loop system to achieve target heart rate. 8 normal volunteers given total of 18 closed-loop intravenous infusions at ramp rates of 4, 8 or 12 bpm/min with revision 1 of the CLA to maximum infusion rate 0.8 µg/kg/min or maximum total dose of 10 µg/kg. **Mean Total Dose:** 4.72±0.44 µg/kg **Range of total dose:**1.99-8.05 µg/kg **Mean infusion rate:** 0.21±0.02 µg/kg/min **Range of Mean Infusion Rates:** 0.088-0.359 µg/kg **Mean Maximum infusion rate:** 0.58±0.04 µg/kg/min **AE:** 38% bradycardia, 29% tachycardia **SAE**: none **Lab AE**: none
0117 Pharmacodynamics/ Testing of ESA System
Completed three-way crossover to test the ability of the closed-loop system to achieve target heart rate. 8 normal male volunteers 21-38 y/o received total of 19 closed-loop infusions at ramp speeds of 4 and 8 bpm to maximum infusion rate of 0.8 µg/kg/min or maximum total dose of 10 µg/kg. **Mean Total Dose:** 4.59±0.48 µg/kg **Range of total dose:** 1.66-8.35 µg/kg **Mean infusion rate:** 0.16±0.01 µg/kg/min **Range of mean infusion rates:** 0.083-0.244 µg/kg/min **Mean Maximum infusion rate:** 0.32±0.02 µg/kg/min **AE:** ECG changes to non-sinus.**AE:** chest pain and non-sinus rhythm led to withdrawal of 2 subjects **SAE:** none. **Lab**: none.
0126 Pharmacodynamics/ Single treatment testing of ESA System
Completed, open-label, dose-ranging study of closed-loop intravenous arbutamine. 20 normal volunteers (36-74 y/o M/F 16/4 were given closed-loop IV ARB to ramp speed of 4 or 8 bpm to maximum of 0.8 µg/kg/min. **Mean total dose:** 4.82±0.45 µg/kg **Range of total dose:** 1.24-9.98 µ/kg **Mean infusion rate:** 0.20±0.01 µg/kg/min **Range of infusion rates:** 0.14-0.34 µg/kg/min **Mean maximum infusion rate:** 0.39±0.03 µ/kg/min **AE:** arrhythmias (20%) hypotension (10%).
SAE none **Lab**: transient decrease K^+ in 7 subjects.

Phase II (Studies in patients with known or suspected CAD)

Open-Loop Studies

0107 Pharmacodynamics in CAD (ESA vs. atrial pacing, ECG/ECHO) Completed, open-label comparison with atrial pacing for efficacy and safety.4 male subjects 57-59 y/o with known CAD and demonstrable wall motion abnormality on atrial pacing were given ascending dose titration at 0.025, 0.05, 0.1 and 0.2 µg/kg/min (0.4 and 0.6 µg/kg/min in one patient) at 3 minute intervals. All patients received 0.5 mg atropine for TEE. **Mean total dose:** 1.06±0.17 µg/kg to 4.73 µg/kg **AE:** none **SAE:** none **Lab**:no hypokalemia **DEATHS**:one fatal MI in patient who did not receive drug
0108 Pharmacodynamics in CAD (pre-/post-PTCA, ESA vs. ETT, ECG/ECHO)
Completed, open-label, sequential comparison study. 10 normal volunteers (ages 36-75, M/F 9/1) underwent ETT and ESA titration with IV ARB 0.025, 0.05, 0.1, 0.2, 0.4, 0.6, 0.8 and 1.1 µg/kg/min in increments of 3 minutes each pre- and post-PTCA to assess echo and ECG changes in comparison with those produced pre- and post- PTCA. **Mean total dose:** 2.1 to 5.33±0.4 µg/kg **AE:** one patient had termination of infusion for angina and 9 beats of VT **SAE:** none **Deaths:** none **Lab**: transient decrease in K^+ in one patient.
0112 Diagnostic Use in CAD (crossover design ESA vs. ETT, ECG/ECHO)
Completed, open-label randomized cross-over study. 13 patients (43-74 y/o, M/F 11/2) underwent ETT and ESA with IV ARB titration in doses of 0.1, 0.2, 0.3, 0.4 µg/kg/min for 8 min each dose until ----.**Mean total dose:** 2.49±0.26 µg/kg to 7.54±0.35 µg/kg **AE:** PVC, SVT in 2 patients **Lab:** no hypokalemia. **SAE:** none.
0115 Pharmacodynamics in CAD (open-loop vs. closed-loop in patients with paradoxical bradycardic/hypotensive response to dobutamine)
Completed study. 3 patients known to have paradoxical hypotensive response to dobutamine were randomized to either open-loop (IV ARB 0.1, 0.2, 0.3, or 0.4 µg/kg/min for 3 min each) or closed-loop (HR ramp 4 bpm/min to max of 6.5 µg/kg) infusion. Endpoints were (1) hypotension, (2) signs of syncope, ischemia or AE (3) end of infusion regimen **Mean total dose:** 1.09 ± µ/kg **Range of total dose:** 0.68-1.62 µ/kg **AE:** paradoxical hypotension **SAE:** none. No regimen prevented repeated paradoxical hypotensive, bradycardic response.

0119 Drug-drug pharmacodynamic interaction
(dose-ranging at trough of propranolol, atenolol, PCO)
Completed, open-label, randomized cross-over study. 20 male patients 39-67 y/o were pretreated with propranolol 160 mg/day, atenolol 50 or 100 mg/day, or PCO for 7-10 days preceding infusion. Each underwent ESA testing 24 hours post pretreatment, each infusion rate given in increments of 10 minutes each: IV ARB 0.15, 0.21,and 0.3 µg/kg/min in 10 min steps (baseline), IV ARB 0.28, 0.4, and 0.56 µg/kg/min (after atenolol), 0.4, 0.56 and 0.8 µg/kg/min (after propranolol). Endpoints included (1) end of infusion regimen (2) ECG or echo changes of ischemia (3) intolerable adverse events **Mean total dose:** 1.19±0.13 to 6.73±0.14 µg/kg (ARB alone), 2.78±0.07 to 11.93±0.38 µkg (atenolol), 8.07 to 17.64±0.16 µg/kg (propranolol) **AE:** hypotension 10%, angina 60%, bradycardia 10%, headache 5% with equal frequency across treatment groups **SAE:** none **Lab**: transient hypokalemia in one patient.

0121 Diagnostic Use in CAD (cross-over ARB vs. ETT, ECG/ECHO)
Completed, randomized, crossover study comparing ETT to open-loop ARB. 45 patients (32-75 y/o, M/F 41/4) received IV ARB 0.1, 0.2, 0.3 and 0.4 µg/kg/min in 8 minute increments. Endpoints included (1) end of infusion regiment (2) angina or ECG/ECHO changes of ischemia (3) intolerable adverse events **Mean total dose:** 0.41±0.37 to 7.80±0.15 µg/kg **AE:** hypotension (11%), dyspnea 20%, dizziness 11% **Lab**: 5 case hypokalemia <3.0 mmol/L **SAE:** none

Closed-Loop Studies

0115 Pharmacodynamics in CAD (4 bpm/min)
see description under open-loop studies above
0120 Pharmacodynamics in CAD (6 bpm/min and 10 bpm/min)
Completed open-label randomized cross-over study to compare slow vs. fast ramp speeds in closed-loop administration. 70 patients (33-71 years, M/F (64/6) underwent ESA testing using either 6 bpm/min or 10 bpm/min ramp speeds to max infusion rate of 0.8 µg/kg/min IV ARB with assessment of ECG and echo detection of ischemic wall segments. **AE:** no difference in rate of occurrence with low and high slope, PVC 32%, hypokalemia was associated with multiple episodes of PVCs and one episode of Sustained VT 20 beats. **SAE:** none.
0130 Pharmacodynamics in CAD (8 bpm/min) (hemodynamic effects and efficacy patients undergoing cardiac catheterization)
Ongoing, multicenter, open label, single treatment evaluation of the acute cardiac and peripheral hemodynamic effects of closed-loop intravenous arbutamine. 12 patients undergoing cardiac catheterization were given closed-loop IV ARB at ramp of 8 bpm/min to maximum of 10 µg/kg. **Total dose:** 1.55±00.28 µg/kg **Mean infusion rate:** 0.15±0.01 µg/kg/min **Maximum infusion rate:** 0.26±00.03 µg/kg/min **AE:** Hypotension 25%, resolving with d/c of IV ARB or treatment with beta-blockers. PVCs and VT, they attribute VT to catheter. **Lab**: No hypokalemia reported **SAE:** Hypotension in 3/12 (25%), resolving with discontinuation of ARB and/or beta-blockade **Deaths:** none
0132 diagnostic use in CAD (cross-over ESA vs. ETT, ECHO)
Ongoing, multicenter, open-label, randomized, crossover evaluation of the safety and efficacy of the ESA vs. ETT in inducing echocardiographic changes of myocardial ischemia. 10 patients with CAD underwent closed-loop administration of ARB at 8 bpm/min to max infusion rate of 0.8 µg/kg/min or max total dose of 10 µg/min with implementation of HOLD HR feature at peak HR at which Echo images obtained. **Mean total dose:** 2.81±0.44 µg/kg **Mean infusion rate:** 0.20±0.02 µg/kg/min. **Maximum infusion rate:** 0.34±0.04 µg/kg/min. **AE**: 4 patients with AE. No Ae in ETT **SAE**:none **Deaths:****one****.**

Phase III (Studies in patients with known or suspected CAD)

The parameters for drug administration were standardized throughout all Phase III studies: heart rate slope of 8 bpm/min to a goal of 85% age-predicted maximum heart rate, infusion rate 0.8 µg/kg/min, maximum dose 10 µg/kg. A total of 697 patients were enrolled in five studies: three sensitivity studies (0122,0123,0127), one specificity study (0128), and one uncontrolled trial to evaluate the hold HR feature of the device (0129) ESA discs with dosing data were

available only for 95% (662/697) of the patients enrolled in Phase III studies, the remaining 5% (35/697) were not available because of operator error on the data logger.

Closed-Loop Studies

0122 Diagnostic Use in CAD (cross-over ESA vs. ETT, ECG only)
Completed, multi-center, open-label, randomized cross-over study comparing ESA vs. ETT. 244 patients (33-80 y/o, M/F 210/34) were given IV ARB 0.8 µg/kg/min to max 10 µg/kg. **Mean total dose:** 2.98±0.14 µ/kg **Range of total dose:** 0.51-9.98 µg/kg **Mean infusion rate:** 0.22±0.00 N/kg/min **Range of mean infusion rate:** 0.09-0.50 µg/kg/min **Mean maximum infusion rate:** 0.39±0.01 µg/kg/min. **AE:** hypotension 5%, rhythm disorders 8%, headache 12% **SAE:** unstable angina 3, VF 2, Afib 1, MI 1. **Lab**: transient hypokalemia without arrhythmias.

0123 Diagnostic use in CAD (crossover ESA vs. ETT, ECHO only)
Completed, multicenter, randomized, crossover study comparing ESA vs. ETT. 175 patients (37-86 y/o, M/F 148/27) given IV ARB at 8 bpm/min to max 0.8 µg/kg/min or 10 µg/kg. **Mean total dose:** 3.52±0.19 µg/kg **Range of total dose:** 0.28-9.94 µg/kg **Mean infusion rate:**0.22±0.01µ/kg/min **Range of mean infusion:** 0.10-0.45 µg/kg/min **Mean maximum infusion:** 0.40±0.01 µg/kg/min **AE:** rhythm disorders 8%, hypotension 9%, headache 8% **SAE:** unstable angina 3, VF 2, Afib 1, MI 1. hypotension 6%ESA vs. 1%ETT. Hypokalemia without arrhythmias, one decrease in rbc and wbc. **SAE:** one MI/VF (not related to drug), one hemorrhagic CVA

0127 Diagnostic use in CAD (crossover ESA vs. ETT, Radioisotope Imaging)
Completed, multicenter, open-label, randomized cross-over study. 151 patients (30-78 y/o, M/F 126/25) **Mean total dose:** 3.29±0.17 µg/kg **Range of total dose:** 0.58-9.86 µg/kg **Mean infusion rate:** 0.23±0.01 µg/kg/min **Range of mean infusion rate:** 0.12-0.47 µg/kg/min **Mean maximum infusion rate:** 0.42±0.01 µg/kg/min **AE:** Rhythm ETT 3% ESA 0%, hypotension 5%ESA 0% ETT, headache 9%. **Lab**: Hypokalemia but no arrhythmias. **SAE:** AF 1, ESA 2, VT, PE 1 at 27 days resulting in death.

0128 Diagnostic Use (specificity in low probability of CAD)
Completed, multicenter, open label, single treatment evaluation in patients with low likelihood of CAD using ECG, ECHO, and SPECT endpoints. 63 CAD patients referred after negative ETT (20-70 y/o, M/F 60/3) given IV ARB at 8 bpm/min the max of 0.8 µg/kg/min or 10 µg/min. **Mean total dose:** 4.47±0.23 µg/kg **Range of total dose:** 1.62-9.45 µg/kg **Mean infusion rate:** 0.27±0.01 µg/kg/min **Range of mean infusion rate:** 0.16-0.45 µg/kg/min **Mean infusion rate:** 0.52±0.02 µg/kg/min **AE:** hypotension 8%, dizziness 13%, headache 14% **LAB AE**: none **SAE:** none

0129 Evaluation of the "Hold HR" feature
Completed, multicenter, open label, single treatment study. 64 patients with CAD (39-76 y/o, M/F 46/18) underwent ESA at 8 bpm/min to max 0.8 µg/kg/min or 10 µg/kg. **Mean total dose:** 3.37±0.27 µg/g **Range of total dose:** 0.54-9.97 µg/kg **Mean infusion rate:** 0.21±0.01 µg/kg/min **Range of mean infusion rate:** 0.08-0.44 µ/kg/min **Mean maximum infusion rate:** 0.38±0.02 µg/kg/min **AE:** rhythm 13%, hypotension 9%, **Lab:** hypokalemia. **SAE:** none.

Phase IIIB (Studies in patients with known or suspected CAD)

0135 Safety evaluation of closed-loop ESA vs. ETT using parameters of ventilation, hormones, metabolic substrates. and oxygen uptake
Ongoing, open-label, randomized, crossover comparison of ESA vs. ETT. Three patients with CAD underwent closed-loop ESA at 8 bpm/min to maximum of 0.8 µg/kg/min or 10µg/kg. **Mean total dose:** 1.54±0.57 µg/kg **Mean infusion rate:** 0.17±0.03 µg/kg/min **Maximum infusion rate:** 0.25±0.06 µg/kg/min **AE:** none **SAE**:none **Deaths:**none. The metabolic endpoint results of this study were not submitted with the 4/19/94 Safety Update.

0136 Diagnostic use in CAD (cross-over ESA vs. ETT, ECG/ECHO/SPECT)
Ongoing, open-label, randomized, cross-over evaluation of the efficacy of ESA vs. ETT to induce ECG, ECHO and SPECT endpoints. 4 patients with CAD underwent ESA at 8 bpm/min to max of 0.8 µg/kg/min or 10 µg/kg total IV dose. **Total dose:** 4.53±0.12 µg/kg **Mean infusion rate:** 0.27±0.04 µg/kg/min **Maximum infusion rate** 0.56±0.10 µg/kg/min **AE:** see **SAE:** One patient suffered multiple episodes of

VT/VF considered related to ESA **Deaths:** none

0137 Open-label, closed-loop evaluation of limb lead configuration in patients and normals

Ongoing, multicenter, open-label, single test evaluation of ESA system using two ECG lead configurations for the detection of heart rate in the presence of poor ECG quality. 40 patients and 38 volunteers underwent ESA at 8 bpm/min to max 0.8 µg/kg/min or 10 µg/min total iv dose **Mean total dose:** 4.78±0.38 µg/kg (volunteers), 2.51±0.25 µg/kg (patients) **Mean infusion rate:**
0.29±0.01 µg/kg/min (volunteers), 0.21±0.01 µg/kg/min (patients) **Maximum infusion rate:** 0.55±0.03 µg/kg/min (volunteers), 0.36±0.02 µg/kg/min (patients) **AE:** tremor 26%, headache 13%, hypotension 8% **SAE:** dizziness 10%, headache 8%, tremor 8%, hypotension 8%, PVC couplets 8% **Deaths:** none

SUMMARY OF ARBUTAMINE EXPOSURE

Phase I: Initial development of arbutamine focused on delivery by both the intravenous and transdermal route. Development of transdermal arbutamine was halted in Phase I, after it was found that there was about 95% incidence of local reactions at the electrode site with both drug and placebo, that transdermal delivery lead to variability in absorption, and that the hemodynamic effects were delayed/prolonged when the drug was administered by this route. Development of intravenous administration proceeded with comparison of open- and closed-loop administration.

Study #	0104	0105	0110	0116	0118
Number of subjects	6	8	2 placebo, 4 propranolol, 4 metoprolol	1 placebo, 2 propranolol, 1 atenolol	7 placebo 32 atropine
Mean Total Dose (µg/kg)	5.10±0.73	1.75±0.01	9.80±0.04 pco 9.84±0.00 pro 9.84±0.01 met	15.4±2.2 prop 6.82 aten 0.95 pco	3.48±0.00 pco 3.34±0.08 atro
Mean Duration (minutes)		16.99±2.42	21.08±0.00 all	27.25±2.75 prop 18.67 aten 4.75 PCO	29.92±0.0 pco 29.19±0.40 atro
Mean Infusion Rate (µg/kg/min)	0.3 constant				
Range of Infusion Rates (µg/kg/min)		0.05-0.20	0.05-1.10	0.4-0.8	0.05-0.2

Extent of Arbutamine Exposure in Phase 1 Closed-Loop Studies (Mean ± SE)[1]

Study #	0111	0117	0126
Number of Subjects	8	8	20
Number of Infusions	18	19	20
Mean Total Dose/Infusion (µg/kg)	4.72 ± 0.44	4.59 ± 0.48	4.82 ± 0.45
Actual Range of Total Dose (µg/kg)	1.99 - 8.05	1.66 - 8.35	1.24 - 9.98
Mean Overall Test Time[1] (minutes)	37.6 ± 2.5	32.6 ± 1.7	35.8 ± 3.4

[1] Table 2 vol 1.97 p63.

Mean Total Drug Infusion Time[2] (minutes)	22.3 ± 1.5	27.4 ± 1.3	23.9 ± 1.7
Mean Infusion Rate (µg/kg/min)	0.21 ± 0.02	0.16 ± 0.01	0.20 ± 0.01
Range of Mean Infusion Rates (µg/kg/min)	0.088 - 0.359	0.083 - 0.244	0.14 - 0.34
Mean Maximum Infusion Rate (µg/kg/min)	0.58 ± 0.04	0.32 ± 0.02	0.39 ± 0.03

[1]The mean overall test time includes the times between actual drug delivery, e.g., period prior to restarting the infusion after resolution of an alarm.
[2] Total drug infusion time is a summation of periods of actual drug delivery.

Phase II development involved the administration by both open-loop and closed-loop routes, with variation in the infusion rates and closed-loop algorithm/ramp rates. Mean maximal dose delivered spanned a larger range in open-loop infusions as compared to closed-loop infusions: 0.41-7.80 µg/kg open-loop vs. 1.46-3.34 µg/kg closed-loop. Mean maximal infusion rate for closed-loop studies ranged from 0.19-0.44 µg/kg/min. Closed-loop infusions are summarized in the tables on next page.

Extent of Arbutamine Exposure in Phase 2 Closed-Loop Studies (Mean ± SE)[2]

Study #	0115[3] 4 bpm/min	0120 6 bpm/min	0120 10 bpm/min	0130[4] 8 bpm/min
Number of Patients	2	68	63	11
Mean Total Dose/Infusion (µg/kg)	1.46 ± 0.94	3.34 ± 0.25	3.33 ± 0.28	1.50 ± 0.30
Actual Range of Total Dose (µg/kg)	0.52 - 2.39	0.62 - 9.47	0.42 - 9.38	0.46 - 3.52
Mean Overall Test Time[1] (minutes)	11.25 ± 6.0	15.80 ± 0.71	13.15 ± 0.73	9.55 ± 1.12
Mean Total Infusion Duration[2] (minutes)	11.25 ± 6.0	15.10 ± 0.65	12.37 ± 0.64	9.15 ± 1.11
Mean Infusion Rate (µg/kg/min)	0.12 ± 0.02	0.21 ± 0.01	0.25 ± 0.01	0.15 ± 0.01
Actual Range of Mean Infusion Rate (µg/kg/min)	0.10 - 0.14	0.11 - 0.42	0.12 - 0.46	0.10 - 0.26
Mean Maximum Infusion Rate (µg/kg/min)	0.19 ± 0.06	0.37 ± 0.02	0.44 ± 0.02	0.25 ± 0.03

[1]The mean overall test time includes the times between actual drug delivery, e.g., period prior to restarting the infusion after resolution of an alarm.
[2] total drug infusion time is a summation of periods of actual drug delivery.
[3]Both patients also received open-loop administration of arbutamine

[2] Table 4, vol 1.97, p058.

Phase III development involved administration via closed-loop algorithm with a uniform ramp-rate of 8 bpm/min, uniform maximal infusion rate of 0.8 µg/kg/min, and a uniform maximal total dose of 10 µg/kg. The actual range of mean maximal infusion rates was well below the preset ceiling, ranging from Likewise, the actual range of total dose was well below the preset maximum, ranging from .

Extent of Arbutamine Exposure in Phase 3 Closed-Loop Studies[3]

Study #	0122	0123	0127	0128	0129	Total
Number of Patients	244	175	151	63	64	697
Number of Patients with Dose Data	228	164	149[3]	61	61	663[3]
Mean Total Dose/Infusion (µg/kg)	2.98± 0.14	3.52 ± 0.19	3.29 ± 0.17	4.47 ± 0.23	3.37 ± 0.27	3.35 ± 0.09
Actual Range of Total Dose (µg/kg)						
Mean Overall Test Time[1] (minutes)	13.28 ± 0.38	16.24 ± 0.61	14.48 ±0.53[4]	17.63 ± 0.68	15.73 ± 0.72	14.90 ± 0.26[5]
Mean Total Drug Infusion Time[2] (minutes)	12.45 ± 0.35	14.38 ± 0.54	13.27 ± 0.43	16.12 ± 0.48	14.67 ±0.59	13.65 ± 0.22
Mean Infusion Rate (µg/kg/min)	0.22 ± 0.00	0.22 ± 0.01	0.23 ± 0.01	0.27 ± 0.01	0.21 ± 0.01	0.23 ± 0.0
Actual Range of Mean Infusion Rate (µg/kg/min)						
Mean Maximum Infusion Rate (µg/kg/min)	0.39 ± 0.01	0.40 ± 0.01	0.42 ± 0.01	0.52 ± 0.02	0.38 ± 0.02	0.41 ± 0.01

[1] Mean overall test time included times between actual drug delivery, e.g., period prior to restarting the infusion after resolution of an alarm. Data obtained from the case report form (CRF).
[2]Total drug infusion time is a summation of periods of actual drug delivery.
[3]One patient (0127-66-9991) included twice (two ESA tests).
[4]N=150; one patient (0127-52-9991) with no device disk data [5]N=698

SUMMARY OF INFUSION PARAMETERS FOR PHASE I, II, AND III STUDIES

Summary of Mean Total Dose Ranges and Infusion Parameters for Phase 1, 2 and 3 Studies[4]

	Phase 1	Phase 2	Phase 3
Range of Mean Total Dose (µg/kg) Open loop (β-blocker) Open-loop Closed-loop			
Mean Infusion Rate* (µg/kg/min)	0.16 - 0.21	0.12 - 0.25	0.21- 0.27

[3] Table 5 vol 1.97 p61.

[4] Table 6, vol 1.97, p63.

Mean Max Infusion Rate* (μg/kg/min)	0.32 - 0.58	0.19 - 0.44	0.38 - 0.52
Mean Infusion Duration* (minutes)	22.3 - 27.4	9.15 - 15.10	12.45 - 16.12
Mean Overall Test Time* (minutes)	32.6 -37.6	9.55 - 15.80	13.28 - 17.63

[1]Subjects in **study 0110 (Vol. 1.45, pp. 210-215)** were pretreated with either IV propranolol or metoprolol, and in **study 0116 (Vol. 1.50, p. 161)** with either oral propranolol or atenolol. [2]Patients in **study 0119 (Vol. 1.53, p. 197)** were pretreated with either oral propranolol or atenolol.

SIGNIFICANT AND POTENTIALLY SIGNIFICANT ADVERSE EVENTS

Overview of collection of adverse events. Patients underwent screening examination/laboratories/ECG and medical questionnaire 1-14 days prior to first stress test. In protocols involving only one test, the follow-up examination occurred 1-14 days after the test. In protocols involving more than one stress test, the second stress test took place 20 hours to 14 days after the first stress test, and Patients returned for the final follow-up visit 24 hours to 7 days after the second stress test, a which time the examination and questionnaire used in the initial screening visit were readministered. In addition, spontaneous complaints were also recorded, and blood samples were taken for clinical pathology. Adverse events were recorded throughout the study period, as were serious adverse events that occurred up to 30 days following study completion.

Phase I: All subject-volunteered and investigator-observed events, including arrhythmias, were recorded as adverse events

Phase II: All patient-volunteered and investigator-observed events were recorded as adverse events, but arrhythmias were recorded separately in some studies

Phase III: All patient-volunteered and investigator-observed events were recorded. However, the "anticipated events" associated with stress testing (tachycardia, tachypnea, dyspnea, fatigue and leg cramps) were recorded as adverse events only if the intensity and duration were greater than would be expected with routine stress testing, and all arrhythmias (including those routinely associated with routine stress testing and considered benign) were recorded by the investigator. Again, arrhythmias were classified as anticipated events or adverse events according to the severity and duration expected with routine stress testing.
Follow-up visits scheduled 1-7 days post stress testing, and adverse events collected for 30 days post stress testing. Of the 697 patients with ECG data recorded on ESA disc, 95% (662/697) produced analyzable data.

DEATHS ----------

Phase I: None in 136 normal volunteers in 12 studies (0102, 0103, 0104, 0105, 0110, 0116, 0117, 0118, 0125, 0126)

Phase II: One death in 176 patients in 8 studies (0107, 0108, 0112, 0115, 0119, 0120, 0121, 0130) Patient 0107-A-200 died of myocardial infarction 2 weeks post atrial pacing. Patient did not receive arbutamine.

Phase III: One death in 697 patients in 5 studies (0122, 0123, 0127, 0128, 0129) Massive pulmonary embolus per autopsy report, 27 days post arbutamine, not considered related to drug. Case discussed below.

Pulmonary embolus/ death: Patient 0127-64-0210. 51 WM with history of diabetes, PVD, PUD, right adrenal mass, esophageal candidiasis. Medications record not available. Underwent ESA testing with radionuclide imaging and follow-up. ETT was not performed because of severe claudication. Twenty-six days after ESA testing, before coronary angiography, developed serve epigastric distress, diaphoresis and syncope. Patient was hospitalized, and, shortly after admission, developed acute shortness of breath, chest, pain, hypotension, bradycardia. This deteriorated into electromechanical dissociation. Attempts at resuscitation were unsuccessful. Autopsy revealed massive left pulmonary embolus, which was considered to be the cause of death. The event was not considered to be related to drug because of the 27 day period between ESA testing and death.

SERIOUS ADVERSE EVENTS ----------

The criteria for a serious adverse event included one that was life-threatening or one which required hospitalization. In the clinical development program of 1009 normal volunteers and patients, the overall incidence of serious adverse events was 1.4% (14/1009), with an incidence of drug-related serious adverse events of 0.6% (6/1009). The overall incidence of ventricular fibrillation was 0.2%, atrial fibrillation 0.2%, myocardial infarction 0.1%, and severe angina rate of 0.1%.[5] The incidence by phase of development is outlined below:

Phase I: There were no serious adverse events in 136 normal volunteers

Phase II: There were no serious adverse events reported in any of 176 patients .

Phase III: There were fourteen serious adverse events in were reported during Phase III testing in 697 subjects, for an overall incidence of 2.0%. Of these 43% (6/14) were considered possibly/probably related to drug, and 57% (8/14) were not attributable to drug. Individual cases are summarized below.

---

[5] For listing of comparable rates for dobutamine, adenosine, and dipyridamole, refer to brief review of the literature at the end of the NDA review.

Serious Adverse Events in Phase 3 Patients[6]

Pt #	Age/Sex	HT cm	WT kg	Treatment	Onset Time after Rx	Adverse Event	Duration	Sev[1]	Act[2]	Out[3]	Drug Rel[4]	Device Rel[4]	ETT Rel[4]
0122-03-0098	58 WM	171	99	Arbutamine	6 min	Atrial fibrillation	3 hours	3	2,3	1	4	1	1
0122-18-1291	58 WM	170	80	Arbutamine	During infusion	Ventricular tachycardia/ fibrillation	8 min	3	3,5, 6	1	4	1	1
0122-22-1342	60 WF	167	91	Arbutamine	11 days	Unstable angina	30 min	2	3	1	2	1	1
0122-22-1343	71 WM	179	99	Exercise	20 days	Unstable angina	6 hours	3	2,3	1	2	1	1
0122-23-1778	71 WM	178	100	Arbutamine	20 hours	Inferior MI	3 hours	3	3,6	1	3	1	1
0122-24-1206	50 WM	160	78	Arbutamine	3 min	Ventricular tachycardia/ fibrillation	1 min	3	2,3, 6	1	4	1	1
0122-26-1162	41 WM	168	75	Arbutamine	>1 hour	Unstable angina	1 hour	3	3,6	1	3	1	1
0123-34-0012	63 WM	180	83	Exercise	3 days	CVA	7 days	2	3	1	2	1	1
0123-46-1002	56 WM	174	89	Arbutamine	2 days	Acute MI	2 hours	3	2,3, 6	3	1	1	1
0127-53-0071	46 WF	165	124	Arbutamine	10 days	Unstable angina	1 day	3	2,3, 6	1	2	1	1
0127-59-0269	67 WM	178	96	Arbutamine	During infusion	Atrial fibrillation	5 hours	2	3	1	4	1	1
0127-64-0210	51 BM	180	94	Arbutamine	27 days	Pulmonary embolus	8 hours	3	3	5	1	1	1
0127-67-0387	58 WM	178	68	Exercise	3 days	Ventricular tachycardia	1 day	2	3,6	1	1	1	1
0127-70-0464	67 WM	173	88	Arbutamine	2 days	Unstable angina	2 days	2	3,6	1	1	1	1

[1]SEVERITY
1=Mild
2=Moderate
3=Severe

C=Caucasian
B=Black

[2]ACTION TAKEN
1=None
2=Other Medication
3=Hospitalization
4=Dosage Reduced
5=Drug Discontinued
6=Other

[3]OUTCOME
1=Recovered
2=Under Treatment
3=Residual Sequelae
4=Lost to Follow-up
5=Death

[4]DRUG RELATIONSHIP
1=Unrelated
2=Remote
3=Possible
4=Probable
5=Related

[6] Table 143, vol 1.98

SERIOUS ADVERSE EVENTS CONSIDERED RELATED TO ARBUTAMINE

Serious Adverse Events in Patients Related* to Arbutamine[7]

	Phase 2 N=176	Phase 3 N=697	Overall N=873
Ventricular fibrillation	0	2 (0.3%)	2 (0.2%)
Atrial fibrillation	0	2 (0.3%)	2 (0.2%)
Myocardial infarction	0	1 (0.1%)	1 (0.1%)
Severe angina	0	1 (0.1%)	1 (0.1%)

*Investigator opinion "possible" or "probable"

Clinical and Device Summary of Serious Adverse Events in Phase 3 Patients Related to Arbutamine[8]

Pt #	Adverse Event	Angiogram Results	Reason Test Discontinued (Clinical event)	Total Test Time (min:sec)	Total Dose (µg/kg)	Infusion Intervals and Reasons for Discontinuation	
						Duration (min:sec)	Reason for Discontinuation
0122-03-0098	Atrial Fibrillation	66% RCA	Device Saturation Alarm	25:55	6.46	13:45 6:25 4:45	Saturation alarm Saturation alarm Saturation alarm
0122-18-1291	Ventricular tachycardia/ fibrillation	70% LAD 100% RCA	By Investigator (Ventricular fibrillation)	15:10	2.72	12:00 1:35	Saturation alarm Ventricular fibrillation
0122-23-1778	Inferior MI	89% LAD 100% RCA	Device Saturation Alarm	7:40	1.36	7:40	Saturation alarm
0122-24-1206	Ventricular tachycardia/ fibrillation	63% LAD 66% LCx 100% RCA	By Investigator (Angina)	13:00	3.31	3:15 9:15	Irregular HR alarm Angina
0122-26-1162	Unstable angina	71% LCx 100% RCA	By Investigator (Angina)	9:45	2.09	9:45	Angina
0127-59-0269	Atrial fibrillation	100% LAD 100% LCx	Device Target HR Achieved (SVT)*	8:35	1.57	8:35	Target HR achieved

CASE SUMMARIES OF SERIOUS ADVERSE EVENTS: SERIOUS ADVERSE EVENTS CONSIDERED RELATED TO ARBUTAMINE

0122-18-1291 ventricular fibrillation

58 WM h/o hypercholesterolemia, hypertension, smoking, prior inferior Q-wave MI and cardiac catheterization showing 70% distal LAD, 100% mid-RCA. Withdrawn from β-adalat (atenolol 50 mg/nifedipine 20 mg PO QD) 48 hours prior to ESA testing. No other medication listed. Nine minutes into ESA testing developed anginal pain, twelve minutes into testing developed ST depression in AVL. Patient approaching his target HR of 137 bpm with a rate of 135 bpm, when he developed sinus arrhythmia, falling HR and frequent PVCs. ESA device terminated infusion for fall in HR at about 120 bpm and SBP 190/110. Sinus arrhythmia and PVCs persisted for one minute after discontinuation, and restarted testing. Ninety (90) seconds after restart. he developed 4 successive episodes of VT/ VF over a period of 4 minutes, each requiring 360 joule cardioversion. Serum potassium levels drawn one hour after the event were normal. He was admitted for observation. The patient received no further treatment, and was discharged without

[7] Table 146, Vol 1.98, p271.

[8] Adapted from Table 145, vol 1.98, p269.

sequelae after 48 hours observation. Event was listed as probably related to arbutamine.

0122-24-1206 ventricular tachycardia/fibrillation

50 WM with a history of three prior myocardial infarctions. Cardiac catheterization showing severe triple vessel disease (63% LAD, 55% CXM, 66% CXM, 100% mid RCA). Medications included diltiazem SR 90 mg po bid, isosorbide mononitrate 20 mg po bid, ASA 75 mg po qd. Arbutamine infusion given for twelve minutes to 123 bpm. Investigator discontinued the infusion because of chest pain and ischemic (>1.0 mm depression) ECG changes in the anteroseptal leads. He developed multi-focal PVCs, nonsustained VT, atrial fibrillation, deteriorated into VT/VF three minutes into the recovery period. Patient successfully cardioverted with 200 joules. Received lidocaine bolus and lidocaine IV infusion for three hours after the event. Subsequent recovery was uneventful, with no evidence of myocardial infarction. Listed as probably related to arbutamine.

0122-03-0098 atrial fibrillation

58 WM with hypertension, angina, and cardiac catheterization showing 66% RCA stenosis. Medications including nifedipine 30 mg po qd, lovastatin 20 mg po qd, ASA 325 mg po qd, cimetidine 800 mg po qd. Arbutamine infusion given for 14 minutes, but developed heart rate saturation without restart of arbutamine infusion at 119 bpm. ESA testing was resumed for 6 minutes, the terminated a second time for falling heart rate. The infusion was restarted a second time for nearly five minutes, but again terminated for HR saturation at 120 bpm. Atrial fibrillation (VR 155 bpm) occurred 6 minutes into recovery period and lasted 3 hours necessitating admission for observation. The patient was treated with esmolol (175 mg IV), adenosine (6 mg IV, and verapamil (5 mg IV) and digoxin (1 mg IV). Converted to normal sinus rhythm after additional digoxin load (0.25 mg). Recovery was uneventful. Listed as probably related to arbutamine.

0127-59-0269 nonsustained ventricular tachycardia/ atrial fibrillation

68 WM two prior myocardial infarctions COPD, stable angina. Cardiac catheterization showing 100% CXM1, 100% CXM2. Medications included diltiazem 240 mg po qd, nitroglycerin 27 mg qd (verify unusual dose). During ESA testing developed multifocal PVC and nonsustained ventricular tachycardia, then atrial fibrillation 8.5 minutes into the infusion. The atrial fibrillation lasted 4 hours and 47 minutes and terminated spontaneously.

0122-23-1778 inferior myocardial infarction

71 WM with known hypertension, CAD and stable angina. Cardiac catheterization showing 65% proximal LAD, 69% mid LAD, 89% mid LAD, 100% mid RCA. Medications included metoprolol 200 mg po qd, nifedipine 40 mg po qd, enalapril 20 mg po qd, furosemide 80 mg po qd, with per protocol discontinuation of metoprolol 48 hours prior to ESA testing. Initially randomized to ETT, and had prolonged chest pain and ischemia ECG changes. Arbutamine was infused per protocol for 8 minutes, but developed heart rate saturation at 84 bpm with accompanying alarm. The infusion was terminated. Six minutes after discontinuation of infusion, the patient experienced a rise in HR to 94 bpm. The infusion was mistakenly given into the arm with the blood pressure cuff, and thus there may have been a delay in the distribution of the drug to the systemic circulation. Patient suffered inferior myocardial infarction to 6 a.m. the next day, and was treated with intravenous nitroglycerin and streptokinase. The patient made an uneventful recovery. Event listed as probably related to the arbutamine testing.

0122-26-1162 unstable angina

41 WM with a history of angina and prior MI. Cardiac catheterization showing 71% CXM, 100% RCA. Medications included diltiazem 180 mg po qd, ASA 325 mg po qd. ETT uneventful. ESA testing to 105 bpm and protocol endpoint of angina, without diagnostic ST-T wave changes. The pain resolved 10 minutes into the recovery period, after the patient given sublingual NTG spray. One hour post the ESA test, the patient developed severe chest pain while walking up a hill. Pain lasted about one hour. The patient was admitted for observation, treated with intravenous NTG and oral beta-blocker, ruled out for myocardial infarction by enzymes and serial ECGs. Event was considered as possibly related to arbutamine.

SERIOUS ADVERSE EVENTS NOT CONSIDERED RELATED TO ARBUTAMINE

0127-64-0210 Pulmonary embolus/ death: Patient 0127-64-0210. 51 WM with history of diabetes, PVD, PUD, right adrenal mass, esophageal candidiasis. Medications record not available. Underwent ESA testing with radionuclide imaging and follow-up. ETT was not performed because of severe claudication. Twenty-six days after ESA testing, before coronary angiography, developed serve epigastric distress, diaphoresis and syncope. Patient was hospitalized, and, short;y after admission, developed acute shortness of breath, chest, pain, hypotension, bradycardia. This deteriorated into electromechanical dissociation. Attempts at resuscitation were unsuccessful. Autopsy revealed massive left pulmonary embolus, which was considered to be the cause of death. The event was not considered to be related to drug because of the 27 day period between ESA testing and death.

0123-46-1002 Myocardial infarction/ventricular fibrillation
56 WM underwent ESA testing without complications, and completed follow-up visit, and immediately underwent cardiac catheterization/PTCA with stenting. Immediately suffered ventricular fibrillation and myocardial infarction after acute stent occlusion. Intracoronary streptokinase injection re-opened stent, and repeat PTCA was performed. The patient was discharged without further events. The event was listed as remotely related to arbutamine.
0122-22-1342 Unstable angina 60 WF history of angina and two vessel CAD. Medications included amlodipine 50 mg po qd, atenolol 100 mg po qd, ASA 150 mg po qd, and simvastatin 20 mg po qd. As per protocol, atenolol as withdrawn for 48 hours prior to testing, and the ESA and ETT testing proceeded without complications. Coronary angiography was completed 11 days post ESA testing. One hour post catheterization, the patient developed retrosternal chest pain associated with significant ST depression in the lateral leads. Chest pain responded to an intravenous infusion of nitroglycerine. The patient was admitted for observation and did not experience any further episodes of chest pain. There is no record of serial CK-MB or ECG in the CRF. The relationship to the drug was considered remote.
0122-22-1343 Unstable angina 71 WM history of hypertension and angina. Both arbutamine and exercise stress tests were performed with no adverse events reported during the tests. ESA was positive and ETT was negative. Twenty five days after the arbutamine stress test (18 days after the exercise stress test) the patient experienced chest pain at rest and was admitted to the hospital where the symptoms responded to a regiment of intravenous NTG at 2 mg/hr, atenolol 50 mg po qd, and nifedipine 30 mg po qd. It is not listed in the patient summary whether the patient was ruled out for MI. Since the events occurred 25 days after the arbutamine test, the relationship was again considered "remote".
0123-34-0012 Cerebrovascular accident 62 WM with a history of hypertension, COPD, smoking, atypical chest pain developed new neurologic deficits post cardiac catheterization. Multiple embolic strokes were documented in the cerebellum and left temporal lobe. The event occurred three days post ESA and two days post ETT, and was considered "remotely" related to arbutamine.
0127-53-0071 Unstable angina 46 WF with history of prior myocardial infarction, hypertension, asthma, diabetes mellitus, and hypercholesterolemia underwent ESA testing. 10 days after testing progressive chest pressure for three days and was treated with intravenous heparin, nitroglycerin, and tissue plasminogen activator. Underwent emergent CABG for triple vessel disease. The event was judged to be "remotely" related to arbutamine testing.
0127-67-0387 ventricular tachycardia 58 wm with a history of AMI and totally occluded LAD. Medications included metoprolol, diltiazem, enalapril, coumadin. Metoprolol was withdrawn 48 hours prior to ESA testing as per protocol. Underwent ETT testing. Three days post arbutamine stress testing developed chest pain and rapid heart rate, and was hospitalized with ventricular tachycardia, which was treated with lidocaine and metoprolol. Definitive therapy included endocardial ablation, aortic valve replacement, and AICD placement. The patient did not undergo ESA testing, thus the event was only "remotely" related to the drug.
0127-70-0464 unstable angina 67 WM with hypertension, stable exertional angina, hypercholesterolemia, and transient ischemic attacks. Medication list unavailable. Underwent ETT testing without complications. Two days post ETT testing had a "typical" attack of exertional angina, followed by three episodes of chest pain at rest. The patient was hospitalized and "ruled out" for myocardial infarction by serial ECGs and enzymes. Patient declined to participate in the ESA testing and is considered a study dropout. Event was "unrelated " to arbutamine.

EVENTS THAT LEAD TO EARLY WITHDRAWALS ----------

Since arbutamine is a diagnostic adjunct rather than a therapeutic agent, the definition of an early withdrawal or a study dropout differs from that in a therapeutic clinical trial. Stress testing is conducted to adverse events that are clinically acceptable endpoints (angina, fatigue, ST segment depression, ECHO akinesis/dyskinesis, etc.), so that subjects were not considered withdrawals if testing was discontinued for these events. Patients were defined as withdrawals if the adverse event(s) was the reason that they did not complete all visits and study procedures. Also, these accepted clinical endpoints were not categorized as adverse events unless they exceeded in severity or duration the expected clinical event.

Phase I: 13% (16/136) normal volunteers withdrew from ESA testing because of adverse events.[9] None of these were rated as serious. Of these events, 69% (11/16) were considered probably/possibly related to arbutamine administration, and 31% (5/16) were not considered related to the drug. Of those events leading to withdrawal, 44% were rated as moderate and 19% were rated severe. 25% required further treatment beyond stopping the infusion. Events are outlined in the table below, and individual cases are summarized at the end of the section. Events that required further medication are discussed under that section of the review.

Early Withdrawals from Phase 1 Studies of Normal Volunteers[10]

Pt #	Age/Sex	HT cm	WT kg	Onset Time after Rx	Adverse Event	Duration	Sev[1]	Act[2]	Out[3]	Drug Rel[4]
0102-A-016	23 WM	186	78	24 hours	Lymphadenitis	Unknown	2	2	4	1
0103-A-001	27 WM	184	77	24 minutes	PVCs	<1 minute	2	1	1	2
0110-A-001	19 WM	185	70	During infusion	Hypotension	NAV	NAV	5	NAV	NAV
0110-A-002	23 WM	180	80	During infusion	Hypotension	NAV	NAV	5	NAV	NAV
0110-A-004	27 WM	192	76	During infusion	Hypotension	NAV	NAV	5	NAV	NAV
0111-A-004	27 WM	176	69	End infusion	Bradycardia	1 minute	1	5	1	5
0111-A-006	33 WM	172	66	During infusion	Bradycardia	7 minutes	1	5	1	5
0111-A-008	39 WM	176	81	During infusion	Bradycardia	3 episodes totaling 7 min	1	5	1	5
0116-A-001	33 WM	168	66	During infusion	Tremor	14 minutes	3	5	1	5
0116-A-005	19 WM	185	71	During infusion	PVCs	9 hrs. 13 min	3	2,5	1	5
0116-A-013	35 WM	180	79	End infusion	Tremor	8 minutes	3	1	1	5
0117-A-002	38 WM	174	72	During infusion	Chest pain	4 minutes	2	5	1	4
0117-A-006	21 WM	184	71	24 minutes	ECG changes	2 minutes	2	1	1	4
0118-A-005	60 WM	185	93	4 minutes	Supraventricul ar tachycardia	26 minutes	2	2,6	1	4
0118-A-017	60 WM	165	69	During infusion	Supraventricul ar tachycardia	9 minutes	2	2,5, 6	1	4
0118-A-018	60 WM	163	65	During infusion	PVCs	42 minutes	2	5	1	4

See codes next page.

[9] There is a discrepancy in the number of early withdrawals reported in Section 4.5.1.3, vol 1.98, p250-51 (corroborated in Table 141, vol 1.98, p251) and those reported in section 4.1.2.5., vol 1.97, p106-7. Section 4.1.2.5 lists the number of test discontinuations as 16, with only none of these being considered study withdrawals, as the other seven completed follow-up visits. Section 4.5.1.3 lists sixteen study withdrawals and discusses all cases. For the reviewer's analysis, the number of 16 has been used.

[10] Adapted from table 141, vol 1.98, p251.

[1]SEVERITY
1=Mild
2=Moderate
3=Severe

[2]ACTION TAKEN
1=None
2=Other Medication
3=Hospitalization
4=Dosage reduced
5=Drug Discontinued
6=Other

[3]OUTCOME
1=Recovered
2=Under Treatment
3=Residual Sequelae
4=Lost to Follow-up
5=Death

[4]DRUG RELATIONSHIP
1=Unrelated
2=Remote
3=Possible
4=Probable
5=Related

NAV = Not available
C=Caucasian
I=American Indian

Phase II: 2.8% (5/165) withdrew from Phase II because of adverse events. All were from CS0120.[11] Of these events, 80% (4/5) were considered probably/possibly related to arbutamine administration, and 20% (1/5) were not considered related to the drug. Of the events leading to withdrawal, 60% were rated as moderate, 0% were rated severe, and 40% required treatment in addition to discontinuation of the infusion. Events are outlined in the table below, and individual cases are summarized at the end of this section.

Early Withdrawals from Phase 2 Patient Studies[12]

Pt #	Age/Sex	HT cm	WT kg	Treatment	Onset Time after Rx	Adverse Event	Duration	Sev[1]	Act[2]	Out[3]	Drug Rel[4]
0120-A-008	50 AM	183	96	Arbutamine, 6 bpm/min	6 min into infusion	Angina	14 minutes	2	2.5	1	5
0120-B-003	40 WM	167	77	NA	Prior to infusion	Pain at IV cannula site	34 minutes	1	5	1	1
0120-D-018	73 WM	181	103	Arbutamine, 10 bpm/min	55 minutes	Fatigue	9 hours, 30 minutes	1	1	1	3
0120-E-004	65 WM	175	89	Arbutamine, 6 bpm/min	4 minutes	Ventricular bigeminy	1 minute	2	5	1	5
0120-K-001	54 WM	173	65	Arbutamine, 6 bpm/min	During infusion	Idioventricular rhythm	5 minutes	2	2	1	3

[1]SEVERITY
1=Mild
2=Moderate
3=Severe

[2]ACTION TAKEN
1=None
2=Other Medication
3=Hospitalization
4=Dosage Reduced
5=Drug Discontinued
6=Other

[3]OUTCOME
1=Recovered
2=Under Treatment
3=Residual Sequelae
4=Lost to Follow-up
5=Death

[4]DRUG RELATIONSHIP
1=Unrelated
2=Remote
3=Possible
4=Probable
5=Related

Phase III: 1.0% (7/697) withdrew prematurely from Phase III studies because of adverse events. Of these events, 43% (3/7) were considered probably/possibly related to arbutamine administration, and 57% (4/7) were not considered related to the drug. Of those events leading to withdrawal, 57% (4/7) were rated as moderate and 29% (2/7) were rated severe. 86% (6/7) required further treatment (including cases requiring hospital admission) other than stopping the infusion. Events are outlined in the table below, and individual cases are summarized at the end of the section.

[11] There is a discrepancy between the number of withdrawals listed in section 4.2.2.4, vol 1.97, p140, and the number listed under section 4.5.2.3, vol 1.98, p256 and Table 142, vol 1.98, p257. For the sake of the review, the higher number is used.

[12] Adapted from table 142, vol 1.98, p257.

Early Withdrawals from Phase 3 Patient Studies[13]

Pt #	Age/ Sex	HT cm	WT kg	TEST	Onset Time after Rx	Adverse Event	Duration	Sev[1]	Act[2]	Out[3]	Drug Rel[4]	Device Rel[4]	ETT Rel[4]
0122-12-0289	51 WM	180	100	ETT	NAV	Angina at rest	1 day	2	6	1	1	1	3
0122-16-1433	63 WM	178	91	N/A*	N/A*	Vasovagal episode	10 min	1	1	1	1	1	1
0122-18-1291	58 WM	170	80	ESA	During infusion	Ventricular tachycardia/ fibrillation	4 min	3	2,3 5,6	1	4	1	1
0122-24-1206	50 WM	160	78	ESA	3 min	Ventricular tachycardia/ fibrillation	1 min	3	2,3 6	1	4	1	1
0127-59-0269	67 WM	178	96	ESA	During infusion	Atrial fibrillation	5 hrs	2	3,5	1	4	1	1
0127-67-0387	58 WM	178	68	ETT	3 days	Ventricular tachycardia	1 day	2	2,3	1	1	1	1
0127-70-0464	67 WM	173	67	ESA	2 days	Unstable angina	2 days	2	3,6	1	1	1	1

*Patient fainted upon insertion of intravenous cannula on the day of arbutamine stress test; patient never received arbutamine.
For numerical codes refer to key with table on page 20.

EVENTS LEADING TO WITHDRAWAL: RELATED TO ARBUTAMINE

Phase I

Subject 0103-A-001 27 WM developed PVCs 24 minutes after receiving transdermal arbutamine. Initially listed as remotely related to drug, there was subsequent evidence to implicated delayed absorption in some of these events. The development of transdermal arbutamine was aborted during Phase I of development.
Subject 0110-A-001 19 WM experienced a fall in BP to 82/37 after 13 minutes of infusion, accompanied by dizziness, nonspecific chest pain, and flushing. All resolved with discontinuation of the infusion.[14**]
Subject 0110-A-002 23 WM received first infusion of arbutamine without sequelae. He developed nausea and hypotension to 98/45 during his second infusion of arbutamine, which resolved within 2 minutes of discontinuation of the infusion.**
Subject 0110-A-004 27 WM developed hypotension during first infusion of arbutamine. During a second infusion of arbutamine he developed. BP 91/38 associated with pallor, dizziness, and diaphoresis, and horizontal ST depression.**
Subject 0111-A-004 27 WM developed bradycardia, with precipitous decline in HR from 117 to 59 bpm. The infusion was immediately terminated, and the patients HR returned to 110 bpm within 10 seconds.
Subject 01112-A-006 33 Wm developed bradycardia lasting 7 minutes, characterized by a HR fall from 131 to 101 bpm despite increasing the infusion rate from 0.45 µg/kg/min to 0.8 µg/kg/min.. After drug delivery was discontinued, the patient's HR gradually returned to 131 bpm.
Subject 0111-A-008 39 WM experienced three episodes of HR decline by 20-30 bpm during one ESA test. With each episode, the infusion was temporarily terminated and the episode resolved. The subject was not given further testing.
Subject 0116-A-001 33 WM was pretreated with propranolol. He developed severe tremor of the lower extremities lasting 14 minutes and resolving with discontinuation of the drug[15***]
Subject 0116-A-005 19 WM was pretreated with atenolol. He developed severe PVCs, chest pain, and dizziness during infusion. PVCs resolved with lidocaine bolus and infusion. Subject monitored for 8 hours without further events.***
Subject 0116-A-013 35 WM developed tremor of the lower extremities at the end of an infusion, which lasted for eight minutes ***

---

[13] Adapted from table 144, vol 1.98, p267.

[14] ** Study 110 was prematurely discontinued by the investigator after 3 of 4 normal volunteers developed 3 episodes of significant hypotension. In the Integrated summary of Safety, the relationship to arbutamine is reported as NAV (not available), but they are included here because they resulted in the decision to discontinue this study, and thus were presumed to be drug related.

[15] *** Study 116 was terminated early by the sponsor because of the severity and frequency of adverse events.

Subject 0117-A-002 38 WM developed chest pain during infusion, which was not associated with ECG changes and resolved 4 minutes after discontinuation of the infusion.
Subject 0117-A-006 21 WM developed nonischemic ECG changes (ectopic atrial rhythm) at the end 24 minutes into the infusion, lasting 2 minutes after termination of the infusion.
Subject 0118-A-005 60 WM received 11 µg/kg atropine pretreatment. He developed SVT, occurring 4 minutes into the infusion. He was initially treated with carotid massage, but the SVT resolved only after he was treated with propranolol.
Subject 0118-A-017 60 WF pretreated with 11 µg/kg atropine. She developed transient SVT 24 minutes into the infusion, then 5 minutes later developed persistent SVT , lasting 9 minutes after termination of the infusion and administration of IV propranolol.
Subject 0118-A-018 60 WF pretreated with 6 µg/kg atropine. She developed PVCs during arbutamine infusion and lasting 29 minutes into the recovery period.

Phase II

0120-A-008 severe angina
50 AM with a history of HTN, asthma, stable angina. Medications included atenolol 50 mg po qd, isosorbide dinitrate 40 mg, allopurinol 100 mg, salbutamol inhaler. Atenolol withdrawn 72 hours prior to the stress test. He developed severe angina 6 minutes into an infusion at 6 bpm/min, the infusion was stopped 6 minutes later. The episode resolved in 14 minutes after the infusion was stopped and the patient treated with 4 puffs SL glycerol trinitrate spray and propranolol 1 mg IV.
0120-D-018 severe fatigue
73 WM with history of HTN and angina . Medications included amiloride 5 mg po qd, diltiazem 180 mg po qd, ranitidine 300 mg po qd, domperidone 40 mg po qd, carbasalate 100 mg po qd, diclofenac 100 mg po qd, and pindolol 10 mg po qd (discontinued 72 hours prior to testing). He underwent ESA testing at 10 bpm/min for 24 minutes. Thirty minutes after testing, he complained of fatigue, which lasted 9 hours and 30 minutes, and was considered possibly related to drug.
0120-E-004 ventricular bigeminy
65 WM with a history of myocardial infarction, PUD, tuberculosis. Medications included digoxin 0.1 mg po qd, Captopril 50 mg PO ?d, ASA 100 mg po qd, omeprazole 20 mg po qd, oxetacain 125 mg po qd. He developed ventricular bigeminy 4 minutes into ESA testing at 6 bpm/min. The episode resolved within one minute after discontinuation of drug. The event was considered possibly related to drug.
0120-K-001 idioventricular rhythm
54 WM with documented two vessel disease and baseline atrial and ventricular ectopy. Medications included diltiazem 180 mg po qd and ASA 75 mg po qd. The patient was randomized to low slope (6 bpm/min) infusion, which was terminated for HR saturation. Four minutes later the patient developed SVT and an accelerated idioventricular rhythm, both of which lasted for 5 minutes. The patient was treated with IV lignocaine, and the ectopy resolved within 30 minutes The event was considered possibly related to drug.

Phase III

0122-18-1291 ventricular fibrillation
58 WM h/o prior inferior Q-wave MI and cardiac catheterization showing 70% distal LAD, 100% mid-RCA. Withdrawn from Beta-adalat (atenolol 50 mg/ nifedipine 20 mg) 48 hours prior to ESA testing. No other medication listed. Testing restarted after saturation alarm. Four successive episodes of VT/ VF over a period of 4 minutes, each requiring 360 joule cardioversion. The patient received no further treatment, and was discharged without sequelae after 48 hours observation. Event was listed as probably related to arbutamine.
0122-24-1206 ventricular tachycardia/fibrillation
50 WM three prior MI. Cardiac catheterization showing severe triple vessel disease (63% LAD, 55% CXM, 66% CXM, 100% mid RCA). Medications included diltiazem 180 mg qd, isosorbide mononitrate 40 mg qd, ASA 75 mg po qd. Arbutamine infusion discontinued because of chest pain and ischemic (>1.0 mm depression) ECG changes. Multi-focal PVCs, nonsustained VT, atrial fibrillation, deteriorated into VT/VF three minutes into recovery period. Patient successfully cardioverted with 200 Joules. Subsequent recovery was uneventful, with no evidence of myocardial infarction. Listed as probably related to arbutamine.
0127-59-0269 nonsustained ventricular tachycardia/ atrial fibrillation
68 WM two prior myocardial infarctions COPD, stable angina. Cardiac catheterization showing 100% CXM1, 100% CXM2. Medications included diltiazem 240 mg po qd, nitroglycerin 27 mg qd (verify unusual dose). During ESA testing developed multifocal PVC and nonsustained ventricular tachycardia, then atrial fibrillation 8.5 minutes into the infusion. The atrial fibrillation lasted 4 hours and 47 minutes and terminated spontaneously.

EVENTS LEADING TO WITHDRAWAL: NOT RELATED TO ARBUTAMINE

Phase I

Subject 0102-A-016 23 WM developed infection in his right heel and inguinal lymphadenitis 24 hours after receiving arbutamine. He was treated with appropriate antibiotics.

Phase II

0120-B-003 pain at IV site 40 WM with severe pain at IV cannula site lasting 34 minutes

Phase III

0122-12-0289 unstable angina 51 WM completed ETT testing on first day of protocol. Later that day, he developed chest pain at rest, and was evaluated by his private physician, at which time ECG was without new ischemic changes. Patient decline further participation in the protocol and did not undergo ESA testing.

0122-16-1433 syncope 63 WM completed ETT on first day of protocol. On the day of ESA testing, he suffered a syncopal episode during insertion of intravenous canula. Patient withdrew from further participation in the protocol.

0127-67-0387 ventricular tachycardia 58 wm with a history of AMI and totally occluded LAD. Medications included metoprolol, diltiazem, enalopril, coumadin. Metoprolol was withdrawn 48 hours prior to ESA testing as per protocol. Underwent ETT testing. Three days post arbutamine stress testing developed chest pain and rapid heart rate, and was hospitalized with ventricular tachycardia, which was treated with lidocaine and metoprolol. Definitive therapy included endocardial ablation, aortic valve replacement, and AICD placement. The patient did not undergo ESA testing, thus the event was only "remotely" related to the drug.

0127-70-0464 unstable angina 67 WM with hypertension, stable exertional angina, hypercholesterolemia, and transient ischemic attacks. Medication list unavailable. Underwent ETT testing without complications. Two days post ETT testing had a "typical" attack of exertional angina, followed by three episodes of chest pain at rest. The patient was hospitalized and "ruled out" for myocardial infarction by serial ECGs and enzymes. Patient declined to participate in the ESA testing and is considered a study dropout. Event was "unrelated
" to arbutamine.

ADVERSE EVENTS THAT REQUIRED DISCONTINUATION OF TESTING--

Phase I Of the 122 Phase I subjects receiving arbutamine, 13% (16/122) required termination of the infusion because of adverse events. Nine of the sixteen (56% of discontinuations and 7.4% (9/122) overall) did not complete the protocol and were considered studies dropouts. Of these events, none were rated as serious.

Phase I Adverse Events Requiring Discontinuation of Test[16]

Adverse event	No. Subjects (N=122)
Arrhythmia	4.9 % (6/122)
Hypotension	5.7 % (7/122)
Tremor	1.6 % (2/122)
Chest pain	0.8 % (1/122)

[16] Adapted form Table 18, Vol 1.97, p 106.

Phase II Of the patients receiving IV arbutamine, 42% (70/165) experienced a total of 143 adverse events that required termination of the infusion. Of those in whom the infusion was discontinued, 7.1% (5/70) withdrew from further testing. Events are outlined in the table below.

Phase II Adverse Events Requiring Discontinuation of Test[17]

Adverse Event	ESA	
Total # patients	42 % (70/165)	% of total events
Angina	21 % (34/165)	34 % (49/143)
Hypotension	11 % (18/165)	14 % (20/143)
Arrhythmia	9.1% (15/165)	17 % (24/143)
Dizziness	7.9 % (13/165)	13 % (18/143)
Other	14 % (23/165)	22 % (32/143)

Phase III 13% (88/697) of patients had 119 events that required termination of ESA testing. Of those in whom the infusion was discontinued, 2 were withdrawn from further study participation. 2.5% (11/432) of patients undergoing ETT required discontinuation of the test for adverse events. Events are outlined in the table below.

Phase III Adverse Events Requiring Discontinuation of Test[18]

Adverse event	ESA (N=697)	ESA	ETT (N=432)	ETT
Total # patients	13 % (88/697)	% of total events	2.5 % (11/432)	% of total events
Arrhythmia	4.9 % (34/697)	28.5 % (34/119)	1.2 % (5/432)	45 % (5/11)
Hypotension	4.9 % (34/697)	28.5 % (34/119)	0.2% (1/432)	9.0 % (1/11)
Tremor/twitching	1.4 % (10/697)	8.4 % (10/119)	----	----
Angina Pectoris	0.7 % (5/697)	4.2 % (5/119)	----	----
Hypertension	0.7 % (5/697)	4.2 % (5/119)	0.2 % (1/432)	9.0 % (1/11)
Other	2.6 % (18/697)	15 % (18/119)	0.9 % (4/432)	36 % (4/11)

[17] Adapted form Table 25, Vol 1.97, p141.

[18] Adapted form Table 50, Vol 1.97, p239.

Of the 88 patients who halted ESA testing for adverse events, 8 required additional treatment:

Patient 0122-18-1291 VF necessitating DC cardioversion. Probably related to arbutamine. Discussed under "serious adverse events".
Patient 0122-24-1206 AFIB deteriorating into VF and requiring DC cardioversion. Probably related to arbutamine. Discussed under "serious adverse events."
Patient 0127-59-0259 Atrial fibrillation requiring hospitalization. Probably related to arbutamine. Discussed under "serious adverse events."
Patient 0123-48-0364 angina treated with SL NTG with resolution
Patient 0127-60-9991 angina treated with SL NTG with resolution
Patient 0128-76-0051 junctional rhythm treated with IV atropine with resolution
Patient 0127-68-0428 developed hypotension and was treated with IV saline
Patient 0123-44-1296 developed ventricular bigeminy, associated with 4 mm ST depression, and was treated with IV propranolol with resolution
Patient 0127-54-0110 developed nonsustained VT and received a precordial thump

From the data above, it is evident that the discontinuation rate for ESA testing exceeds that for ETT testing, and that the events that lead to discontinuation were not infrequently clinically significant. Of all the events that lead to discontinuation of Phase III ESA testing, 29 % were hypotension and 29 % were arrhythmias, and these are discussed in detail in sections that follow. The arrhythmias that lead to discontinuation are summarized below:

Incidence of Arrhythmias Causing Termination of Phase III ESA Tests[19]

	0122 N=244	0123 N=175	0127 N=151	0128 N=63	0129 N=64	**Total N=697**
Total # Patients	*10 (4.1%)	†9 (5.1%)	7 (4.6%)	2 (3.2%)	6 (9.4%)	**34 (4.9%)**
Ventricular						
Bigeminy	4 (1.6%)	†1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	**6 (0.9%)**
Couplet	3 (1.2%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	2 (3.1%)	**6 (0.9%)**
Triplet	2 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**2 (0.3%)**
Trigeminy	1 (0.4%)	1 (0.6%)	1 (0.7%)	0 (0.0%)	1 (1.6%)	**4 (0.6%)**
VT	1 (0.4%)	2 (1.1%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	**4 (0.4%)**
AIVR	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	2 (3.1%)	**3 (0.4%)**
PVC	1 (0.4%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**3 (0.4%)**
VF	*1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**1 (0.1%)**
Supraventricular						
SVT	0 (0.0%)	2 (1.1%)	2 (1.3%)	0 (0.0%)	0 (0.0%)	**4 (0.6%)**
AF	0 (0.0%)	0 (0.0%)	2 (1.3%)	0 (0.0%)	0 (0.0%)	**2 (0.3%)**
Coronary Sinus	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**1 (0.1%)**
Other						
Bradycardia	2 (0.8%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	**5 (0.7%)**
Junctional	1 (0.4%)	0 (0.0%)	1 (0.7%)	1 (1.6%)	0 (0.0%)	**3 (0.4%)**
Sinoatrial Block	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	**1 (0.1%)**

*Includes patient 0122-18-1291 with ventricular fibrillation; not included in **Table 51.**
†Includes patient 0122-44-1296 with ventricular bigeminy; not included in **Table 51.**

19 Table 52, vol 1.97, p243.

ADVERSE EVENTS BY SEVERITY----------

RATING OF ADVERSE EVENTS

Adverse events occurring during testing were all recorded, regardless of severity and whether or not they could be ascribed to ESA or ETT. This included adverse events that were spontaneously offered by patients and those which were elicited by questionnaire. Adverse events during arbutamine and exercise testing were categorized as follows:

Mild-tolerated or resolved without intervention
Moderate-resolved or tolerated with intervention, including discontinuation of infusion or exercise
Severe-not tolerated or resolved with treatment

This severity scale was uniform across all phases of development and in normal volunteers and patients with CAD. During Phase III the events were further categorized into those which were expected endpoints during stress testing ("anticipated events") and those which were unexpected or exceeded expectation in duration or severity ("adverse events"). The overall incidence of adverse and anticipated events is summarized below, with discussion of those rated as severe immediately following the tables. Incidence tables from all three phases of development are found later in the review.

SEVERITY OF ADVERSE EVENTS PER PATIENT: ALL PHASES

	Phase I (N=122)[20]	Phase II (N=165)[21]	Phase III ESA (N=697)	Phase III ETT (N=432)	p-value Phase III ESA vs. ETT
Overall Adverse Anticipated	75 % (91/122)	72 % (119/165)	 51 % (352/697) 80 % (555/697)	 9.0 % (39/432)	0.0000
Mild	53 % (64/122)	38 % (62/165)	32 % (226/697)	4.2 % (18/432)	0.0000**
Moderate Treated with Medication	19 % (23/122) 3.3 % 94/122)	30 % (50/165) 6.3 % (11/176)	17 % (120/697) 3.4 % (24/697)	4.6 % (20/432)	0.0000**
Severe	3.3 % (4/122)	4.2% (7/165)	0.9 % (6/697)	0.2 % (1/432)	0.261**
Drug Related yes no	 70 % (86/122) 4.1 % (5/122)	 70 % (115/165) 2.4 % (4/165)	 45 % (315/697) 5.3 % (37/697)	 ---- ----	

** P-values by Fisher's exact test.

[20] Total of 136 volunteers were recruited. 122 volunteers received intravenous administration of arbutamine and are therefore used for the comparison with Phase II and Phase III patients who all received intravenous arbutamine

[21] Total number of patients in phase II 186, but 11 patient from 0130 not included in this analysis, which includes studies 0107, 0108, 0112, 0115, 0119, 0120,0121. Adverse event data for 0130 presented separately

SEVERITY OF ADVERSE EVENTS PER EVENT: ALL PHASES

	Phase I (N=284)	Phase II (N=405)	Phase III ESA (N=665)	Phase III ETT (N=53)
Mild	84 % (231/284)	68 % (309/405)	74 % (492/665)	53 % (28/53)
Moderate	16.2 % (46/284)	29 % (89/405)	25 % (166/665)	47 % (24/53)
Severe	2.5 % (7/284)	3.2 % (7/405)	1.1 % (7/665)	1.9 % (1/53)
Related yes no	 90 % (255/284) 10 % (29/284)	 91 % (280/309) 9.4 % (29/309)	 87 % (578/665) 13 % (87/665)	 ---- ----

The overall rate of adverse events was higher in ESA than in ETT, and 87-91% of these events were drug related. A greater percentage of the adverse events (per total events) during ESA testing were rated as mild, but the incidence (per total number of patients) of moderate and severe events during ESA testing exceeded that in exercise testing.

Below is a summary of adverse events listed above as "severe", categorized by the phase of development. The listing below is by patient: Note that often more than one event occurred in the same subject. Note also that subjects are discussed in further detail in other sections of the review.

Phase I Seven adverse events (2.5%) in 4 normal volunteers were considered "severe":

(1) Subject 0116-A-001: was pretreated with propranolol 160 mg qd x 4 days. He suffered **tremors** at the highest rate of infusion 0.8 µg/kg/min necessitating termination of the infusion
(2) Subject 0116-A-013: (CS0116 vol 1.50 p038, vol 1.98 p 250) received no pretreatment but suffered **tremors** at 0.2 µg/kg/min necessitating termination of the infusion
(3) Subject 0110-A-001: developed **dizziness, headache, flushing,** and **palpitations** during arbutamine infusion at 0.4 (?-0.6) µg/kg/min. Infusion terminated, and symptoms resolved 7 minutes post discontinuation of infusion, except for flushing, which took 20 minutes to resolve.
(7) Subject 0116-A-005: developed **multifocal PVCs**, which required discontinuation of the infusion at 0.-- µg/kg/min and treatment with IV lidocaine (CS0116 vol 1.50 p036; vol 1.98 p250)

Phase II Ten adverse events (3.2%) in seven patients were judged by the investigator to be "severe":

(1) Patient 0121-A-011 with a history of hypertension, ventricular and supraventricular ectopy experienced **supraventricular tachycardia** lasting 3 minutes, hypertension (BP=189/116) and atypical chest pressure. All events resolving within one minute of termination of arbutamine infusion.1.59 330
(2) Patient 0121-C-004 developed **dyspnea** (vol1.59, p333)
(3) Patient 0108-A-002 developed severe **angina** pre-PTCA, which resolved with treatment with isosorbide dinitrate. Patient withdrawn from the study and post-PTCA test not performed. (vol1.44, p045)
(4) Patient 0119-A-015 was pretreated with atenolol. He experienced severe **dizziness** associated with **hypotension** and runs of **idioventricular rhythm**, all resolving within 3 minutes of termination of the infusion. (vol1.54, p16)
(5) Patient 0121-C-010 experienced **hypotension**, with a fall in BP to 70/40 mmhg associated with a junctional rhythm of 48 bpm, occurring at 20 minutes of infusion. The drug was discontinued. The hypotension resolved within 6 minutes, with BP 115/75, and sinus rhythm was restored within 8 minutes. (vol1.59, p 334)
(6) Patient 0121-B-007 experienced **hypotension**, with a drop in BP over two minutes from 137/75 to 98/55 mmHg, occurring during minutes infusion. (vol1.59, p 334)
(7) Patient 0121-C-002 developed **dizziness** associated with sinus tachycardia and **hypertension** (BP 188/121) thought secondary to arbutamine "overdosage" when the infusion was given through the same line as normal saline at 30 cc/hour. The infusion was discontinued and the patient given Metoprolol 2 mg IV, with resolution of the hypertension and tachycardia within 2 minutes and the dizziness within 7 minutes.
(vol1.59, p 333)

Phase III Seven (1.1%) adverse events in 6 patients during ESA testing and one (1.9%) during ETT testing were judged to be "severe" (i.e. not tolerated):

(1) Patient 0122-22-1343 Unstable angina 71 WM history of hypertension and angina. Both arbutamine and exercise stress tests were performed with no adverse events reported during the tests. ESA was positive and ETT was negative. Twenty five days after the arbutamine stress test (18 days after the exercise stress test) the patient experienced chest pain at rest and was admitted to the hospital where the symptoms responded to a regiment of intravenous NTG at 2 mg/hr, atenolol 50 mg po qd, and nifedipine 30 mg po qd. It is not listed in the patient summary whether the patient was ruled out for MI. Since the events occurred 25 days after the arbutamine test, the relationship was again considered "remote".
(2) Patient 0127-53-0071 Unstable angina 46 WF with history of prior myocardial infarction, hypertension, asthma, diabetes mellitus, and hypercholesterolemia underwent ESA testing. 10 days after testing progressive chest pressure for three days and was treated with intravenous heparin, nitroglycerin, and tissue plasminogen activator. Underwent emergent CABG for triple vessel disease. The event was judged to be "remotely" related to arbutamine testing.
(3) Patient 0122-18-1291 VF 58 WM h/o hypercholesterolemia, hypertension, smoking, prior inferior QWMI and cardiac catheterization showing 70% distal LAD, 100% mid-RCA. Withdrawn from β-adalat (atenolol 50 mg/nifedipine 20 mg PO QD) 48 hours prior to ESA testing. No other medication listed. Nine minutes into ESA testing developed anginal pain, twelve minutes into testing developed ST depression in AVL. Patient approaching his target HR of 137 bpm with a rate of 135 bpm, when he developed sinus arrhythmia, falling HR and frequent PVCs. ESA device terminated infusion for fall in HR at about 120 bpm and SBP 190/110. Sinus arrhythmia and PVCs persisted for one minute after discontinuation, and restarted testing. Ninety (90) seconds after restart. he developed 4 successive episodes of **VT/ VF** over a period of 4 minutes, each requiring 360 joule cardioversion. Serum potassium levels drawn one hour after the event were normal. He was admitted for observation. The patient received no further treatment, and was discharged without sequelae after 48 hours observation. Event was listed as probably related to arbutamine.
(4) Patient 0122-24-1206 VT/VF 50 WM with a history of three prior myocardial infarctions. Cardiac catheterization showing severe triple vessel disease (63% LAD, 55% CXM, 66% CXM, 100% mid RCA). Medications included diltiazem SR 90 mg po bid, isosorbide mononitrate 20 mg po bid, ASA 75 mg po qd. Arbutamine infusion given for twelve minutes to 123 bpm. Investigator discontinued the infusion because of chest pain and ischemic (>1.0 mm depression) ECG changes in the anteroseptal leads. He developed multi-focal PVCs, nonsustained VT, atrial fibrillation, deteriorated into VT/VF three minutes into the recovery period. Patient successfully cardioverted with 200 joules. Received lidocaine bolus and lidocaine IV infusion for three hours after the event. Subsequent recovery was uneventful, with no evidence of myocardial infarction. Listed as probably related to arbutamine.
(5) Patient 0122-03-0098 AFIB 58 WM with hypertension, angina, and cardiac catheterization showing 66% RCA stenosis. Medications including nifedipine 30 mg po qd, lovastatin 20 mg po qd, ASA 325 mg po qd, cimetidine 800 mg po qd. Arbutamine infusion given for 14 minutes, but developed heart rate saturation without restart of arbutamine infusion at 119 bpm. ESA testing was resumed for 6 minutes, the terminated a second time for falling heart rate. The infusion was restarted a second time for nearly five minutes, but again terminated for HR saturation at 120 bpm. **Atrial fibrillation** (VR 155 bpm) occurred 6 minutes into recovery period and lasted 3 hours necessitating admission for observation. The patient was treated with esmolol (175 mg IV), adenosine (6 mg IV, and verapamil (5 mg IV) and digoxin (1 mg IV). Converted to normal sinus rhythm after additional digoxin load (0.25 mg). Recovery was uneventful. Listed as probably related to arbutamine.
(6) Patient 0127-67-0385 severe angina 3 minutes into infusion and lasting for 9 minutes after termination of the infusion. (CM 0127, Vol. 1.82, p179).
(7) Patient 0127-64-0210 Chest Pain/Pulmonary embolus/Death: Patient 0127-64-0210. 51 WM with history of diabetes, PVD, PUD, right adrenal mass, esophageal candidiasis. Medications record not available. Underwent ESA testing with radionuclide imaging and follow-up. ETT was not performed because of severe claudication. Twenty-six days after ESA testing, before coronary angiography, developed serve epigastric distress, diaphoresis and syncope. Patient was hospitalized, and, shortly after admission, developed acute shortness of breath, chest, pain, hypotension, bradycardia. This deteriorated into electromechanical dissociation. Attempts at resuscitation were unsuccessful. Autopsy revealed massive left pulmonary embolus, which was considered to be the cause of death. The event was not considered to be related to drug because of the 27 day period between ESA testing and death.

ADVERSE EVENTS (MODERATE) TREATED WITH MEDICATION----------

PHASE I

IV Medications Administered for Adverse Events in Phase 1 Subjects

Patient number	Adverse events(s)	Medication
0104-A-003	Hypertension	propranolol 0.5 mg IV
0116-A-005	PVCs	lidocaine 100 mg IVB, then 2 mg/min
0118-A-005	SVT	propranolol 1 mg IV
0118-A-017	SVT	propranolol 1 mg IV

PHASE II

IV Medications Administered for Adverse Events or Anticipated Events in Phase 2 Patients

Patient Number	Adverse event(s)	Medication
0115-A-001	Dyspnea, dizziness	Atropine 0.8 mg IV
0120-A-008	Angina	Propranolol 1 mg IV
0120-F-005	Hypotension	Metoprolol 2 mg IV
0120-F-006	PVCs, angina	Metoprolol 1 mg IV
0120-F-007	PVCs, ischemia	Metoprolol 5 mg IV
0120-K-001	Idioventricular rhythm	Lignocaine 100 mg IV
0120-K-005	Hypotension	Saline IV
0121-C-002	Hypertension, tachycardia	Metoprolol 2 mg IV
0121-C-007	Hypotension, tachycardia, angina	Metoprolol 5 mg IV
0130-99-0003	Angina	propranolol 12 mg NTG 550 µg SL
0130-99-0004	Hypotension, angina, dizziness	Propranolol 1 mg IV

PHASE III

Further treatment, above that of terminating the arbutamine infusion, was given for adverse (3% of patients) and anticipated (11% of patients) events during this phase of development. With the exception of one case of atrial fibrillation, which lasted three hours, all events resolved within minutes of treatment.

IV Medications Administered for Adverse Events or Anticipated Events in Phase 3 Patients

Adverse event	NTG	Metoprolol	Esmolol	Propranolol	Other
Total Number	7 (1.0%)	6 (0.9%)	1 (1.0%)	1 (0.1%)	11 (1.6%)
Arrhythmias		4 (0.6%)	1 (0.1%)	1 (0.1%)	5 (0.7%)
Tachycardia		2 (0.3%)			
Vent bigeminy		1 (0.1%)		1 (0.1%)	
Vent fib					1 (0.1%)
Vent tach					1 (0.1%)
Atrial fib			1 (0.1%)		1 (0.1%)
Vent couplets		1 (0.1%)			
Junctional					1 (0.1%)
Bradycardia					1 (0.1%)
ECG ischemia		4 (0.6%)		1 (0.1%)	
Headache					4 (0.6%)
Angina	4 (0.6%)				
Hypotension					3 (0.4%)
Paresthesia	2 (0.3%)				
Chest pain	1 (0.1%)				
Myocardial ischemia	1 (0.1%)				
Hypertension		1 (0.1%)			
Dizziness					1 (0.1%)
Sweating					1 (0.1%)

"Other" includes atropine (3), lidocaine (1), adenosine (1), digoxin (1), verapamil (1), ibuprofen (2), saline (3), ASA (1), acetaminophen (1).

Since arbutamine has a pharmacokinetic half-life of 8 minutes and a pharmacodynamic half-life of 15 minutes, the initial treatment for adverse events is termination of the infusion. Pharmacologic reversal of adrenergic stimulation with intravenous β-blockade (esmolol, metoprolol, propranolol) is the antedate of choice. All three of these agents was used in treated adverse events during therapeutic dosing of arbutamine and were shown to be effective against arbutamine induced tachycardia, hypertension and angina. The

Mechanism of angina in this setting is increased myocardial demand secondary to β1-mediated tachycardia and inotropy, and it was treated successfully with both selective and non-selective β-blockade during the development program. Metoprolol was effective in a range of 2.5-50 mg IV in 11 patients, esmolol was effective in doses ranging from 10-80 mg IV in 6 patients, and propranolol in doses from 0.5-2.0 mg IV in 3 patients. Given that these adverse events are present without overdosage, there should be sufficient statement made in the labelling regarding the treatment of protracted angina/ischemia.

As discussed in the section on hypotension, the underlying pathophysiology of hypotension during catecholamine (dobutamine) stress testing could be one of two mechanisms: β_2-mediated peripheral vasodilation or vagal reflex-mediated, possibly via the Bezold-Jarisch reflex. The occurrence of bradycardia with 17% of the cases of hypotension implicates possible vagal reflex mechanisms in at least a subset of these cases. Although the development of hypotension during ESA testing has not been shown to be associated with a worse prognosis, there exists no systematic evaluation of the treatment of this hypotension in cases that are either profound, associated with anginal chest pain, or not resolved with termination of test infusion. If the above pathophysiologic mechanisms underlie the hypotension associated with arbutamine, then one would speculate that nonselective β-blockade should be preferable to β_1-selective blockade in cases without bradycardia, and atropine would be the treatment of choice in cases with concomitant bradycardia. Further investigation of the treatment of hypotension with "therapeutic/diagnostic" doses and with overdose is warranted, with appropriate statements made in the drug labelling.

ANTICIPATED EVENTS----------

As discussed earlier in the review, anticipated events were those which were expected during catecholamine stress testing: palpitations, tremor, tachycardia, tachypnea, shortness of breath, and angina. For ETT this also included fatigue and leg cramps. Overall, the incidence of anticipated events was 80% (555/697) for those undergoing ESA and 91% (342/432) for those undergoing ETT.

Incidence of Anticipated Events[22]

Who Preferred Term	ESA (%) N=697	ETT (%) N=432	p-value
Total Number of Patients	555 (80%)	392 (91%)	0.0000
Angina Pectoris	354 (51%)	231 (54%)	0.3805
Tachycardia	253 (36%)	46 (11%)	0.0000
Palpitation	184 (26%)	20 (4.6%)	0.0000
Dyspnea	143 (21%)	206 (48%)	0.0000
Respiratory Disorder	28 (4.0%)	24 (5.6%)	
Chest Pain	22 (3.2%)	6 (1.4%)	
Fatigue	NAP	158 (37%)	
Cramps, Legs	NAP	32 (7.4%)	

NOTE: Terms used above include the following descriptions:
Angina Pectoris = Atypical and typical angina
Dyspnea = Shortness of breath
Respiratory Disorder = Tachypnea
Chest Pain = Nonspecific chest pain
NAP=Not applicable
Patients may have experienced more than one event

Of those undergoing ESA testing, 26% (182/697) had anticipated events that required discontinuation of testing. For those undergoing ETT, 55% (240/432) had events that required discontinuation of testing.

Anticipated Events Requiring Discontinuation of ESA and ETT[23]

Anticipated Event	ESA N=697	ETT N=432	p-value
Total # Patients	182 (26%)[1]	240 (56%)[2]	0.0000
Angina Pectoris	166 (24%)[1]	119 (28%)[2]	0.16085
Dyspnea	17 (2.4%)	60 (14%)	0.0000
Palpitation	7 (1.0%)	2 (0.5%)	
Tachycardia	4 (0.6%)	1 (0.2%)	
Chest Pain	4 (0.6%)	1 (0.2%)	
Respiratory Disorder	2 (0.3%)	3 (0.7%)	
Fatigue	NAP	83 (19%)	
Cramps, Legs	NAP	11 (2.5%)	

[1]Includes patient 0122-01-0026 whose infusion was discontinued; placed in "Other" on data listings.
[2]Includes patient 0122-06-0222 whose angina was reason for stopping the test; action not recorded on CRF.NAP=Not Applicable

[22] Table 55, p254, Vol 1.97.

[23] Table 58, vol 1.97, p259.

The incidence of anticipated events during ESA testing was not found to be related to dose:

ESA PROTOCOLS 0122, 0123, 0127, 0128, 0129
ANTICIPATED EVENTS: INCIDENCE BY TREATMENT WITHIN TOTAL ARBUTAMINE DOSE
ALL PATIENTS

	ARBUTAMINE: TOTAL DOSE		
ANTICIPATED EVENT	<2.0 µg/kg (N=221)	2.0-4.0 µg/kg (N=237)	>4.0 µg/kg (N=204)
NUMBER OF PATIENTS WITH EVENTS	171(77.4%)	195(82.3%)	163(79.9%)
MYO-,ENDO-,PERICARDIAL DISORDERS	131(59.3%)	120(50.6%)	83(40.7%)
ANGINA PECTORIS	131(59.3%)	120(50.6%)	83(40.7%)
HEART RATE AND RHYTHM DISORDERS	106(48.0%)	135(57.0%)	117(57.4%)
TACHYCARDIA	74(34.4%)	94(39.7%)	74(36.3%)
PALPITATION	50(22.6%)	69(29.1%)	57(27.9%)
RESPIRATORY SYSTEM DISORDERS	52(23.5%)	56(23.6%)	39(19.1%)
DYSPNEA	49(22.2%)	49(20.7%)	35(17.2%)
RESPIRATORY DISORDER	7(3.2%)	12(5.1%)	7(3.4%)
CHEST PAIN (noncardiac)	5(2.3%)	7(3.0%)	10(4.9%)

* DOES NOT INCLUDE 35 PATIENTS WITH MISSING DOSING INFORMATION

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Of the anticipated events that occurred during ESA testing, 99.5% were rated as mild to moderate (77% mild and 23% moderate) and 0.4% were rated as severe. Those events rated as severe included 3 patients with angina during ESA and 1 with fatigue during ETT. These are discussed in the section on severe adverse events. Of all the anticipated events that occurred during ESA testing, 2.3% (23/984) required treatment in addition to termination of the arbutamine infusion. The treatment of both adverse and anticipated events was left to the clinical judgement of the investigator, with no protocol guidelines for uncontrolled or controlled treatment of adverse events. Both nitrates and β-blockers were used to treat anginal chest pain associated with ESA testing, with adequate patient response to both. There is no data on whether selective or non-selective β-blockade is more effective in this setting.

Incidence of Anticipated Events During ESA Stress Test Treated with Medication

Anticipated Event N=697	SL NTG or GTN	Metoprolol	Esmolol	Propranolol	Unknown
Total # of Patients	59 (8.5%)	4 (0.6%)	6 (0.9%)	2 (0.3%)	6 (0.9%)
Angina	**58 (8.3%)**[1]	**4 (0.6%)**[2]	**6 (0.9%)**	**2 (0.3%)**	**5 (0.7%)**
Palpitation	**1 (0.1%)**	0 (0.0%)	0 (0.0%)	**1 (0.1%)**	**1 (0.1%)**
Dyspnea	**1 (0.1%)**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chest Pain	**1 (0.1%)**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachycardia	**1 (0.1%)**	0 (0.0%)	0 (0.0%)	**1 (0.1%)**	0 (0.0%)
Respiratory Disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatigue	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cramps, Leg	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

NOTE: **More than one event could be treated with one medication.**

[1]Includes patient 0122-23-1779 who was administered IV NTG; not in data listings.
[2]Patient 0127-55-0027 experienced atypical and typical angina, counted as one event.
NTG: Nitroglycerin
GTN: Glyceryl trinitrate

OVERDOSAGE

The GenESA device sets the maximum infusion rate (0.8 µg/kg/min) and the maximal total dose (10 µg/kg), thus limiting the chances of overdosage during closed-loop administration. As seen in earlier sections, the actual rate of delivery and total dose both fell well within the range preset by the device.

Two patients in study 0121 were considered to have received excessive dose of arbutamine during **open-loop** administration, in which the dose of arbutamine was manually titrated by the investigator. One patient received multiple doses by **closed-loop** administration.

Patient 0121-C-001 received arbutamine simultaneously with an intravenous infusion of normal saline running at 30 cc/hr. The patient experienced a sudden rise in heart rate, which resolved without sequelae after termination of the infusion. The total dose receive is unknown.
Patient 0121-C-002 received arbutamine simultaneously with an intravenous infusion of normal saline running at 30

cc/hr. The patient experienced a sudden rise in both heart rate and systolic blood pressure and was treated with 2 mg of intravenous metoprolol. The patient recovered without sequelae.
The total dose received is unknown.
Patient 0128-72-007 received two ESA tests within 45 minutes. The initial test was halted for heart rate saturation after the patient received 4.4 µg/kg of arbutamine. The device would not allow the investigator to override the device because it sensed irregular heart rate, which was not observed by the investigator on simultaneous real-time ECG. Hence, the investigator began retesting from the beginning of the protocol, the dose of the second test was not recorded. The patient suffered no adverse sequelae.

The most clinically concerning adverse events associated with arbutamine overdosage are malignant cardiac arrhythmias, ventricular tachycardia and ventricular fibrillation, especially in patients with ischemic heart disease. Also, since arbutamine induces myocardial ischemia, overdosage could precipitate severe ischemia which could lead to infarction. Also, systolic hypertension is known to be an adverse event at therapeutic arbutamine dosages, and this effect could be exaggerated in the setting of overdosage.

Since arbutamine has a pharmacokinetic half-life of 8 minutes and a pharmacodynamic half-life of 15 minutes, the initial treatment of overdosage is termination of the infusion. Pharmacologic reversal of adrenergic stimulation with intravenous β-blockade (esmolol, metoprolol, propranolol) is the antidote of choice. Each of these agents was used in treating adverse events during therapeutic dosing of arbutamine and was shown to be effective against arbutamine induced tachycardia, hypertension and angina. Metoprolol was effective in a range of 2.5-50 mg IV in 11 patients, esmolol was effective in doses ranging from 10-80 mg IV in 6 patients, and propranolol in doses from 0.5-2.0 mg IV in 3 patients.

Hemodialysis and charcoal hemoperfusion have not been shown to accelerate arbutamine elimination and would likely be inappropriate to be used with a drug with a pharmacokinetic half-life of 8 minutes.

Arbutamine transiently lowers serum potassium, therefore, serum potassium should be measured on all patients suspected of overdosage. However, judgement should be exercised in replacement of potassium, since hypokalemia results primarily from an intracellular shift.

As discussed in the section on hypotension, the underlying pathophysiology of hypotension during catecholamine (dobutamine) stress testing could be one of two mechanisms: β_2-mediated peripheral vasodilation or vagal reflex-mediated, possibly via the Bezold-Jarisch reflex. The occurrence of bradycardia with 17% of the cases of hypotension implicates vagal reflexes in at least a subset of these cases. Although the development of hypotension during ESA testing has not been shown to be associated with a worse prognosis, there exists no systematic evaluation of the treatment of this hypotension in cases that are either profound, associated with anginal chest pain, or so not resolve with

termination of testing. If the above pathophysiologic mechanisms underlie the hypotension associated with arbutamine, then one would speculate that nonselective β-blockade should be preferable to β_1-selective blockade in cases without bradycardia, and atropine would be the treatment of choice in cases with concomitant bradycardia. Further investigation of the treatment of hypotension with "therapeutic/diagnostic" doses and with overdose is warranted, with appropriate statements made in the drug labelling.

The angina induced during ESA testing can be of sufficient magnitude to be classified as an adverse event, and may persist for up to 30 minutes post termination of the infusion. The mechanism of angina in this setting is increased myocardial demand secondary to β_1-mediated tachycardia, and was treated successfully with both selective and non-selective β-blockade during the development program. Given that these adverse events are present without overdosage, there should be sufficient statement made in the labelling regarding the treatment of protracted angina/ischemia associated with overdosage.

Catechol-induced arrhythmias were treated with both β-blockade and lidocaine during development, but no systematic study of the efficacy in treating arrhythmias was undertaken.

There exists at least one case in the data base of "bolus" infusion after the infusion was made into the arm on which the blood pressure cuff was used. If the ESA system is to be used as device and drug, it may be advisable to make mention of this in the labelling.

OVERALL SAFETY ANALYSIS----------

ADR INCIDENCE TABLES for all three phases of development are listed on the subsequent pages. The overall incidence of events with ESA testing is greater than with ETT testing. There exist predictable adverse events related to the mechanism of the drug: headache and flushing from vasodilation, tachycardia and palpitations form the inotropic/chronotropic effect, and tremor from systemic effects of the catecholamine. These are generally mild-moderate and self-limited. However, the incidence of more serious side effects such as arrhythmia, angina, myocardial ischemia, myocardial infarction, hypotension and hypertension were also more frequent with ESA testing (2.4% vs. 0.9%) and are discussed in detail in subsequent sections. Adverse events of note, either for their frequency or severity, have been highlighted in **bold**.
A brief review of the literature for historical comparison to alternative methods of pharmacologic stress testing is included at the end of the NDA Review.

ESA PROTOCOLS 0102, 0104, 0105, 0110, 0111, 0116, 0117, 0118, 0125, 0126
ADVERSE EVENTS: INCIDENCE IN NORMAL VOLUNTEERS BY SEVERITY WITHIN TREATMENT
ALL PATIENTS

ADVERSE EVENT - WHO PREFERRED TERM	ARBUTAMINE (N=122) MILD	MODERATE	SEVERE
NUMBER OF PATIENTS WITH EVENTS	**64(52.5%)**	**23(18.9%)**	**4(3.3%)**
HEART RATE AND RHYTHM DISORDERS	**56(45.9%)**	**18(14.8%)**	**2(1.6%)**
TACHYCARDIA	**39(32.0%)**	**3(2.5%)**	**0(0.0%)**
PALPITATION	**37(30.3%)**	**11(9.0%)**	**1(0.8%)**
SINUS TACHYCARDIA	5(4.1%)	0(0.0%)	0(0.0%)
PREMATURE CONTRACTION(S) JUNCTIONAL	5(4.1%)	0(0.0%)	0(0.0%)
BRADYCARDIA	**3(2.5%)**	**2(1.6%)**	**0(0.0%)**
PREM CONTR VENT	3(2.5%)	0(0.0%)	1(0.8%)
PREM CONTR ATRIAL	2(1.6%)	1(0.8%)	0(0.0%)
PREM CONTR ORIGIN UNKNOWN	2(1.6%)	1(0.8%)	0(0.0%)
JUNCTIONAL RHYTHM	**2(1.6%)**	**1(0.8%)**	**0(0.0%)**
TACHYCARDIA SUPRAVENTRICULAR	**1(0.8%)**	**2(1.6%)**	**0(0.0%)**
SINUS BRADYCARDIA	1(0.8%)	0(0.0%)	0(0.0%)
TACHYCARDIA JUNCTIONAL	**1(0.8%)**	**0(0.0%)**	**0(0.0%)**
TACHYCARDIA MULTIFOCAL ATRIAL	1(0.8%)	0(0.0%)	0(0.0%)
AV BLOCK FIRST DEGREE	**1(0.8%)**	**0(0.0%)**	**0(0.0%)**
SINUS ARRHYTHMIA	1(0.8%)	0(0.0%)	0(0.0%)
BIGEMINY ATRIAL	1(0.8%)	0(0.0%)	0(0.0%)
PREM CONTR VENT, MULTIFOCAL	0(0.0%)	1(0.8%)	0(0.0%)
CENTR & PERIPH NERVE SYST DISORDERS	**27(22.1%)**	**5(4.1%)**	**3(2.5%)**
HEADACHE	**17(13.9%)**	**0(0.0%)**	**1(0.8%)**

PROGRAM: /dat/esa/ndaiss/sas/programs/aes2_phase1
PHASE I

TABLE
ESA PROTOCOLS 0102, 0104, 0105, 0110, 0111, 0116, 0117, 0118, 0125, 0126
ADVERSE EVENTS: INCIDENCE IN NORMAL VOLUNTEERS BY SEVERITY WITHIN TREATMENT
ALL PATIENTS

	ARBUTAMINE (N=122)		
ADVERSE EVENT - WHO PREFERRED TERM	MILD	MODERATE	SEVERE
CENTR & PERIPH NERVE SYST DISORDERS	**27(22.1%)**	**5(4.1%)**	**3(2.5%)**
TREMOR	**5(4.1%)**	**2(1.6%)**	**2(1.6%)**
DIZZINESS	**4(3.3%)**	**1(0.8%)**	**1(0.8%)**
HYPOESTHESIA	3(2.5%)	1(0.8%)	0(0.0%)
PARESTHESIA	2(1.6%)	2(1.6%)	0(0.0%)
SENSORY DISTURBANCE	1(0.8%)	0(0.0%)	0(0.0%)
SPEECH DISORDER	1(0.8%)	0(0.0%)	0(0.0%)
TWITCHING	1(0.8%)	0(0.0%)	0(0.0%)
HYPERKINESIA	0(0.0%)	1(0.8%)	0(0.0%)
BODY AS A WHOLE- GENERAL DISORDERS	20(16.4%)	4(3.3%)	0(0.0%)
PAIN	9(7.4%)	0(0.0%)	0(0.0%)
CHEST PAIN	**6(4.9%)**	**4(3.3%)**	**0(0.0%)**
FATIGUE	**6(4.9%)**	**0(0.0%)**	**0(0.0%)**
RIGORS	3(2.5%)	0(0.0%)	0(0.0%)
ASTHENIA	2(1.6%)	0(0.0%)	0(0.0%)
HEADACHE	**1(0.8%)**	**0(0.0%)**	**0(0.0%)**
HOT FLUSHES	1(0.8%)	0(0.0%)	0(0.0%)
MALAISE	1(0.8%)	0(0.0%)	0(0.0%)
GASTRO-INTESTINAL DISORDERS	12(9.8%)	1(0.8%)	0(0.0%)
NAUSEA	6(4.9%)	1(0.8%)	0(0.0%)

PROGRAM: /dat/esa/ndaiss/sas/programs/aes2_phase1
PHASE I

TABLE
ESA PROTOCOLS 0102, 0104, 0105, 0110, 0111, 0116, 0117, 0118, 0125, 0126
ADVERSE EVENTS: INCIDENCE IN NORMAL VOLUNTEERS BY SEVERITY WITHIN TREATMENT
ALL PATIENTS

	ARBUTAMINE (N=122)		
ADVERSE EVENT - WHO PREFERRED TERM	MILD	MODERATE	SEVERE
GASTRO-INTESTINAL DISORDERS	12(9.8%)	1(0.8%)	0(0.0%)
ABDOMINAL PAIN	4(3.3%)	0(0.0%)	0(0.0%)
DYSPEPSIA	1(0.8%)	0(0.0%)	0(0.0%)
DYSPHAGIA	1(0.8%)	0(0.0%)	0(0.0%)
AUTONOMIC NERVOUS SYSTEM DISORDERS	11(9.0%)	2(1.6%)	0(0.0%)
MOUTH DRY	10(8.2%)	0(0.0%)	0(0.0%)
SWEATING INCREASED	1(0.8%)	1(0.8%)	0(0.0%)
SALIVA INCREASED	0(0.0%)	1(0.8%)	0(0.0%)
RESPIRATORY SYSTEM DISORDERS	9(7.4%)	0(0.0%)	0(0.0%)
DYSPNEA	**6(4.9%)**	**0(0.0%)**	**0(0.0%)**
PHARYNGITIS	2(1.6%)	0(0.0%)	0(0.0%)
COUGHING	1(0.8%)	0(0.0%)	0(0.0%)
UPPER RESP TRACT INFECTION	1(0.8%)	0(0.0%)	0(0.0%)
CARDIOVASCULAR DISORDERS GENERAL	7(5.7%)	6(4.9%)	0(0.0%)
ECG ABNORMAL SPECIFIC	**7(5.7%)**	**0(0.0%)**	**0(0.0%)**
HYPOTENSION	**3(2.5%)**	**4(3.3%)**	**0(0.0%)**
HYPERTENSION	**0(0.0%)**	**1(0.8%)**	**0(0.0%)**
ECG ABNORMAL	0(0.0%)	1(0.8%)	0(0.0%)

PROGRAM: /dat/esa/ndaiss/sas/programs/aes2_phase1
PHASE I

TABLE
ESA PROTOCOLS 0102, 0104, 0105, 0110, 0111, 0116, 0117, 0118, 0125, 0126
ADVERSE EVENTS: INCIDENCE IN NORMAL VOLUNTEERS BY SEVERITY WITHIN TREATMENT
ALL PATIENTS

	ARBUTAMINE (N=122)		
ADVERSE EVENT - WHO PREFERRED TERM	MILD	MODERATE	SEVERE
VASCULAR (EXTRACARDIAC) DISORDERS	6(4.9%)	2(1.6%)	1(0.8%)
FLUSHING	3(2.5%)	1(0.8%)	1(0.8%)
HOT FLUSHES	3(2.5%)	0(0.0%)	0(0.0%)
THROMBOPHLEBITIS ARM	1(0.8%)	0(0.0%)	0(0.0%)
PALLOR	0(0.0%)	1(0.8%)	0(0.0%)
PLATELET, BLEEDING & CLOTTING DISORDERS	3(2.5%)	0(0.0%)	0(0.0%)
PHLEBITIS	3(2.5%)	0(0.0%)	0(0.0%)
PSYCHIATRIC DISORDERS	3(2.5%)	0(0.0%)	0(0.0%)
ANXIETY	1(0.8%)	0(0.0%)	0(0.0%)
EUPHORIA	1(0.8%)	0(0.0%)	0(0.0%)
CONCENTRATION IMPAIRED	1(0.8%)	0(0.0%)	0(0.0%)
MUSCULO-SKELETAL SYSTEM DISORDERS	2(1.6%)	0(0.0%)	0(0.0%)
HYPERTONIA	1(0.8%)	0(0.0%)	0(0.0%)
CHEST PAIN	1(0.8%)	0(0.0%)	0(0.0%)
SKIN AND APPENDAGES DISORDERS	1(0.8%)	1(0.8%)	0(0.0%)
RASH	1(0.8%)	0(0.0%)	0(0.0%)

PROGRAM: /dat/esa/ndaiss/sas/programs/aes2_phase1
PHASE I

TABLE
ESA PROTOCOLS 0102, 0104, 0105, 0110, 0111, 0116, 0117, 0118, 0125, 0126
ADVERSE EVENTS: INCIDENCE IN NORMAL VOLUNTEERS BY SEVERITY WITHIN TREATMENT
ALL PATIENTS

	ARBUTAMINE (N=122)		
ADVERSE EVENT - WHO PREFERRED TERM	MILD	MODERATE	SEVERE
SKIN AND APPENDAGES DISORDERS	1(0.8%)	1(0.8%)	0(0.0%)
BULLOUS ERUPTION	0(0.0%)	1(0.8%)	0(0.0%)
RESISTANCE MECHANISM DISORDERS	1(0.8%)	0(0.0%)	0(0.0%)
PHARYNGITIS	1(0.8%)	0(0.0%)	0(0.0%)
APPLICATION SITE DISORDERS	1(0.8%)	0(0.0%)	0(0.0%)
PARESTHESIA	1(0.8%)	0(0.0%)	0(0.0%)
METABOLIC AND NUTRITIONAL DISORDERS	1(0.8%)	0(0.0%)	0(0.0%)
THIRST	1(0.8%)	0(0.0%)	0(0.0%)
HEARING AND VESTIBULAR DISORDERS	1(0.8%)	0(0.0%)	0(0.0%)
TINNITUS	1(0.8%)	0(0.0%)	0(0.0%)
WHITE CELL AND RES DISORDERS	0(0.0%)	1(0.8%)	0(0.0%)
LYMPHADENOPATHY	0(0.0%)	1(0.8%)	0(0.0%)

PROGRAM: /dat/esa/ndaiss/sas/programs/aes2_phase2
PHASE II

TABLE
ESA PROTOCOLS 0107, 0108, 0112, 0115, 0119, 0120, 0121
ADVERSE EVENTS: INCIDENCE BY SEVERITY WITHIN TREATMENT
ALL PATIENTS

ADVERSE EVENT - WHO PREFERRED TERM	ARBUTAMINE (N=165) MILD	ARBUTAMINE (N=165) MODERATE	ARBUTAMINE (N=165) SEVERE	ETT (N=58) MILD	ETT (N=58) MODERATE	ETT (N=58) SEVERE
NUMBER OF PATIENTS WITH EVENTS	**62(37.6%)**	**50(30.3%)**	**7(4.2%)**	**6(10.3%)**	**8(13.8%)**	**8(13.8%)**
HEART RATE AND RHYTHM DISORDERS	**55(33.3%)**	**15(9.1%)**	**2(1.2%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
PREM CONTR VENT	**30(18.2%)**	**1(0.6%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
PALPITATION	**20(12.1%)**	**2(1.2%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
PREM CONTR ATRIAL	7(4.2%)	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
TACHYCARDIA SUPRAVENTRICULAR	**7(4.2%)**	**0(0.0%)**	**1(0.6%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
PREM CONTR VENT, COUPLETS	4(2.4%)	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
TACHYCARDIA VENTRICULAR	**3(1.8%)**	**1(0.6%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
BIGEMINY VENTRICULAR	2(1.2%)	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
BRADYCARDIA	**1(0.6%)**	**3(1.8%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
IDIOVENTRICULAR RHYTHM ACCEL RATE 60-100	**1(0.6%)**	**1(0.6%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
PREM CONTR VENT, TRIPLETS (RATE NAV)	1(0.6%)	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
JUNCTIONAL RHYTHM	**1(0.6%)**	**1(0.6%)**	**0(0.0%)**	**0(0.0%)**	**09 0.0%)**	**0(0.0%)**
AV BLOCK FIRST DEGREE	**1(0.6%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
BIGEMINY ATRIAL	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
TRIGEMINY VENTRICULAR	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
PREM CONTR VENT, TRIPLETS (RATE<=100)	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
BUNDLE BRANCH BLOCK LEFT	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
FIBRILLATION ATRIAL	**1(0.6%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
TACHYCARDIA	0(0.0%)	3(1.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
PREM CONTR ORIGIN UNKNOWN	0(0.0%)	2(1.2%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
SINOATRIAL BLOCK	**0(0.0%)**	**1(0.6%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
IDIOVENTRICULAR RHYTHM: RATE NAV	**0(0.0%)**	**0(0.0%)**	**1(0.6%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
CENTR & PERIPH NERVE SYST DISORDERS	**30(18.2%)**	**10(6.1%)**	**2(1.2%)**	**1(1.7%)**	**0(0.0%)**	**0(0.0%)**
HEADACHE	**15(9.1%)**	**3(1.8%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
DIZZINESS	**12(7.3%)**	**6(3.6%)**	**2(1.2%)**	**1(1.7%)**	**0(0.0%)**	**0(0.0%)**
TREMOR	9(5.5%)	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
PARESTHESIA	1(0.6%)	2(1.2%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
HYPOESTHESIA	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
BODY AS A WHOLE- GENERAL DISORDERS	22(13.3%)	3(1.8%)	0(0.0%)	2(3.4%)	1(1.7%)	1(1.7%)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20420

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

APR - 2 1997

DATE:

NDA 20-420

DATE RECEIVED BY HFD-110: November 8, 1996, Amendment.

DRUG NAME: Arbutamine (GenESA System).

SPONSOR: Gensia Inc.

INDICATION: Diagnostic Adjunct (Drug and System of Delivery Device) for Diagnosis of Coronary Artery Disease.

DOCUMENTS REVIEWED: Dr. Rodin's Review (Dated 03/19/97)[1]; Dr. Fenichel's Memo (Dated 03/20/97)[2]; Published Paper by G. A. Diamond et. al.[3]; and Published Paper by G. A. Diamond et. al.[4]

INTRODUCTION

The statistical review of the original submission of GenESA System (Date of submission 12/23/93) was completed on 11/07/94. A non-approval letter was issued to the sponsor on 04/06/1995. Later after some negotiation with the agency, the sponsor submitted amendments on 10/25/95, 04/11/1996, and 11/08/96. No statistical review was required for the amendments. Concerning the latest amendment of November 8, 1996, in-house meeting Dr. Raymond L. Lipicky, Director of the

---

[1] - Dr. Steven M. Rodin, from the Division of Cardio Renal Drug Product of FDA (HFD-110); the primary medical reviewer of the GenESA submission (NDA 20-420). His review of the final amendment completed is dated on March 19, 1997.

[2] - Dr. Robert R. Fenichel, from the Division of Cardio Renal Drug Products of FDA (HFD-110); the secondary medical reviewer of the GenESA submission (NDA 20-420). His review of the final ammendment completed is dated on March 20, 1997.

[3] - George A. Diamond and James S. Forrester; Analysis of Probability as An Aid in the Clinical Diagnosis of Coronary-Artery Disease; The New England Journal of Medicine, June 14, 1979 (1350 - 1358).

[4] - George A. Diamond, James S. Forrester, Michael Hirsch, Howard, M. Staniloff, Ran Vas, Daniel S. Berman, and H. J. C. Swan; Application of Conditional Probability Analysis to the Clinical Diagnosis of Coronary Artyery Disease; Journal of Clinical Investigation, Vol. 65, May 1980 (1210-1221).

Division of Cardiorenal Drug Products of FDA (HFD-110), indicated that a formal statistical review of this amendment is not necessary; however, this reviewer should help Dr. Rodin and Dr. Fenichel in their review.

METHODOLOGY

In his review, Dr. Rodin has performed analyses called "Conditional Probability Analyses" (page 15 of the review), using "**Bayesian Method**" proposed by G. A. Diamond et. al. (See Footnotes 3 and 4 below).

The methodology uses Formula (1) to compute the "**Post-Test Likelihood**" of **presence** of CAD given that the diagnostic test result was the **presence** of CAD. The formulas use the information on sensitivity, specificity, and the "**Pre-Test Likelihood**" of presence of CAD.

$$(1)\quad PTL(D+|T+)=\frac{\Pi(D+).SEN}{\Pi(D+).SEN+[1-\Pi(D+)].[1-SPE]},$$

where:

SEN = Sensitivity
SPE = Specificity
Π(D+) = Pre-Test Likelihood of presence of CAD.
PTL(D+ | T+) = Conditional probability of presence of CAD given that the diagnostic test result was the presence of CAD.

In addition, the interest was also to compute the Post-Test Likelihood of **presence** of CAD given that the diagnostic test result was the **absence** of CAD. This post-test likelihood is computed through the Formula (2).

$$(2)\quad PTL(D+|T-)=\frac{\Pi(D+).(1-SEN)}{\Pi(D+).(1-SEN)+[1-\Pi(D+)].SPE},$$

Where:

PTL(D+ | T-) = Conditional probability of presence of CAD given that the diagnostic test result was the absence of CAD.

The derivation of Formulas (1) is presented in the appendix attached in the back.

In his secondary review of the latest amendment, Dr. Fenichel has used Formulas (1) and (2) and asked this reviewer to find a methodology to construct 95% confidence intervals (**95% CI**) for the estimated post-test likelihood(s) of CAD (Table 3a on page 5 of Dr. Fenichel's Memo).

The foundation of Formula (1) is supposed to be based on the Bayes' Theorem (in Probability Theory), but, with some modification. In any rate, this reviewer will not comment on the theoretical foundation, application, and the interpretation of the results by using these formulas. Therefore, the objective of this review is to compute the requested 95% confidence intervals for PTL(D+ | T+) and PTL(D+ | T+).

VARIANCE FORMULA

The formulas which approximately calculate the variance of PTL(D+ | T+) and PTL(D+ | T-) was derived through the Taylor Series expansion of the Formulas (1) and (2), using the only the linear term of the expansion. For the expansion the term P(D+) was taken as a constant value and the quantities sensitivity and specificity were taken as the variables. Thus, PTL(D+ | T+) and PTL(D+ | T-) are functions of sensitivity and specificity and we can represent them by $f(SEN, SPE)$. Then, the general formula for the approximate variance is given by:

$$(3)\quad Variance = \left(\frac{\partial f}{\partial SEN}\right)^2 Var(SEN) + \left(\frac{\partial f}{\partial SPE}\right)^2 Var(SPE).$$

The terms $(\partial f/\partial SEN)$ and $(\partial f/\partial SPE)$ are evaluated at the values of sensitivity and specificity. The formulae for the variances are:

$$(4)\quad Var[P(D+|T+)] = \frac{(P(D+)[1-P(D+)](1-SPE)^2}{(p(D+)SEN+[1-P(D+)](1-SPE)^4}.Var(SEN) + \frac{(P(D+)[1-P(D+)]SEN)^2}{(p(D+)SEN+[1-P(D+)][1-SPE]^4}.Var(SPE).$$

$$(5)\quad Var[P(D+|T-)] = \frac{(P(D+)[1-P(D+)]SPE)^2}{(p(D+)(1-SEN)+[1-P(D+)]SPE)^4}.Var(SEN) + \frac{(P(D+)[1-P(D+)](1-SEN)^2}{(p(D+)(1-SEN)+[1-P(D+)]SPE)^4}.Var(SPE).$$

Where,

$$(6)\quad Var(SEN) = \frac{SEN(1-SEN)}{N_{SEN}} \quad and \quad Var(SPE) = \frac{SPE(1-SPE)}{N_{SPE}},$$

and N_{SEN} ($N_{+\bullet}$ in Table I) and N_{SPE} ($N_{-\bullet}$ in Table I) are the number of subjects diagnosed by angiogram as having CAD and not having CAD, respectively.

NUMERICAL RESULTS

The numerical results presented in **Tables I - IV** based on the data given by Dr. Fenichel. The data consist of sensitivity and specificity of the GenESA System in conjunction with Thallium and Sestamibi as well as the pooled data of Thallium and Sestamibi tests.

Table I: The Sensitivity and Specificity Data

Adjunct	N+•	N-•	N••	P(D+) = N+/N	Sensitivity	Specificity
Thallium	128	20	148	128/148 = 0.865	0.85	0.45
Sestamibi	65	21	87	65/87 = 0.747	0.63	0.67
Pooled	193	41	234	193/234 = 0.849	0.77	0.56

N+• = Number of patients diagnosed as having CAD with angiogram
N-• = Number of patients niagnosed as not having CAD with angiogram
N•• = Total number of subjects with an angiography test
P(D+) = Proportion of Subjects Diagnosed as Having CAD with angiogram

APPEARS THIS WAY
ON ORIGINAL

Table II: Point Estimates and 95% Confidence Intervals for Post-Test Likelihoods for the Thallium Data

Pre-Test Likelihood of Presence of CAD	Post-Test Likelihood of Presence of CAD Given that Thallium Test Diagnosed the Presence of CAD			Post-Test Likelihood of Presence of CAD Given that Thallium Test Diagnosed Absence of CAD		
	Point Estimate	95% CI		Point Estimate	95% CI	
		Lower Bound	Upper Bound		Lower Bound	Upper Bound
0.865 *	**0.907**	**0.873**	**0.941**	**0.695**	**0.562**	**0.828**
0.100	0.145	0.095	0.195	0.038	0.015	0.061
0.200	0.276	0.196	0.357	0.082	0.035	0.129
0.300	0.396	0.299	0.492	0.132	0.060	0.204
0.400	0.505	0.404	0.605	0.192	0.095	0.289
0.500	0.604	0.508	0.701	0.262	0.141	0.383
0.600	0.696	0.611	0.782	0.348	0.206	0.490
0.700	0.781	0.712	0850	0.453	0.298	0.609
0.800	0.859	0.811	0.908	0.587	0.435	0.739
0.900	0.932	0.907	0.958	0.762	0.648	0.876

* : The Bold Face values are calculated based on the likelihood of presence of CAD based on data presented in Table I. The number **0.865** is the proportion of subjects with presence of CAD diagnosed by angiogram.

Table III: Point Estimates and and 95% Confidence Intervals for Post-Test Likelihoods for the Sestamibi Data

Pre-Test Likelihood of Presence Positive CAD	Post-Test Likelihood of Presence of CAD Given that Sestamibi Test Diagnosed Presence of CAD			Post-Test Likelihood of Presence of CAD Given that Sestamibi Test Diagnosed Absence of CAD		
	Point Estimate	95% CI		Point Estimate	95% CI	
		Lower Bound	Upper Bound		Lower Bound	Upper Bound
0.765 *	**0.855**	**0.777**	**0.934**	**0.631**	**0.529**	**0.7331**
0.100	0.175	0.083	0.267	0.058	0.034	0.082
0.200	0.323	0.184	0.462	0.121	0.075	0.168
0.300	0.450	0.292	0.608	0.191	0.124	0.259
0.400	0.560	0.403	0.717	0.269	0.183	0.355
0.500	0.656	0.512	0.800	0.356	0.257	0.456
0.600	0.741	0.619	0.863	0.453	0.345	0.561
0.700	0.817	0.721	0.912	0.563	0.456	0.670
0.800	0.884	0.819	0.949	0.688	0.595	0.782
0.900	0.945	0.912	0.978	0.833	0.772	0.893

* : The Bold Face values are calculated based on the likelihood of presence of CAD based on data presented in Table I. The number **0.765** is the proportion of subjects with presence of CAD diagnosed by angiogram.

Table IV: Point Estimates and and 95% Confidence Intervals for Post-Test Likelihoods for the Pooled Thallium and Sestamibi Data

Pre-Test Likelihood of Positive CAD	Post-Test Likelihood of Presence of CAD Given that Thallium or Sestamibi Test Diagnosed the **Presence** of CAD			Post-Test Likelihood of Presence of CAD Given that Thallium or Sestamibi Test Diagnosed the **Absence** of CAD		
	Point Estimate	95% CI		Point Estimate	95% CI	
		Lower Bound	Upper Bound		Lower Bound	Upper Bound
0.825 *	**0.892**	**0.858**	**0.926**	**0.659**	**0.575**	**0.744**
0.100	0.163	0.115	0.211	0.044	0.028	0.059
0.200	0.304	0.229	0.379	0.093	0.061	0.125
0.300	0.429	0.342	0.515	0.150	0.102	0.197
0.400	0.538	0.451	0.626	0.215	0.152	0.278
0.500	0.636	0.554	0.718	0.2911	0.214	0.368
0.600	0.724	0.653	0.795	0.381	0.293	0.470
0.700	0.803	0.747	0.859	0.489	0.396	0.583
0.800	0.875	0.836	0.914	0.622	0.534	0.710
0.900	0.940	0.920	0.960	0.787	0.724	0.850

* : The Bold Face values are calculated based on the likelihood of presence of CAD based on data presented in Table I. The number **0.825** is the proportion of subjects with presence of CAD diagnosed by angiogram.

Comment:

The values in **Table IV** correspond to values in **Table 3a** of Dr. Fenichel. The confidence intervals in Table IV are narrower than those given in Table 3a, but not by much.

Kooros Mahjoob, Ph.D.
Mathematical Statistician

This review consists of 6 pages which includes text and 4 tables and one appendix attached.

Concur: Dr. Chi 4/21/97

CC:

Arch. NDA 20-420

HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Fenichel
HFD-110/Dr. Rodin
HFD-110/Mrs. Morgenstern
HFD-110/Mr. Beuhler
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Chron.

K. Mahjoob: 4-5301:Biometrics 1/Team 1:km.

APPENDIX

This appendix presents the formulae and the computations for the quantities sensitivity, specificity, postive predictive value and post-test likelihood of presence of CAD derived by the application of Bayes Theorem, in the GenESA review.

		GenESA New Test		
		T+	T-	
Angigram (Gold)	D+	N_{++}	N_{+-}	$N_{+\cdot}$
	D-	N_{-+}	N_{--}	$N_{-\cdot}$
		$N_{\cdot+}$	$N_{\cdot-}$	$N_{\cdot\cdot}$

RELEVANT QUANTITIES:

$$\textit{Pre-Test Prevalance of Disease: } P(D+) = \frac{N_{+\cdot}}{N_{\cdot\cdot}}$$

$$\textit{Pre-Test Sensitivity: } P(T+|D+) = \frac{P(T+\&D+)}{P(D+)} = \frac{N_{++}}{N_{+\cdot}}$$

$$\textit{Pre-Test Specificity: } P(T-|D-) = \frac{P(T-\&D-)}{P(D-)} = \frac{N_{--}}{N_{-\cdot}}$$

$$\textit{Positive Predictive Value } PPV =: P(P+|T+) = \frac{P(T+\&D+)}{P(T+)} = \frac{N_{++}}{N_{\cdot+}}$$

USING THE BAYES' THEOREM

This formula is derived by application of Bayes' Theorem and

$$PPV\ Post\text{-}Test\ Likelihood: = P(P+|T+) = \frac{P(D+).SEN}{P(D+).SEN + [1 - P(D+)].[1 - SPE]} = \frac{N_{++}}{N_{\bullet+}}$$

APPLICATION

In Application the P(D+) is replaced by Π(D+) which is the likelihood of presence of CAD and is obtained from the sources other than the data set for which the Sensitivity and Specificity were calculated.

$$PPV\ Post\text{-}Test\ Likelihood: = P(P+|T+) = \frac{\Pi(D+).SEN}{\Pi(D+).SEN + [1 - \Pi(D+)].[1 - SPE]}$$

In conclusion the last formula is no longer a derivable from the Bayes Theorem..

Statistical Review and Evaluation

DATE: APR - 6 1995

NDA#: 20-420

APPLICANT: Gensia

NAME OF DRUG: GenESA System (arbutamine HCl)

DOCUMENTS REVIEWED: Volume 1.1 Dated 5/14/94 and Undated Volume 1.7

I. Background

Volume 1.1 contained the sponsor's stability data and analyses of the product in prefilled syringes and vials when stored at various temperatures and for various lengths of time. Volume 1.7, pp. 319-435, represents an earlier submission with fewer data points.

In discussion with Dr. Short (HFD-110) it was decided that the Division of Biometrics analyze the potency results of the various studies of the drug product at the 5, the 22, and the 30 degree Celsius storage conditions.

II. Sponsor's Results

Appendix I in Volume 1.1 contains the sponsor's stability reports. The sponsor reports 12 months data on the drug substance, 16 months data of arbutamine HCl 0.05 mg/mL in 20 mL prefilled syringes and 16 months data of the product in 20 mL vials, a study which was run in parallel to the syringe study. There are also 36 months data of the product which had been synthesized by an earlier, the IND, process. This product is labeled as arbutamine HCl 1mg/20mL in 20 mL vials.

The sponsor reports the assay results of the two drug substance lots and concludes without analysis that the data support a three year expiration dating when stored at -15 ± 5 degrees Celsius.

From the two drug substance lots three production lots of arbutamine 0.05 mg/mL sterile solution were made and filled into 20 mL prefilled syringes. The syringes were stored on their sides. Data at various temperatures were collected for up to 16 months. The sponsor evaluated the potency data from the 5 degree C, the recommended storage condition, statistically. It was found that intercepts between lots were significantly different whereas slopes between lots were not. Computing the 95 % lower confidence limit on the common slope and using the 100 % LC as the "normalized" intercept, the sponsor computed release specifications (≥ 93.72 %

LC based on three determinations) which would assure with at least 95 % confidence that a batch of arbutamine would qualify for a three year expiration dating period. The data from all temperatures were also used in an Arrhenius plot which confirmed the percent loss/year obtained from the statistical analysis. The sponsor concluded that a three year expiration dating period at 5 ± 3 degrees Celsius is justified.

The sponsor also compared results from syringes with those obtained from vials. Two drug production lots had been filled into both vials and syringes. The sponsor plotted the potency results from 5, 30, and 40 degrees C and concluded that there were no differences between the syringes and vials, nor that the orientation (upright or inverted) of the vials mattered.

There were also four vial lots with 36 months data which had been synthesized by on older process. The stability data from 5 degrees C storage were tested using least squares regression for differences in slopes between lots and vial configurations and for differences in intercepts between lots. The lower 95 % confidence limit of the slope estimates was used to compute the release specification that would assure a three year expiration dating period. An Arrhenius plot showed a strong correlation of the kinetic relationship estimates based on the regression methodology and this method. The sponsor concludes that the product has maintained satisfatory stability at 5 degrees C and recommends a three year shelf life.

III. Reviewer's Results

The stability of the drug substance lots was not investigated by this reviewer.

The sponsor's method of computing the lower 95 % confidence limit of the slope estimate and then working backwards to the minimum release criteria given this slope and a three-year expiration date is not appropriate. The statistical method for the analysis of stability data is outlined in the FDA "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics" and the sponsor should be informed of it. Also "normalizing" the intercept to 100 % LC can result in biasing results towards a longer expiration dating period than the data truely support. In his analysis of the 36 months vial data the sponsor speaks of least squares regression for testing certain interaction terms. It appears that the sponsor actually performed an ANOVA analysis but the lack of detailed results make it impossible to reproduce the sponsor's analysis. His approach appears reasonable in terms of testing whether vial orientation and slope estimates have a significant interaction. However, the level of significance of the test and other details of the analysis were not submitted. This reviewer chose to analyze each set of data (i.e. orientation, temperature, etc.) separately.

The stability program of the Division of Biometrics first tests the data whether they support a model of individual, parallel, or of a common regression line(s). After determining the model, the expiration dating period is set by the earliest intersection of a 95 % confidence band around the regression line(s) with the corresponding specification limit.

In the first study two drug substance lots were divided into three drug product lots, i.e drug substance lot ZP92550P is the source lot for both drug product lot XP2S501 and XP2S503. Drug product lot XP2S502 was made from the raw material lot ZP82550P. When the drug product lots were filled into prefilled syringes with arbutamine at 0.05 mg/mL and stored at 5 degrees C for 16 months the data regressed to parallel regression lines, each estimating extrapolated expiration dating periods of over 64 months. The same three product lots stored at 22 degrees C regressed to a common regression line and estimated an extrapolated expiration dating period of 35 months. When stored at 30 degrees C there were only 12 months data available. These regressed to parallel regression lines which estimated expiration dating periods between 14 and 16 months (Tables 1-3).

From Gensia raw material lot numbers 36601-102-10B, -10A, and 38811-76A four drug product lots were created and filled in vials where the raw material lot -10A was the source for the drug product lots XP0P002 and -003. For three of these lots 36 months data were available and for lot XP1J014 24 months data were available. As mentioned before these drug product lots were synthesized with the older process. For ease of reference this reviewer used the label arbutamine HCl, 1mg/20mL, as it appeared on the sponsor's data sheets. When stored in the upright positon at 5 degrees C the data regressed to individual lines and the lots estimated expiration dating periods ranging from 35 to 84 months. The same lots stored inverted at the same temperature regressed to parallel lines estimating expiration dating periods between 51 and 58 months. At controlled room temperature (25-30 degrees C) the upright vials regressed to parallel lines with resulting estimated expiration dating periods ranging from 17 to 22 months. The corresponding inverted vials regressed to a common line with an estimated expiration dating period of 19 months. The vials were also stored at 30 degrees for 24 months. In the upright position the data regressed to individual lines with estimating expiration dating periods between 11 and 15 months. In the inverted position parallel lines estimated expiration dating periods between 10 and 13 months (Tables 4A/B-6A/B).

Two of the three drug product lots of the above syringe study were also filled into 20 mL vials, sterile solution, and stored upright and inverted for 16 months. At 5 degrees C the data from the upright vials regressed to parallel lines with estimated expiration dating periods of 47 and 55 months. The corresponding results from the inverted vials were 49 and 54 months. The vials were not

studied at 22 degrees C but at 30 degrees C for 12 months. At this temperature the two lots of the upright vials regressed to a common line with a resulting estimated expiration dating period of 15 months. The corresponding inverted vials estimated expiration dating periods of 19 and 20 months (Tables 7A/B-8A/B).

The above findings are summarized a table below.

Drug Substance Lot	Product Lot	Product	Temperature/ Storage Position	Est. Exp. Date
ZP192550P	XP2S501	Arbutamine 0.05 mg/mL (Sterile Solution) in 20 mL Prefilled Syringes	5 Degrees C	>64
ZP182550P	XP2S502	"	"	>64
ZP192550P	XP2S503	"	"	>64
	ALL	"	22 Degrees C	35
	XP2S501	"	30 Degrees C	16
	XP2S502	"	"	14
	XP2S503	"	"	16
36601-102-10B	XP0P001	Arbutamine 1mg/20mL (Aseptic) in 20 mL Vials	5 Degrees C Upright	35
36601-102-10A	XP0P002	"	"	42
36601-102-10A	XP0P003	"	"	42
38811-76A	XP1J014	"	"	84

	XP0P001	"	5 Degrees C Inverted	51
	XP0P002	"	"	54
	XP0P003	"	"	54
	XP1J014	"	"	58
	XP0P001	"	25-30 Degrees C/Upright	17
	XP0P002	"	"	20
	XP0P003	"	"	19
	XP1J014	"	"	22
	ALL	"	25-30 Degrees C/Inverted	19
	XP0P001	"	30 Degrees C/ Upright	11
	XP0P002	"	"	15
	XP0P003	"	"	11
	XP1J014	"	"	11
	XP0P001	"	30 Degrees C/ Inverted	10
	XP0P002	"	"	13
	XP0P003	"	"	11
	XP1J014	"	"	12
ZP192550P	XP2S501F1	Arbutamine 0.05 mg/mL (Sterile Solution) in 20 mL Vials	5 Degrees C/ Upright	47
ZP182550P	XP2S502F1	"	"	55

	XP2S501F1	"	5 Degrees C/ Inverted	49
	XP2S502F1	"	"	54
	ALL	"	30 Degrees C/ Upright	15
	XP2S501F1	"	30 Degrees C/ Inverted	20
	XP2S502F1	"	"	19

Summary and Conclusion

The Division of Biometrics was requested to determine the expiration dating period for the product in vials and syringes when stored at 5, at 22, and at 30 degrees Celsius.

The findings indicate that when Arbutamine 0.05 mg/mL is stored at its recommended temperature of 5 degrees Celsius and filled either into 20 mL prefilled syringes or 20 mL vials that the extrapolated expiration dating periods are at least 47 months. One lot from the product derived from the older synthesized process estimated only 35 months as an expiration dating period when stored in the upright position. All other batches estimated 42-84 months.

At higher temperatures the product exhibited heat sensitivity and did not estimated the requested 36 months expiration dating period in a single case, even when 24 months actual data were available.

The sponsor should be notified to use the FDA Guideline in analyzing stability data.

Roswitha E. Kelly

Concur: Karl K. Lin, Ph.D. 3/6/95

cc: HFD-110/NDA 20-420 Original
HFD-110/Dr. R. Waters
HFD-110/Dr. J. Short
HFD-710/Chron
HFD-715/Dr. Fairweather
HFD-715/Dr. Lin
HFD-715/R. Kelly
HFD-715/DRU 2.2.1 GenESA System (arbutamine Hcl), Gensia
HFD-715/RKELLY/4/04/95/GenESA.rev

Table 1.

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Prefilled Syringes
At 5 Degrees C

TIME	_501	_502	_503
0	100.1	99.5	101.0
1	101.6	99.3	101.3
3	101.6	100.6	102.2
6	101.4	100.4	100.0
9	100.0	99.4	101.2
12	100.4	100.0	100.5
16	101.3	99.4	100.7

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Prefilled Syringes
At 5 Degrees C

SOURCE	SS	DF	MS	F	P
A	6.40	4	1.60	3.36395	0.03733
B	6.19	2	3.09	6.51015	0.00922
C	0.21	2	0.10	0.21776	0.80681
D	7.13	15	0.48		
E	212393.50	6	35398.92		

****
* Statistical Analysis: *
* Key to sources of variation *
* A = sep. intercep, sep slope \| com intercep, com slope *
* B = sep. intercep, com slope \| com intercep, com slope *
* C = sep. intercep, sep slope \| sep intercep, com slope *
* D = Residual *
* E = Full Model *
****

Table 1 con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 0.05 mg/mL
Prefilled Syringes
At 5 Degrees C

		Est. Exp. Dating Period
Batch 501 Fitted Line:	Y = 101.074 - 0.0238 X	> 64 Months
Batch 502 Fitted Line:	Y = 99.960 - 0.0238 X	> 64 Months
Batch 503 Fitted Line:	Y = 101.146 - 0.0238 X	> 64 Months

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 2.

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Prefilled Syringes
At 22 Degrees C

TIME	_501	_502	_503
0	100.1	99.5	101.0
3	101.1	99.9	100.7
6	99.3	98.3	97.6
9	98.8	98.0	98.4
12	98.0	97.8	98.6

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Prefilled Syringes
At 22 Degrees C

SOURCE	SS	DF	MS	F	P
A	1.72	4	0.43	0.62530	0.65631
B	1.55	2	0.78	1.12845	0.36535
C	0.17	2	0.08	0.12215	0.88646
D	6.19	9	0.69		
E	147444.72	6	24574.12		

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Table 2 con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 0.05 mg/mL
Prefilled Syringes
At 22 Degrees C

	Est. Exp. Dating Period
All Batches Fitted Line: Y = 100.4 - 0.21 X	35 Months

Table 3:

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Prefilled Syringes
At 30 Degrees C

TIME	_501	_502	_503
0	100.1	99.5	101.0
1	101.0	98.9	100.2
3	99.7	98.5	99.5
6	95.0	94.9	96.8
9	95.2	94.4	95.7
12	94.3	92.8	94.8

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Prefilled Syringes
At 30 Degrees C

SOURCE	SS	DF	MS	F	P
A	7.29	4	1.82	2.24572	0.12485
B	7.11	2	3.56	4.37934	0.03732
C	0.18	2	0.09	0.11210	0.89488
D	9.74	12	0.81		
E	170701.87	6	28450.31		

```
**********************************************************
* Statistical Analysis:                                  *
*      Key to sources of variation                       *
* A = sep. intercep, sep slope | com intercep, com slope  *
* B = sep. intercep, com slope | com intercep, com slope  *
* C = sep. intercep, sep slope | sep intercep, com slope  *
* D = Residual                                           *
* E = Full Model                                         *
**********************************************************
```

Table 3 con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 0.05 mg/mL
Prefilled Syringes
At 30 Degrees C

		Est. Exp. Dating Period
Batch 501 Fitted Line:	Y = 100.497 - 0.5704 X	16 Months
Batch 502 Fitted Line:	Y = 99.447 - 0.5704 X	14 Months
Batch 503 Fitted Line:	Y = 100.947 - 0.5704 X	16 Months

Table 4H:

The SAS System
Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Upright Vials
At 5 Degrees C

TIME	J014	P001	P002	P003
0	100.8	99.7	100.2	100.8
1	100.4	98.9	99.5	99.6
3	101.3	98.3	99.8	99.8
6	100.4	98.4	98.8	99.5
9	99.8	100.8	101.9	101.0
12	100.1	95.2	97.3	96.9
18	100.3	97.3	98.5	97.6
24	99.3	95.5	97.3	97.3
36	.	91.7	93.2	92.9

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Upright Vials
At 5 Degrees C

SOURCE	SS	DF	MS	F	P
A	34.19	6	5.70	3.70834	0.00810
B	25.89	3	8.63	5.61727	0.00399
C	8.29	3	2.76	1.79942	0.17110
D	41.48	27	1.54		
E	340252.27	8	42531.53		

****
* Statistical Analysis: *
* Key to sources of variation *
* A = sep. intercep, sep slope \| com intercep, com slope *
* B = sep. intercep, com slope \| com intercep, com slope *
* C = sep. intercep, sep slope \| sep intercep, com slope *
* D = Residual *
* E = Full Model *
****

Table 4A con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 1mg/20mL
Upright Vials
At 5 Degrees C

		Est. Exp. Dating Period
Batch J014 Fitted Line:	Y = 100.792 - 0.0539 X	84 Months
Batch P001 Fitted Line:	Y = 99.724 - 0.1992 X	35 Months
Batch P002 Fitted Line:	Y = 100.577 - 0.1715 X	42 Months
Batch P003 Fitted Line:	Y = 100.690 - 0.1909 X	42 Months

Table 4B :

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Inverted Vials
At 5 Degrees C

TIME	J014	P001	P002	P003
0	100.8	99.7	100.2	100.8
1	100.8	99.7	99.1	99.1
3	100.8	98.5	99.6	99.8
6	99.7	98.7	99.1	98.9
9	98.1	101.2	100.3	101.9
12	99.8	97.1	96.9	96.0
18	100.5	98.3	98.5	97.5
24	97.1	95.1	97.3	97.4
36	.	92.7	94.1	94.9

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Inverted Vials
At 5 Degrees C

SOURCE	SS	DF	MS	F	P
A	10.44	6	1.74	1.06088	0.40972
B	7.87	3	2.62	1.60069	0.21236
C	2.56	3	0.85	0.52107	0.67142
D	44.27	27	1.64		
E	340181.41	8	42522.68		

****
* Statistical Analysis: *
* Key to sources of variation *
* A = sep. intercep, sep slope \| com intercep, com slope *
* B = sep. intercep, com slope \| com intercep, com slope *
* C = sep. intercep, sep slope \| sep intercep, com slope *
* D = Residual *
* E = Full Model *
****

Table 4B con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 1mg/20mL
Inverted Vials
At 5 Degrees C

		Est. Exp. Dating Period
Batch J014 Fitted Line:	Y = 101.097 - 0.1531 X	58 Months
Batch P001 Fitted Line:	Y = 99.743 - 0.1531 X	51 Months
Batch P002 Fitted Line:	Y = 100.199 - 0.1531 X	54 Months
Batch P003 Fitted Line:	Y = 100.332 - 0.1531 X	54 Months

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 5A:

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Upright Vials
At 25-30 Degrees C

TIME	J014	P001	P002	P003
0	100.8	99.7	100.2	100.8
1	99.5	98.2	98.8	99.5
3	99.9	97.6	99.0	99.0
6	96.4	94.7	96.7	95.1
9	96.9	96.0	98.7	98.2
12	95.7	89.5	92.7	90.8
18	94.8	90.9	92.0	89.8
24	90.8	87.8	90.8	88.2
36	.	86.5	84.3	86.4

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Upright Vials
At 25-30 Degrees C

SOURCE	SS	DF	MS	F	P
A	24.65	6	4.11	1.34011	0.27409
B	22.23	3	7.41	2.41722	0.08817
C	2.42	3	0.81	0.26300	0.85142
D	82.78	27	3.07		
E	314993.69	8	39374.21		

****
* Statistical Analysis: *
* Key to sources of variation *
* A = sep. intercep, sep slope \| com intercep, com slope *
* B = sep. intercep, com slope \| com intercep, com slope *
* C = sep. intercep, sep slope \| sep intercep, com slope *
* D = Residual *
* E = Full Model *
****

Table 5A con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 1mg/20mL
Upright Vials
At 25-30 Degrees C

		Est. Exp. Dating Period
Batch J014		
Fitted Line:	Y = 100.518 - 0.4020 X	22 Months
Batch P001		
Fitted Line:	Y = 98.302 - 0.4020 X	17 Months
Batch P002		
Fitted Line:	Y = 99.669 - 0.4020 X	20 Months
Batch P003		
Fitted Line:	Y = 99.069 - 0.4020 X	19 Months

Table 5B:

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Inverted Vials
At 25-30 Degrees C

TIME	J014	P001	P002	P003
0	100.8	99.7	100.2	100.8
1	99.5	99.1	98.8	100.0
3	99.8	97.9	99.0	98.9
6	93.6	93.9	95.4	96.0
9	96.2	96.1	98.2	97.7
12	94.2	90.5	92.8	90.1
18	91.4	90.5	91.7	89.6
24	87.9	87.2	89.7	87.6
36	.	83.5	88.5	85.7

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Inverted Vials
At 25-30 Degrees C

SOURCE	SS	DF	MS	F	P
A	26.94	6	4.49	1.38280	0.25727
B	14.12	3	4.71	1.44947	0.25041
C	12.82	3	4.27	1.31613	0.28958
D	87.67	27	3.25		
E	312370.50	8	39046.31		

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Table 5B con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 1mg/20mL
Inverted Vials
At 25-30 Degrees C

		Est. Exp. Dating Period
All Batches Fitted Line:	Y = 99.236 - 0.4269 X	19 Months

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

Table 6A:

The SAS System
Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Upright Vials
At 30 Degrees C

TIME	J014	P001	P002	P003
0	100.8	99.7	100.2	100.8
1	99.7	95.9	96.7	97.4
2	91.1	96.5	98.3	97.6
3	97.8	97.2	98.8	98.4
4	98.2	95.5	97.7	95.2
5	92.8	94.5	96.5	95.9
6	95.1	92.8	95.8	94.8
12	92.6	89.4	91.2	88.9
24	88.3	84.4	88.4	84.1

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Upright Vials
At 30 Degrees C

SOURCE	SS	DF	MS	F	P
A	34.47	6	5.74	1.61507	0.17997
B	18.01	3	6.00	1.68775	0.19227
C	16.46	3	5.49	1.54239	0.22543
D	99.60	28	3.56		
E	325272.04	8	40659.01		

****
* Statistical Analysis: *
* Key to sources of variation *
* A = sep. intercep, sep slope \| com intercep, com slope *
* B = sep. intercep, com slope \| com intercep, com slope *
* C = sep. intercep, sep slope \| sep intercep, com slope *
* D = Residual *
* E = Full Model *
****

Table 6A con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 1mg/20mL
Upright Vials
At 30 Degrees C

			Est. Exp. Dating Period
Batch J014			
Fitted Line:	Y =	97.840 - 0.4239 X	11 Months
Batch P001			
Fitted Line:	Y =	97.749 - 0.5937 X	11 Months
Batch P002			
Fitted Line:	Y =	98.991 - 0.4793 X	15 Months
Batch P003			
Fitted Line:	Y =	99.023 - 0.6686 X	11 Months

Table 6B:

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Inverted Vials
At 30 Degrees C

TIME	J014	P001	P002	P003
0	100.8	99.7	100.2	100.8
1	99.2	97.0	96.7	96.7
2	99.3	96.1	98.2	97.7
3	97.7	97.7	98.9	98.6
4	97.9	95.3	97.5	95.9
5	92.9	95.0	95.5	96.4
6	93.3	93.2	95.8	94.1
12	92.6	88.1	90.1	87.6
24	83.0	83.9	87.7	83.5

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
1mg/20mL in Inverted Vials
At 30 Degrees C

SOURCE	SS	DF	MS	F	P
A	24.14	6	4.02	1.58157	0.18944
B	13.52	3	4.51	1.77112	0.17554
C	10.62	3	3.54	1.39202	0.26579
D	71.23	28	2.54		
E	324641.23	8	40580.15		

****
* Statistical Analysis: *
* Key to sources of variation *
* A = sep. intercep, sep slope \| com intercep, com slope *
* B = sep. intercep, com slope \| com intercep, com slope *
* C = sep. intercep, sep slope \| sep intercep, com slope *
* D = Residual *
* E = Full Model *
****

Table 6B con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 1mg/20mL
Inverted Vials
At 30 Degrees C

		Est. Exp. Dating Period
Batch J014		
Fitted Line:	Y = 99.256 - 0.6422 X	12 Months
Batch P001		
Fitted Line:	Y = 98.067 - 0.6422 X	10 Months
Batch P002		
Fitted Line:	Y = 99.689 - 0.6422 X	13 Months
Batch P003		
Fitted Line:	Y = 98.656 - 0.6422 X	11 Months

Table 7A:

The SAS System

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Upright Vials
At 5 Degrees C

TIME	_501F1	_502F1
0	100.3	99.1
1	101.0	99.7
3	101.8	100.8
6	102.2	100.4
9	101.0	99.8
12	104.3	102.2
16	101.2	99.8

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Upright Vials
At 5 Degrees C

SOURCE	SS	DF	MS	F	P
A	7.24	2	3.62	2.67325	0.11748
B	7.14	1	7.14	5.27590	0.04449
C	0.10	1	0.10	0.07059	0.79587
D	13.54	10	1.35		
E	142743.18	4	35685.80		

```
************************************************************
* Statistical Analysis:                                    *
*      Key to sources of variation                         *
* A = sep. intercep, sep slope | com intercep, com slope     *
* B = sep. intercep, com slope | com intercep, com slope     *
* C = sep. intercep, sep slope | sep intercep, com slope     *
* D = Residual                                             *
* E = Full Model                                           *
************************************************************
```

Table 7A con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 0.05 mg/mL
Upright Vials
At 5 Degrees C

		Est. Exp. Dating Period
Batch 501F1		
Fitted Line:	Y = 101.146 - 0.0804 X	47 Months
Batch 502F1		
Fitted Line:	Y = 99.718 - 0.0804 X	55 Months

Table 7B:

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Inverted Vials
At 5 Degrees C

TIME	_501F1	_502F1
0	100.3	99.1
1	100.7	100.3
3	101.7	100.8
6	100.2	98.9
9	100.9	100.1
12	103.7	102.1
16	101.2	100.5

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Inverted Vials
At 5 Degrees C

SOURCE	SS	DF	MS	F	P
A	3.41	2	1.71	1.41033	0.28870
B	3.40	1	3.40	2.81144	0.12453
C	0.01	1	0.01	0.00922	0.92541
D	12.10	10	1.21		
E	142114.77	4	35528.69		

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Table 7B con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 0.05 mg/mL
Inverted Vials
At 5 Degrees C

		Est. Exp. Dating Period
Batch 501F1		
Fitted Line:	Y = 100.633 - 0.0908 X	49 Months
Batch 502F1		
Fitted Line:	Y = 99.647 - 0.0908 X	54 Months

Table 8A.

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Upright Vials
At 30 Degrees C

TIME	_501F1	_502F1
0	100.3	99.1
1	99.9	99.8
3	98.9	99.0
6	94.2	95.2
12	96.5	94.4

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Upright Vials
At 30 Degrees C

SOURCE	SS	DF	MS	F	P
A	0.95	2	0.48	0.16756	0.84955
B	0.53	1	0.53	0.18621	0.68116
C	0.42	1	0.42	0.14891	0.71289
D	17.04	6	2.84		
E	95546.41	4	23886.60		

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Table 8A con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 0.05 mg/mL
Upright Vials
At 30 Degrees C

		Est. Exp. Dating Period
All Batches Fitted Line:	Y = 99.607 - 0.4266 X	15 Months

Table 8B:

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Inverted Vials
At 30 Degrees C

TIME	_501F1	_502F1
0	100.3	99.1
1	100.0	99.5
3	99.7	99.5
6	97.3	96.5
12	96.5	94.4

Stability Analysis
NDA 20-420 Amendment 001
ARBUTAMINE
0.05 mg/mL in Inverted Vials
At 30 Degrees C

SOURCE	SS	DF	MS	F	P
A	2.84	2	1.42	2.71099	0.14495
B	2.30	1	2.30	4.40125	0.08071
C	0.53	1	0.53	1.02073	0.35134
D	3.14	6	0.52		
E	96621.50	4	24155.37		

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Table 8B con'd:

NDA 20-420/Amendment 001
ARBUTAMINE 0.05 mg/mL
Inverted Vials
At 30 Degrees C

		Est. Exp. Dating Period
Batch 501F1		
Fitted Line:	Y = 100.498 - 0.3950 X	20 Months
Batch 502F1		
Fitted Line:	Y = 99.538 - 0.3950 X	19 Months

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20420

MICROBIOLOGY REVIEW(S)

OCT 20 1994

CONSULTATIVE REVIEW TO HFD-110

DIVISION OF MEDICAL IMAGING, SURGICAL, and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #1
18 October 1994

A. 1. NDA 20-420

APPLICANT Gensia, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

2. PRODUCT NAMES: GenESA® System (Arbutamine sterile solution in combination with the GenESA Device for administration)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The solution is provided in a 20 mL prefilled syringe for direct intravenous infusion.

4. METHOD(S) OF STERILIZATION: The product solution is filtered and aseptically transferred into HYPAK syringes (supplied as sterile)

5. PHARMACOLOGICAL CATEGORY: Adjunct to cardiac imaging which physiologically simulates exercise

6. DRUG PRIORITY CLASSIFICATION: 1S

B. 1. DATE OF INITIAL SUBMISSION: 20 December 1993

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: DMF 501 for Becton Dickinson Pharmaceutical Systems

4. ASSIGNED FOR REVIEW: 10 March 1994

C. REMARKS: This is a combined drug and device application under the jurisdiction of CDER although it is concurrently submitted, in part, to CDRH. CDRH has for review, portions of the submission which apply to the device components of the product.

The submission for consultative microbiology review consists of volumes 1.1, 1.2, 1.3, 1.6, 1.32 and 1.33. Device information is provided in a separate CMC section in volumes 1.8 - 1.15 which were not part of this submission for consultative review.

D. CONCLUSIONS: The application may be recommended for approval for reasons of sterility assurance pending concurrence by the chemistry reviewer that the Stability Protocol is adequate (aspects relating to maintenance of sterility were not addressed relative to stability because the stability program was not part of the consult package).

10-20-94

David Hussong, Ph.D.

10/20/94

cc:

Original NDA 20-420
HFD-160/Consult File
HFD-110/CSO/G. Buehler
drafted by: D. Hussong, 10/18/94
R/D initialed by: P. Cooney, 10/20/94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20420

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

INDEX to Clinical Pharmacology Review

1. IV/transdermal Dose-Ranging Studies in Normal Volunteers

2. Beta-blocker/IV arbutamine Interaction Studies in Normals

3. Atropine/IV arbutamine Interaction Studies in Normals

4. **Beta-blocker/IV arbutamine Interaction Studies in Coronary artery Disease Patients:**

Protocol 0119 (20 patients)

APPEARS THIS WAY
ON ORIGINAL

PROTOCOL 0102 (Clinical study CS0102)

DESIGN SUMMARY:

This was an open-label, single-blind, placebo-controlled (sequential design for the intravenous study), single ascending dose ranging study to determine the safety, pharmacokinetics and pharmacodynamics of intravenous (IV) and transdermal (TD) arbutamine (GP-2-121-3) in 34 normal white male volunteers.

The GenESA™ System (or ESA System) is being developed as a diagnostic test for coronary artery disease. It involves closed loop controlled delivery of arbutamine. The data collected in this study were to be used for development of the ESA System's computerized closed loop algorithm.

PROTOCOL

- **Enrollment Criteria**

Enrolled subjects were healthy male volunteers, with no medical history suggesting significant disease, between 18 and 40 years of age, of average body weight (±15% of the Metropolitan Life Insurance Company averages for Height and Frame). Subjects were housed in research facilities with no alcohol or caffeine.

The following groups were excluded:

a. Females
b. Subjects with a history or presence of any significant disease state, as detected by medical history, physical examination, or laboratory tests.
c. Subjects with a history of significant medication allergies, bronchospasm or other pulmonary diseases, heart disease, thyroid disease, or glaucoma.
d. Subjects who had received prescription drugs within 2 weeks, or over-the-counter drugs within 3 days of the start of the study.
e. Subjects who had received any investigational drugs or participated in a drug research study within 30 days of the start of the study.
f. Subjects with a history of alcohol/drug abuse.

- **Qualifying Criteria**

Subjects underwent an exercise tolerance test (ETT) and had to achieve either their age-predicted maximum heart rate (HR) of 220 - age or a HR of at least 185 bpm. The ETT was stopped at any time if the subject complained of exhaustion, light-headedness, leg cramps, or was unwilling to continue. Subjects were excluded if any of the following occurred during the ETT: asthma, angina, claudication, hypotension, or ECG abnormalities.

- **Treatment Regimen**

After completing the ETT (Day 1), all subjects received three treatments, each separated by 48 hours. On Day 2, each subject received IV placebo for 16 minutes immediately followed by IV

arbutamine for 32 minutes. On Days 4 and 6, each subject received TD arbutamine or placebo for 32 minutes in a randomized, single-blind manner. No treatments were administered on Days 3 and 5. The IV doses were administered using a Perfusor syringe pump.

The doses received by each of the subjects were as follows:

Subject #	I.V. Infusion (µg/kg/min)	TD Electrode Con-centration (mM)	Current (mA/cm^2)
01 - 04			
05 - 08			
09 - 12			
13 - 15			
16			
17 - 19			
21 - 24			
25 - 28			
29			
30 - 31			
32			
33 - 35			

- **Endpoints**

Twelve-lead ECG, HR, and systolic and diastolic blood pressure (SBP/DBP) were measured at 0, 5, and 10 minutes during a 10 minute baseline period (it is not clear when this period was); every 4 minutes during arbutamine administration; then at 2, 6, 10, 20 and 30 minutes or until HR and BPs returned to baseline following termination of arbutamine administration.

Venous blood samples for analysis of plasma arbutamine concentration were obtained at baseline; after 16 and 32 minutes (midpoint and just prior to end-of-infusion, respectively) of IV and TD arbutamine administration; and at 2, 6, 10, 20 and 30 minutes, or until HR and BP had returned to baseline after stopping arbutamine administration.

Drug administration was to be terminated when HR reached 85% of that achieved during ETT.

- **Equipment used**

The ETT was performed using a Dynavit Medtronic 40 bicycle ergometer (Keiper Dynavit GmbH & Co, West Germany). The protocol consisted of an eight stage test with the load increased every 2 minutes by 50 watts (50 to 400 watts range).

HR, SBP, and DBP were measured at screening using methods routinely employed by the investigator. On treatment days, these measurements were made using a Clinical Research Prototype ESA System (Gensia Europe Ltd., Westerham, Kent, England).

All ECGS were obtained using a Marquette Case 12 Model ECG Monitor. Twelve lead ECGs were obtained at the same time as SBP/DBP measurements or when clinically indicated. The sponsor states that due to fusion of the T and P waves at high HR, and because accurate measurement of

the QT interval is not possible during changing HR (using the Marquette Case 12 Model), a cardiologist manually measured the QT and QT_c intervals.

- **Statistical Procedures**

  - **Data set analyzed**

Thirty-five subjects were entered into the study. One subject (#20) withdrew prior to receiving any treatments for a reason unrelated to the study. Thirty-three of the remaining 34 subjects completed the study. Subject #16 withdrew from the study for an adverse event, inguinal lymphadenitis, not related to the study medication after receiving IV arbutamine and is not included in the calculations for transdermal arbutamine.

  - **Handling of missing data**

Subject #20 excluded from all analyses; subject #16 excluded from transdermal analysis; otherwise not described.

  - **Analyses performed**

None described.

- **Subject Characteristics**

All 34 subject were white males aged 26.3 ± 4.1 years (mean ± standard deviation [SD]) of average height (178.1 ± 6.6 cm, mean ± SD) and weight (74.5 ± 8.0 kg, mean

RESULTS - 1. ARBUTAMINE INTRAVENOUS INFUSION

TABLE 1

Baseline Mean (± SD) HR, BP and ECG response to ETT

	BASELINE	EXERCISE	CHANGE
Heart Rate (bpm)	87.5 ± 14.8 (n=34)	189.9 ± 4.6 (n=34)	+102.4 ± 16.0 (n=34)
Systolic Pressure (mmHg)	121.5 ± 9.4 (n=20)	194.0 ± 13.1 (n=20)	+72.5 ± 14.6 (n=20)
Diastolic Pressure (mmHg)	78.1 ± 6.4 (n=20)	87.0 ± 13.4 (n=20)	+8.9 ± 13.0 (n=20)
PR Interval (m.sec)	142.1 ± 24.0 (n=24)	107.5 ± 14.9 (n=24)	-34.6 ± 14.1 (n=24)
QRS Duration (m.sec)	88.6 ± 9.1 (n=25)	86.8 ± 9.34 (n=25)	-1.8 ± 5.8 (n=25)
QT Interval (m.sec)	315.5 ± 22.2 (n=7)	225.7 ± 15.1 (n=7)	-89.9 ± 17.7 (n=7)
QT_c Interval (m.sec)	386.4 ± 13.6 (n=7)	418.6 ± 27.3 (n=7)	+32.1 ± 22.2 (n=7)

TABLE 2

Maximum Change from Baseline in **Heart Rate (HR)** and Time to Maximum Change
Mean (± SD)

Dose (µg/kg/min)	N	**HR CHANGE (bpm)**	T_{MAX} HR (min:sec)	Infusion Duration (min:sec)
Placebo	34	5.8 ± 3.7	7:18 ± 5:00	16:9 ± 0:16
0.0007	4	9.9 ± 4.1	33:34 ± 16:36	31:38 ± 0:16
0.0014	4	6.8 ± 4.8	35:16 ± 17:39	31:58 ± 0:5
0.0028	4	10.9 ± 7.0	40:49 ± 9:24	31:19 ± 0:58
0.0056	4	11.8 ± 4.0	23:06 ± 17:52	31:55 ± 1:37
0.0112	3	9.4 ±7.8	20:25 ± 10:00	30:24 ± 1:10
0.0224	4	**15.6 ± 3.7**	18:24 ± 12:52	31:48 ± 0:14
0.0448	4	**16.7 ± 9.8**	30:10 ± 1:33	31:44 ± 0:10
0.0896	4	**43.6 ± 8.5**	31:48 ± 0:42	31:53 ± 0:16
0.1792	3	**71.8 ± 19.0**	29:35 ± 6:20	31:53 ± 0:08

TABLE 3
HR at, and Time From, End of IV Infusion To A Percent Decrease in **HR**
Mean (± SD)

Dose [N] (µg/kg/min)	HR at infusion end (bpm)	10% (min:sec)	20% (min:sec)	**50% (min:sec)**
0.0007 [4]	59.2 ±10.3	9:56 ± 17:28	10:04 ± 17:34	15:33 ± 19:34
0.0014 [4]	61.9 ± 9.2	3:24 ± 17:35	3:29 ± 17:35	11:11 ± 16:57
0.0028 [4]	66.5 ± 2.1	9:33 ± 10:17	9:38 ± 10:17	14:21 ± 7:19
0.0056 [4]	69.9 ± 5.5	-8.41 ± 17:39	-0:49 ± 13:23	8:41 ± 8:43
0.0112 [3]	80.5 ± 13.3	-9:55 ± 11:10	-9:55 ± 11:08	5:57 ± 7:15
0.0224 [4]	87.9 ± 17.4	-6:46 ± 8:10	1:10 ± 7:21	**106:43 ± 10:39**
0.0448 [4]	81.9 ± 7.2	-1:14 ± 2:00	-1:06 ± 2:01	**06:24 ± 5:55**
0.0896 [4]	108.1 ± 4.8	1:20 ± 0:18	1:55 ± 0:36	**08:45 ± 1:41**
0.1792 [3]	134.4 ± 9.5	1:58 ± 1:14	4:53 ± 0:56	**13:57 ± 8:23**

Table 4
Maximum Change from Baseline in **Systolic Blood Pressure (SBP)** and Time to Maximum Change
Mean (± SD)

Dose [N] (ug/kg/min)	Baseline SBP (mm Hg)	Maximum SBP (mm Hg)	**Change from Base to Max (mm Hg)**	Time from Start to Max SBP (min:sec)
Placebo [34]	122.3 ± 11.3	126.5 ± 10.8	4.2 ± 6.5	6:15 ± 4:42
0.0007 [4]	113.0 ± 7.2	124.0 ± 9.0	11.0 ± 11.3	30:30 ± 9:12
0.0014 [4]	126.0 ± 17.5	129.0 ± 11.6	3.0 ± 7.7	41:49 ± 11:26
0.0028 [4]	122.5 ± 9.9	132.8 ± 9.9	10.3 ± 4.0	34:50 ± 3:36
0.0056 [4]	129.8 ± 7.4	135.5 ± 1.7	5.8 ± 6.2	37:35 ± 25:23
0.0112 [3]	119.7 ± 7.1	141.0 ± 18.0	**21.3 ± 11.8**	29:03 ± 14:49
0.0224 [4]	122.3 ± 8.0	147.5 ± 10.0	**25.3 ± 7.9**	27:15 ± 1:56
0.0448 [4]	124.5 ± 7.3	143.3 ± 5.4	**18.8 ± 6.3**	18:36 ± 3:14
0.0896 [4]	114.3 ± 14.8	151.3 ±18.1	**37.0 ± 11.5**	27:45 ± 6:55
0.1792 [3]	129.7 ± 11.3	177.0 ± 12.3	**47.3 ± 21.3**	19:55 ± 2:15

Table 5
Change from Baseline in **Diastolic Blood Pressure (DBP)** and Time to Maximum Change
Mean (± SD)

Dose [N] (ug/kg/min)	Baseline DBP (mm Hg)	Minimum DBP (mm Hg)	Change from Base to Min (mm Hg)	Time to Min DBP (min:sec)
Placebo [34]	65.8 ± 8.2	61.9 ± 7.5	-3.9 ± 2.8	9:44 ± 5:03
0.0007 [4]	72.5 ± 5.0	65.8 ± 4.5	-6.8 ± 6.0	31:56 ± 12:37
0.0014 [4]	68.5 ± 13.9	61.5 ± 11.4	-7.0 ± 1.8	22:28 ± 20:16
0.0028 [4]	65.8 ± 13.9	56.8 ± 5.4	-9.0 ± 2.9	9:50 ± 4:22
0.0056 [4]	62.5 ± 7.0	56.0 ± 4.7	-6.5 ± 3.1	14:28 ± 15:45
0.0112 [3]	65.7 ± 7.0	62.7 ± 9.8	-3.0 ± 4.6	13:43 ± 11:00
0.0224 [4]	67.8 ± 6.4	63.0 ± 10.6	-4.8 ± 5.2	4:49 ± 3:19
0.0448 [4]	61.3 ± 5.4	54.0 ± 3.5	-7.3 ± 2.6	17:36 ± 8:38
0.0896 [4]	61.3 ± 7.2	52.5 ± 7.6	-8.8 ± 1.0	19:15 ± 10:44
0.1792 [3]	67.7 ± 13.6	57.0 ± 10.8	-10.7 ± 6.7	22:35 ± 12:49

Table 6
Maximum Change from Baseline in Pressure Rate Product (PRP*) and Time to Maximum Change Mean (± SD)

Dose [N] (ug/kg/min)	Baseline PRP (mm Hg x bpm)	Maximum PRP (mm Hg x bpm)	Time to Max PRP (min:sec)
Placebo [34]	8456 ± 1667	9113 ± 1725	6:23 ± 5:06
0.0007 [4]	7251 ± 838	7757 ± 906	24:15 ± 8:56
0.0014 [4]	7830 ± 2245	8449 ± 1894	24:08 ± 13:15
0.0028 [4]	8686 ± 599	9482 ± 1164	32:43 ± 15:54
0.0056 [4]	8203 ± 814	10123 ± 692	32:05 ± 10:59
0.0112 [3]	9866 ± 7.0	11748 ± 9.8	29:03 ± 14:49
0.0224 [4]	9779 ± 2521	13054 ± 2448	24:15 ± 9:03
0.0448 [4]	7689 ± 772	11790 ± 1035	23:06 ± 7:36
0.0896 [4]	7713 ± 1706	15928 ± 2459	31:45 ± 1:41
0.1792 [3]	8954 ± 1777	23332 ± 1295	20:35 ± 2:32

*PRP = (SBP x HR)

Safety Data: The most frequently occurring adverse events from IV arbutamine (N=34) were: tachycardia (N=12, 35.3%); palpitations (N=8, 23.5%); headache (N=5, 14.7%); site pain (N=2, 5.9%); fatigue (N=2, 5.9%); and premature contractions (arrhythmia) (N=1, 2.9%). The difference between tachycardia and palpitations is not described by the sponsor. There were no reports of paradoxical hypotensive reactions. There were no changes in serum potassium even at the highest IV dose of arbutamine.

Table 7
Baseline Mean (± SD) ECG response to Arbutamine Infusion

Dose [N] (ug/kg/min)	Mean Change in QRS Interval (m.sec)	Mean Change in PR Interval (m.sec)	Mean Change in QT Interval (m.sec)	Mean Change in QT_c Interval (m.sec)
0.0112 [3]	2.7 ± 6.1	-13.8 ± 3.4	-3.3 ± 14.5	20.6 ± 6.3
0.0224 [4]	5.5 ± 9.1	-4.1 ± 26.9	-15.0 ± 11.4	30.8 ± 8.3
0.0448 [4]	-2.0 ± 9.4	-25.7 ± 11.4	-9.6 ± 15.3	36.7 ± 20.2
0.0896 [4]	-3.0 ± 10.6	-35.7 ± 15.5	-43.3 ± 32.1	66.7 ± 16.6
0.1792 [3]	-9.1 ± 1.0	-41.6 ± 12.0	-53.3 ± 9.4	55.0 ± 11.8

Pharmacokinetics: Steady state plasma arbutamine concentrations following 0.0448, 0.0896 and 0.1792 µg/kg/min infusion rates ranged from 0.38 to 3.2 ng/mL. The apparent elimination half life, total plasma clearance and volume of distribution (mean ± SD) were 8.2 ± 1.6 minutes, 4.1 ± 1.0 L/hr/kg, and 0.36 ± 0.13 L/kg, respectively, following IV arbutamine.

ESA Model Parameters and Definitions:

Mgain = Model gain is an index that relates the change in HR to the change in infusion rate during the infusion period.

onDelay = time from start of infusion to initial HR response (onset delay)

$t_{1/2}$ = the onset time constant is an index which describes the exponential rate at which the HR increases after the initial onset delay

offDelay = time from end of infusion before HR starts to decrease (offset delay)

$t_{1/2}d$ = the offset time constant is an index of the exponential rate at which HR decreases after the offset delay

Noise = standard deviation of the difference between filtered (running average filter with outlier clipping) and measured HR during the infusion period (i.e., a measure of HR variability).

TABLE 8
Initial ESA Parameter Estimates from IV Arbutamine Data

n=11*	MGain (bpm•µg-1•kg•min)	onDelay (sec)	$t_{1/2}$ (min)	offDelay (sec)	$t_{1/2}d$ (min)	Noise (bpm)
mean	417	80	5.55	50	11.12	4.6
minimum	203	40	0.40	5	2.65	2.7
maximum	833	130	16.96	125	19.92	8.4
SD	193	32	5.75	36.81	4.61	1.8

* Eleven subjects receiving 0.0448, 0.0896 and 0.1792 µg/kg/min infusions had a sufficient HR response to allow the above parameters to be calculated.

RESULTS - 2. ARBUTAMINE TRANSDERMAL (TD)

Table 9
Maximum Change from Baseline in HR and Time to Maximum Change
Mean (± SD)

TD Treatment* [N]	Baseline HR (bpm)	Maximum HR (bpm)	HR_{CHANGE} (bpm)	T_{MAX} HR (min:sec)
Placebo [33]	70.0 ± 9.9	77.8 ± 9.3	7.8 ± 4.2	29:51 ± 19:19
35 (0.4) [4]	58.3 ± 8.9	82.9 ± 11.1	24.6 ± 7.0	40:31 ± 5:05
35 (0.6) [4]	59.7 ± 8.9	106.2 ± 6.6	46.5 ± 14.5	46:46 ± 10:25
35 + 35(0.4) [3]	77.8 ± 6.6	123.5 ± 16.1	45.7 ± 10.1	47:50 ± 8:05
35 + 35(0.6) [4]	76.4 ± 11.2	135.2 ± 11.9	58.8 ± 2.7	49:05 ± 20:34
35 + 70(0.4) [4]	68.8 ± 5.1	108.2 ± 19.9	39.5 ± 16.1	36:11 ± 2:34
70 (0.4) [4]	69.8 ± 4.5	100.2 ± 13.2	30.4 ± 12.1	40:19 ± 8:01
70 (0.6) [3]	69.2 ± 4.1	118.5 ± 8.9	49.3 ± 6.8	50:58 ± 3:37
70 (0.8) [3]	72.9 ± 17.4	126.5 ± 6.4	53.6 ± 15.5	43:58 ± 2:60
70 + 70(0.4) [2]	59.7 ± 7.7	107.4 ± 16.0	47.8 ± 23.7	78:45 ± 18:51
70 + 70(0.6) [2]	72.5 ± 6.0	120.5 ± 13.2	48.0 ± 19.2	52:53 ± 19:09

*Concentration (mM) at Electrode Site(s) with Electrode (mA/cm^2) in parenthesis.

Table 10
HR at, and Time From End of TD Administration To A Percent Decrease in HR
Mean (± SD)

TD Treatment* [N]	HR at End (bpm)	Time for 10% Decrease (min:sec)	Time for 20% Decrease (min:sec)	Time for 50% Decrease (min:sec)
Placebo [33]	68.4 ± 9.2	2:20 ± 19:54	8:16 ± 18:52	18:14 ± 14:44
35 (0.4) [4]	71.8 ± 10.5	13:39 ± 6:55	33:54 ± 16:43	47:40 ± 28:24
35 (0.6) [4]	90.0 ± 2.0	28:40 ± 19:37	42:10 ± 18:02	71:12 ± 1:15
35 + 35(0.4) [3]	103.4 ± 19.9	34:00 ± 18:05	48:48 ± 11:59	72:12 ± 2:59
35 + 35(0.6) [4]	122.0 ± 22.2	35:30 ± 27:11	43:48 ± 22:35	72:40 ± **
35 + 70(0.4) [4]	97.7 ± 22.9	10:31 ± 3:21	23:34 ± 7:52	55:49 ± 10:23
70 (0.4) [4]	85.3 ± 8.5	10:09 ± 10:42	22:48 ± 22:02	42:34 ± 26:36
70 (0.6) [3]	99.1 ± 9.3	32:30 ± 19:07	41:02 ± 12:26	72:57 ± 1:50
70 (0.8) [3]	109.2 ± 4.8	29:00 ± 11:16	44:13 ± 12:18	61:58 ± 8:41
70 + 70(0.4) [2]	82.0 ± 4.1	50:20 ± 17:19	52:13 ± 19:44	69:55 ± **
70 + 70(0.6) [2]	106.0 ± 16.5	40:10 ± 33:56	43:45 ± 29:07	73:20 ± 0:21

*Concentration (mM) at Electrode Site(s) with Electrode (mA/cm^2) in parenthesis.
**Not able to Calculate

Table 11
Maximum Change from Baseline in SBP and Time to Maximum Change
Mean (± SD)

TD Treatment* [N]	Baseline SBP (mmHg)	Maximum SBP (mmHg)	Change in SBP (mmHg)	Time from Start to Max (min:sec)
Placebo[33]	121.1 ± 10.8	130.3 ± 12.3	9.3 ± 6.6	26:24 ± 18:02
35. (0.4) [4]	113.8 ± 9.1	139.3 ± 6.8	25.5 ± 10.1	43:10 ± 6:47
35 (0.6) [4]	122.5 ± 11.7	161.8 ± 7.6	39.3 ± 9.4	37:55 ± 2:22
35 + 35(0.4) [3]	125.0 ± 12.1	159.0 ± 12.0	34.0 ± 6.2	53:48 ± 34:13
35 + 35(0.6) [4]	121.8 ± 4.1	162.0 ± 14.1	40.3 ± 14.1	48:16 ± 9:20
35 + 70(0.4) [4]	116.8 ± 3.1	154.0 ± 8.1	37.3 ± 7.8	40:24 ± 4:58
70 (0.4) [4]	122.3 ± 2.5	153.0 ± 13.2	30.8 ± 14.4	38:05 ± 8:11
70 (0.6) [3]	121.3 ± 12.0	157.7 ± 12.1	36.3 ± 0.6	44:57 ± 15:18
70 (0.8) [3]	122.7 ± 8.5	167.6 ± 11.8	45.0 ± 3.6	46:52 ± 11:00
70 + 70(0.4) [2]	106.5 ± 2.1	138.0 ± 8.5	31.5 ± 6.4	50:28 ± 4:39
70 + 70(0.6) [2]	118.5 ± 6.4	154.5 ± 16.3	35.5 ± 10.0	34:00 ± 3:04

*Concentration (mM) at Electrode Site(s) with Electrode (mA/cm^2) in parenthesis.

Table 12
Maximum Change from Baseline in DBP and Time to Maximum Change
Mean (± SD)

TD Treatment* [N]	Baseline DBP (mmHg)	Minimum DBP (mmHg)	Change in DBP (mmHg)	Time to Max Change (min:sec)
Placebo [33]	65.5 ± 7.3	59.7 ± 7.2	-5.8 ± 2.7	23:37 ± 16:32
35 (0.4) [4]	66.3 ± 5.3	53.3 ± 3.0	-13.0 ± 4.8	41:25 ± 14:29
35 (0.6) [4]	63.5 ± 10.4	54.0 ± 8.3	-9.5 ± 3.5	16:16 ± 5:14
35 + 35(0.4) [3]	64.7 ± 11.6	53.7 ± 11.6	-11.0 ± 3.6	21:48 ± 9:15
35 + 35(0.6) [4]	65.0 ± 8.0	52.3 ± 8.9	-12.8 ± 4.0	59:46 ± 20:43
35 + 70(0.4) [4]	61.3 ± 5.3	54.5 ± 2.6	-6.8 ± 5.6	20:54 ± 6:51
70 (0.4) [4]	61.5 ± 7.3	54.8 ± 3.7	-6.8 ± 4.5	24:39 ± 24:18
70 (0.6) [3]	62.0 ± 10.1	55.3 ± 7.6	-6.7 ± 2.5	43:37 ± 41:40
70 (0.8) [3]	62.3 ± 11.0	53.0 ± 9.0	-9.3 ± 6.4	33:12 ± 22:28
70 + 70(0.4) [2]	57.0 ± 0.0	47.5 ± 4.9	-9.5 ± 4.9	25:58 ± 16:41
70 + 70(0.6) [2]	63.5 ± 2.1	49.0 ± 8.5	-14.5 ± 6.4	45:00 ± 6:50

*Concentration (mM) at Electrode Site(s) with Electrode (mA/cm^2) in parenthesis.

Safety Data: The most frequently occurring adverse events from TD arbutamine (N=33) were: application site reaction (N=31, 93.9%); palpitations (N=21, 63.6%); tachycardia (N=16, 48.5%); paresthesia (N=5, 15.2%); headache (N=4, 12.1%); site pain (N=2, 6.1%); fatigue (N=2, 6.1%); and tremor (N=2, 6.1%). The reactions to placebo TD (N=33) were as follows: application site reaction (N=32, 97%); and paresthesia (N=3, 9.1%). Most subjects experienced skin irritation that persisted for up to 24 hours after drug administration. There were no reports of paradoxical hypotension or hypokalemia.

Table 13
Baseline Mean (± SD) ECG response to Arbutamine TD

Dose (µg/kg/min) [N]	Mean Change in QRS Interval (m.sec)	Mean Change in PR Interval (m.sec)	Mean Change in QT Interval (m.sec)	Mean Change in QT_c Interval (m.sec)
35 (0.4) [4]	6.0 ± 8.0	-40.3 ± 14.5	--------	-------
35 (0.6) [4]	-1.7 ± 9.2	-35.7 ± 18.2	--------	-------
35 + 35(0.4) [3]	-0.4 ± 8.6	-28.0 ± 2.3	-20.0 ± 8.8	73.3 ± 17.6
35 + 35(0.6) [4]	-9.0 ± 3.3	-44.0 ± 9.3	-55.6 ± 13.9	55.6 ± 13.5
35 + 70(0.4) [4]	2.2 ± 9.7	-37.7 ± 12.4	-33.3 ± 19.1	57.5 ± 14.5
70 (0.4) [4]	-4.7 ± 1.3	-24.7 ± 8.2	--------	-------
70 (0.6) [3]	-1.3 ± 9.3	-24.4 ± 0.8	--------	-------
70 (0.8) [3]	-4.9 ± 8.9	-32.0 ± 11.9	-38.3 ± 16.5	63.3 ± 9.4
70 + 70(0.4) [2]	-10.7 ± 9.4	-40.7 ± 4.7	-37.5 ± 22.5	52.5 ± 21.3
70 + 70(0.6) [2]	-2.3 ± 0.5	-30.8 ± 17.2	--------	-------

COMMENTS:

1. Heart Rate (HR): The threshold intravenous infusion rate to produce notable changes in HR over placebo was 0.0224 ug/kg/min. Starting from the 0.0448 ug/kg/min rate, changes in HR appeared linear with dose. The highest HR of 134 ± 9.5 bpm was attained with the highest infusion of 0.1792 ug/kg/min **(equivalent to 5.73 ug/kg)**. However, this HR response was less than that seen during ETT where HR averaged 189.9 ± 4.6 bpm (x .85 = 161.4, average target rate).

   With the three highest IV doses, 30 minutes were required to reach the maximum HR. In assessing the decline in HR after infusion termination, only the 0.1792 ug/kg/min data (N=3) should be considered since HR increases with lower doses were not high enough to easily distinguish between HR in decline from drug versus physiologic HR. Thus, it took roughly 14 minutes for the heart rate increase to decline by 50%. The sponsor estimates the arbutamine half-life to be 8 minutes.

   The sponsor often states that a "steady-state" was observed with respect to HR rise. However, this claim is difficult to interpret given that maximal HRs for the 0.04438, 0.0896, and 0.1792 doses occurred around the time of infusion termination.

   All of the transdermal treatments produced HR changes of at least 25-54 bpm. Increases in current appeared to increase HR as effectively as increasing electrode concentration. The onset of maximal HR varied from 34 to 54 minutes (recall TD time of administration was 32 minutes). The time to 50% decrease in HR varied from 42 to 73 minutes.

2. Systolic Blood Pressure (SBP): With the intravenous infusion, increases in SBP over placebo were first noted at the 0.0112 ug/kg/min concentration. Starting from that dose, there were gradual increases in SBP with increasing doses, although not linear with dose. Again, the highest increase in SBP occurred with the highest (0.1792) dose. As with the HR data, the increase in SBP seen with the 0.1792 dose of 47.3 ± 21.3 mmHg was much less than that seen with the ETT, 72.5 ± 14.6 mmHg.

   The changes in SBP observed with the transdermal treatments did not appear dose-proportionate.

3. Diastolic Blood Pressure (DBP): With the intravenous data, changes in DBP did not appear related to dose, as even the lowest dose infusion of 0.0007 ug/kg/min appeared to decrease DBP somewhat greater than placebo. Again, the greatest decrease in DBP occurred with the highest dose of 0.1792. However, contrary to the ETT which produced an **increase** in the DBP of 8.9 ± 13.0 mmHg, the highest dose of arbutamine produced a **decrease** in the DBP of -10.7 ± 6.7 mmHg.

4. Safety Data:

A. Adverse Reactions: As would be expected with a catecholamine-like agent, the predominant adverse reactions reported with both IV and TD arbutamine were tachycardia and palpitations. The greater reports of "palpitations" with TD arbutamine may be because while all but one of the TD arbutamine treatments resulted in HRs over 100, only two of the IV arbutamine treatments raised HRs over 100.

There were no paradoxical hypotensive reactions, hypokalemic readings or reports of tremors or arrhythmias.

B. QT_c Interval prolonging: a very preliminary observation: A potentially disturbing effect of arbutamine on the QT_c Interval was observed. During the ETT, subjects' HR averaged 189.9 bpm (N=34), and their QT_c interval was prolonged a maximum of **32.1** milliseconds. However, for subjects on IV arbutamine, the 0.0896 ug/kg/min dose (N=4) raised HR to 108.1 with a maximal QT_c prolongation of **66.7** milliseconds while the 0.1792 ug/kg/min dose (N=3) raised HR to 134.4 with a maximal QT_c prolongation of **55.0** milliseconds. TD arbutamine treatments resulted in maximal QT_c prolongations ranging from **52.5 to 73.3** milliseconds. ETT resulted in a maximal QTc interval ≥440 msec in 3/15 subjects (20%); for IV arbutamine (from the 0.0448 dose and up),maximal QTc ≥440 msec occurred in 9/11 subjects (82%); TD arbutamine raised QTc ≥440 msec in 10/18 subjects (55%).

The QT_c is calculated by dividing the QT interval by the square root of the RR interval. Therefore as HR increases, the QT_c interval increases. Thus arbutamine's increase in the QT_c Interval is potentially even more problematic if arbutamine doses are pushed in an attempt to recreate the HRs seen with ETT.

5. Efficacy Questions: In this study, arbutamine did not reach target HR or mimic the effects of ETT on SBP and DBP. Thus, this reviewer is concerned that these differences may result in less cardiac work, leading to an underdiagnosis of perfusion/filling defects uncovered in non-invasive tests. For example, equations for both *left ventricular stroke work* and *left cardiac work* utilize *Mean Arterial Pressure* (MAP) in their numerators. Since MAP is calculated as MAP = DBP + 1/3(SBP - DBP), these differences in DBP and SBP as seen with arbutamine versus ETT may be significant.

PROTOCOL 0104: CLINICAL STUDY REPORT CS0104

DESIGN SUMMARY:

This was a single-blind, single-dose, randomized, placebo-controlled study to determine the safety, pharmacokinetics, and pharmacodynamics of intravenous (IV) and transdermal (TD) arbutamine in 8 normal white male volunteers. The data collected were used for the development of the ESA System's computerized closed loop algorithm.

PROTOCOL

• Enrollment Criteria

The Inclusions and Exclusions were as per PROTOCOL 0102 with the difference that male subjects were to be between 18 and **30** years of age.

• Qualifying Criteria

As per PROTOCOL 0102, subjects performed a symptom limited exercise tolerance test (ETT) (Bruce protocol in this case) to determine if they could achieve their predicted maximal heart rate (HR) of 220-age.

• Treatment Regimen

Between 5 and 14 days prior to study initiation, all subjects performed an ETT. On Day 1, each subject received either a placebo or an arbutamine **0.3** ug/kg/min IV infusion. for **20** minutes or until HR reach 85% of maximal (predicted from the ETT) for $\geq$ 30 seconds. After a washout period on Day 2, subjects received (on Day 3) either two 70 mM arbutamine electrodes at 1.0 mA/cm^2 or two placebo electrodes at 1.0 mA/cm^2 for either 10 minutes or until HR increased to 85% of the subjects ETT predicted rate for $\geq$ 30 seconds. The IV doses were administered using a Perfusor syringe pump.

Of the 8 subjects, subjects #4 and #6 were randomized to placebo.

• Endpoints/Equipment used

HR, systolic blood pressures (SBP), and diastolic blood pressures (DBP) were measured at the screening visits using methods routinely used by the investigator. On treatment days, HR, SBP, and DBP were measured using a Clinical Research Prototype ESA System. HR was measured every 5 seconds and SBP/DBP were measured at -10, -5, and 0 minutes during a 10 minute baseline period, every 2 minutes during drug or placebo administration, and at the following times during the recovery period: 2, 6, 10 and 30 minutes and/or when the HR and SBP/DBP returned to baseline, depending on which took longer to occur.

All ECGs were obtained using a Marquette Case 12 Model ECG Monitor. Twelve lead ECGs were obtained at the same time as SBP/DBP measurements or when clinically indicated. The sponsor states that due to fusion of the T and P waves at high HR, and because accurate measurement of the QT interval is not possible during changing HR (using the Marquette Case 12 Model), a cardiologist manually measured the QT and QT_c intervals.

- **Statistical Procedures**

- **Data Set Analyzed**

All eight subjects completed the trial.

- **Handling of Missing Data**

HR, SBP, and DBP data were calculated for IV arbutamine for only 5 of 6 subjects since subject #3's arbutamine infusion was terminated after achieving SBP of 193 after only 5 minutes.

Due to floppy disk processing errors by the investigator, HR and SBP/DBP data following TD arbutamine in subjects 1 and 3 were inadvertently lost. Therefore, the TD data for subjects 1 and 3 and not included in the analysis of HR and SBP/DBP.

- **Analyses performed**

None described.

- **Subject Characteristics**

Eight adult male caucasian subjects aged 23.5 $\pm$ 3.6 years (mean $\pm$ SD), of average height (179.9 $\pm$ 3.8 cm, mean $\pm$ SD) and weight (75.4 $\pm$ 7.1 Kg, mean $\pm$ SD) .

APPEARS THIS WAY
ON ORIGINAL

RESULTS: 1. ARBUTAMINE IV INFUSION

Maximum average ETT HR was 186.9 + 2.6 bpm (mean + standard deviation). The sponsor states ECG and SBP/DBP data during ETT were not collected.

TABLE 1
Maximum Change from Baseline in Heart Rate (HR)
Mean (± SD)

Dose (µg/kg/min)	N	Baseline HR (bpm)	Maximum HR (bpm)	HR_{CHANGE} (bpm)
Placebo	2	60.3 ± 10.5	68.7 ± 14.9	8.5 ± 4.3
0.3	5	70.5 ± 7.3	140.2 ± 11.5	69.6 ± 10.1

TABLE 2
Time to Maximum HR, and Time From End of IV Infusion To A Percent Decrease in HR
Mean (± SD)

Dose [N] (µg/kg/min)	T_{max} to Max HR (min:sec)	10% (min:sec)	20% (min:sec)	50% (min:sec)
Placebo [2]	33:50 ± 15:40	17:18 ± 11:2	17:20 ± 11:26	24:10 ± 2:00
0.3 [5]	16:21 ± 3:26	0:43 ± 1:37	3:03 ± 2:53	13:02 ± 5:17

Table 3
Maximum Change from Baseline in Systolic Blood Pressure (SBP)* and Time to Maximum Change
Mean (± SD)

Dose [N] (ug/kg/min)	Baseline SBP (mm Hg)	Maximum SBP (mm Hg)	Change from Base to Max (mm Hg)	Time from Start to Max SBP (min:sec)
Placebo [2]	114.5 ± 12.0	121.0. ± 11.3	6.5 ± 0.7	29:33 ± 3:00
0.3 [5]	121.8 ± 11.5	163.8 ± 12.5	42.0 ± 10.4	13:07 ± 9:35

*Subject #3 is excluded because of a rise in SBP to 193 mm Hg after 5 minutes of arbutamine infusion.

Table 4
Change from Baseline in Diastolic Blood Pressure (DBP) and Time to Maximum Change
Mean (± SD)

Dose [N] (ug/kg/min)	Baseline DBP (mm Hg)	Minimum DBP (mm Hg)	Change from Base to Max (mm Hg)	Time from Start to Min DBP (min:sec)
Placebo [2]	61.0 ± 15.6	51.5 ± 3.5	-9.5 ± 12.0	19:25 ± 16:58
0.3 [5]	68.6 ± 8.8	50.4 ± 9.4	-18.2 ± 2.7	10:43 ± 5:33

Table 5
Maximum Change from Baseline in Pressure Rate Product (PRP*) and Time to Maximum Change
Mean (± SD)

Dose [N] (ug/kg/min)	Baseline PRP (mm Hg x bpm)	Maximum PRP (mm Hg x bpm)	Time to Max PRP (min:sec)
Placebo [2]	6930 ± 2443	7435 ± 2403	32:25 ± 10:15
0.3 [5]	8626 ± 1322	21919 ± 1672	17:31 ± 4:17

*PRP = (SBP x HR)

Safety Data: The most frequently occurring adverse events from IV arbutamine (N=6) were: palpitations (N=6, 100%); abdominal pain (N=2, 33.3%); tremor (N=1, 16.7%); chest pain (no further documentation about this)(N=1, 16.7%); hypertension (N=1, 16.7%); malaise (N=1, 16.7%); pharyngitis (N=1, 16.7%).

Subject #3 experienced a rise in SBP to 193 mm Hg after only 5 minutes of IV arbutamine infusion. The subject received 0.5 mg propranolol IV and blood pressure decreased to "normal" (sponsor's language) within 5 or 9 minutes (depending on which section of the sponsor's report is referred to). None of subject #3's lab, age, height, weight, ECG, ETT, HR or DBP data offer clues as to why this episode occurred.

The immediate post arbutamine plasma potassium decreased by 21%: (in mEq/L) from 4.1 to 3.5; 4.3 to 3.4; 3.9 to 3.1; and 3.9 to 3.0 (no potassium data for subject #3).

Table 6
Baseline Mean (± SD) ECG response to Arbutamine Infusion

Dose (µg/kg/min) [N]	Mean Change in QRS Interval (m.sec)	Mean Change in PR Interval (m.sec)	Mean Change in QT Interval (m.sec)	Mean Change in QT_c Interval (m.sec)
Placebo [2]	-4.0 ± 11.3	-10.7 ± 9.4	-18.3 ± 2.4	16.7 ± 4.7
0.3 [5]	-8.7 ± 5.0	-42.8 ± 16.7	-74.0 ± 42.9	81.7 ± 28.6

Pharmacokinetics: Arbutamine plasma concentrations measured immediately prior to the end of the twenty minute 0.3 ug/kg/min infusion ranged from 2.88 to 5.73 ng/ml. The mean total body plasma Clearance was 3.9 L/hr/kg with a half-life of 8.5 minutes.

ESA Model Parameters and Definitions:

Mgain = Model gain is an index that relates the change in HR to the change in infusion rate during the infusion period.

onDelay = time from start of infusion to initial HR response (onset delay)

$t_{1/2}$ = the onset time constant is an index which describes the exponential rate at which the HR increases after the initial onset delay

offDelay = time from end of infusion before HR starts to decrease (offset delay)

$t_{1/2}d$ = the offset time constant is an index of the exponential rate at which HR decreases after the offset delay

Noise = standard deviation of the difference between filtered (running average filter with outlier clipping) and measured HR during the infusion period (i.e., a measure of HR variability).

TABLE 7
Initial ESA Parameter Estimates from IV Arbutamine Data

n=11*	MGain (bpm•µg^{-1}•kg•min)	onDelay (sec)	$t_{1/2}$ (min)	offDelay (sec)	$t_{1/2}d$ (min)	Noise (bpm)
mean	215	51	2.22	39	11.21	7.22
minimum						
maximum						
SD	39	5	0.33	31	3.28	4.16

RESULTS - 2. ARBUTAMINE TRANSDERMAL (TD)

TABLE 8
Maximum Change from Baseline in HR and Time to Maximum Change
Mean (± SD)

TD Dose (mM)	N	Baseline HR (bpm)	Maximum HR (bpm)	HR CHANGE (bpm)
Placebo	2	58.5 ± 6.2	67.5 ± 8.4	9.1 ± 2.2
70 +70	4	73.9 ± 11.5	115.7 ± 9.6	41.8 ± 5.8

TABLE 9
Time to Maximum HR and Time From End of TD Administration To A Percent Decrease in HR
Mean (± SD)

Dose [N] (mM)	Time to Max HR (min:sec)	10% (min:sec)	20% (min:sec)	50% (min:sec)
Placebo [2]	13:48 ± 17:51	4:13 ± 17:44	6:00 ± 20:02	21:28 ± 8:11
70 + 70 [4]	39::10 ± 16:46	35:01 ± 19:55	47:53 ± 24:32	72:35 ± 23:03

Table 10
Maximum Change from Baseline in SBP and Time to Maximum Change
Mean (± SD)

Dose [N] (mM)	Baseline SBP (mm Hg)	Maximum SBP (mm Hg)	Change from Base to Max (mm Hg)	Time from Start to Max SBP (min:sec)
Placebo [2]	120.0 ± 17.0	121.5. ± 14.8	1.5 ± 2.1	15:23 ± 15:23
70 + 70 [4]	114.8 ± 10.0	153.3 ± 11.5	38.5 ± 15.3	28:08 ± 22:52

Table 11
Change from Baseline in DBP and Time to Maximum Change
Mean (± SD)

Dose [N] (mM)	Baseline DBP (mm Hg)	Minimum DBP (mm Hg)	Change from Base to Min (mm Hg)	Time from Start to Min DBP (min:sec)
Placebo [2]	59.0 ± 12.7	49.0 ± 14.1	-10.0 ± 1.4	19:23 ± 10:05
70 + 70 [4]	63.0 ± 5.0	51.5 ± 5.0	-11.5 ± 6.9	50:11 ± 47:39

Table 12
Maximum Change from Baseline in Pressure Rate Product (PRP*) and Time to Maximum Change Mean (± SD)

Dose [N] (mM)	Baseline PRP (mm Hg x bpm)	Maximum PRP (mm Hg x bpm)	Time to Max PRP (min:sec)
Placebo [2]	7005 ± 1264	7519 ± 1438	30:23 ± 9:01
70 + 70 [4]	8106 ± 740	16831 ± 2341	36:08 ± 16:58

*PRP = (SBP x HR)

Safety Data: The most frequently occurring adverse events from TD arbutamine (N=6) were: application site reaction (N=6, 100%); palpitations (N=6, 100%); abdominal pain (N=1, 16.7%); malaise (N=1, 16.7%); headache (N=1, 16.7%); and conjunctivitis (N=1, 16.7%). The reactions to placebo TD (N=2) were limited to application site reaction (N=2, 100%). In subjects administered drug electrodes, one subject experienced minimal erythema which lasted over 24 hours while the remaining 5 subjects experienced definitive erythema (some with papules) lasting over 24 hours. In contrast, only one of the two placebo electrode treated subjects experienced any erythema (minimal) and this resolved within 24 hours.

The immediate post-test plasma potassium decreased by 4% for TD arbutamine as compared to potassium values prior to TD administration.

Table 13
Baseline Mean (± SD) ECG response to Arbutamine TD

Dose (mM) [N]	Mean Change in QRS Interval (m.sec)	Mean Change in PR Interval (m.sec)	Mean Change in QT Interval (m.sec)	Mean Change in QT_c Interval (m.sec)
Placebo [2]	24.7 ± 46.2	12.7 ± 4.7	-3.3	23.3
70 + 70 [5]	-7.9 ± 4.7	-25.8 ± 9.1	-35.6 ± 10.9	53.9 ± 13.9

COMMENTS:

1. Heart Rate (HR): IV Data: In Protocol 0102, HR increased by 71.8 bpm (N=3) with the 0.1792 ug/kg/min dose given over 32 minutes (5.73 ug/kg total dose). In this study, HR increased by 70.5 bpm (N=5) with 0.3 ug/kg/min dose over 20 minutes **(6 ug/kg total dose)**. However, the 0.3 ug/kg dose essentially halved the time required to achieved this maximal HR (29:35 min:sec vs. 16:21 min:sec). Both doses required 13-14 minutes for HR to decline by 50% after terminating IV infusion. However, as with the 0.1792 dose, the goal of 85% of ETT HR was never achieved (targets ranged from 157-163 bpm; HRs achieved ranged from 120.4 - 148.8 bpm).

TD Data: Although increasing HR from baseline by about 42 bpm, the TD form continued to demonstrate slow onset (Tmax of 39 minutes [recall a 10 minute TD delivery time]) and a decrease of 50% in HR requiring 72 minutes after infusion termination.

2. Systolic Blood Pressure (SBP): IV Data: Including subject #3 (who was terminated after only a 5 minute infusion because of an increase in SBP to 193 mm Hg), the 0.3 dose increased SBP by 46.9 mm Hg (N=6), whereas in Protocol 0102, the 0.1792 dose increased SBP by 47.3 mm Hg (N=3). However, the Tmax for the 0.3 dose was once again shorter: 13 minutes versus 20 minutes for the 0.1792 dose. Again, the increase in SBP was much less than that seen with the ETT.

3. Diastolic Blood Pressure (DBP): IV Data: Whereas the 0.1792 dose decreased DBP by 10.7 mm Hg, the 0.3 dose demonstrated a greater decrease of 18.2 mm Hg.

4. Safety Data:

A. Adverse Reactions: Hypokalemia: In Protocol 0102, the 0.1792 dose increased serum potassium by 0.36 mEq/L. However, in this study, the 0.3 dose caused a reduction in serum potassium by 21%.

B. Other Events: The most frequently occurring adverse event from both IV and TD arbutamine was palpitations (100% of subjects studied. All subjects reported application site reaction following the TD arbutamine, symptoms lasting up to 24 hours.

One subject (#3) had a rise in SBP to 193 mm Hg after only 5 minutes into the IV arbutamine infusion. The subject received 0.5 mg propranolol IV and blood pressure decreased to "normal" (sponsor's language) within 5 or 9 minutes (depending on which section of the investigator's report is referred to). No hypotensive events were reported.

C. QTc Interval Prolonging: During the ETT in Protocol 0102, the QTc interval increased by 32 msec; the 0.1792 dose and the 0.3 dose increased the QTc by 55 and 82 msec respectively (both attained at HRs below target rates). Thus a potential concern remains regarding arbutamine's effects on the QTc interval. This concern could be even more problematic if arbutamine indeed causes hypokalemia routinely at higher (0.3 ug/kg/min) doses (hypokalemia can itself contribute to QTc prolongation).

5. Efficacy Questions: Again, as noted in the COMMENTS section of protocol 0102, arbutamine's inability to reach target HR, its effects on SBP less than ETT, and its effects to decrease DBP are of concern in that a suboptimal stress test could result, potentially underdiagnosing conditions such as coronary artery disease.

PROTOCOL 0105: CLINICAL STUDY REPORT CS0105

DESIGN SUMMARY:

This was an open-label, randomized, crossover study of intermittent doses of intravenous (IV) and transdermal (TD) arbutamine in 8 normal white male volunteers. The sponsor considers this regimen to be closer to the non-steady state infusion profile resultant from a delivery system where the operator can stop/start the infusion at random intervals.

PROTOCOL

• Enrollment Criteria

The Inclusions and Exclusions were as per PROTOCOL 0104.

• Qualifying Criteria

As per PROTOCOLs 0102 and 0104, subjects performed a symptom limited exercise tolerance test (ETT) to determine if they could achieve their predicted maximal heart rate (HR) of 220-age.

• Treatment Regimen

On Day 1, all subjects received intermittent IV doses of arbutamine (0.05, 0.10 and 0.20 µg/kg/min; **total dose = 1.75 µg/kg**) given over 5 minutes at each infusion rate with a 20 minute recovery between doses. The order of the dosing regimen was randomized for each subject. On Day 3, following a one day washout, subjects were divided into Group 1 (N=4) and Group 2 (N=4). Group 1 received 5 minute periods of drug administration applied at 0.8, 1.0 and 1.2 mA/cm^2, in random order, with a 20 minute recovery period between doses. Group 2 received arbutamine in a set of five 1 minute pulses with 1 minute washout between each current application applied at 0.8, 1.0 and 1.2 mA/cm^2, administered in random order. All TD doses were administered using one 70 mM arbutamine electrode. A loading current of 1.0 mA/cm^2 was applied for 3 minutes followed by a 3 minute washout period.

• Endpoints/Equipment used

HR, systolic blood pressures (SBP), and diastolic blood pressures (DBP) were measured at the screening visits using methods routinely used by the investigator. On treatment days, HR, SBP, and DBP were measured using a Clinical Research Prototype ESA System. HR was measured every 5 seconds and SBP/DBP were measured at -10, -5, and 0 minutes during a 10 minute baseline period, every 2 minutes during each drug administration period. No ECG readings were reported by the investigator.

- **Statistical Procedures**

- **Data Set Analyzed**

All eight subjects completed the trial.

- **Analyses performed**

None described.

- **Subject Characteristics**

Eight adult male caucasian subjects aged 25.0 ± 4.5 years (mean ± SD), of average height (177.8 ± 7.9 cm, mean ± SD) and weight (71.8 ± 4.4 Kg, mean ± SD) .

RESULTS: 1. ARBUTAMINE IV INFUSION

Maximum average ETT HR was 187.6 + 2.7 bpm (mean + SD). The sponsor states ECG and SBP data during ETT were not collected.

TABLE 1
Maximum Change from Baseline in Heart Rate (HR)
Mean (± SD)

Dose (µg/kg/min)	N	Baseline HR (bpm)	Maximum HR (bpm)	HR CHANGE (bpm)
0.05	8	66.2 ± 6.1	83.6 ± 9.0	17.4 ± 5.5
0.10	8	66.2 ± 6.1	90.2 ± 9.2	24.0 ± 7.9
0.20	8	66.2± 6.1	106.3 ± 5.7	40.1 ± 9.6

TABLE 2
Time to Maximum HR and Time From End of IV Infusion To A Percent Decrease in HR
Mean (± SD)

Dose [N] (µg/kg/min)	Time to Max HR (min:sec)	10% (min:sec)	20% (min:sec)	50% (min:sec)
0.05 [8]	3:51 ± 1:42	-0:33 ± 2:02	-0:08 ± 2:06	7:49 ± 6:57
0.10 [8]	5:26 ± 1:11	0:41 ± 0:57	0:52 ± 1:00	7:13 ± 5:08
0.20 [8]	5:51 ± 0:52	1:34 ± 0:59	2:03 ± 1:16	5:48 ± 3:25

Table 3
Maximum Change from Baseline in Systolic Blood Pressure (SBP) and Time to Maximum Change; Mean (± SD)

Dose [N] (ug/kg/min)	Baseline SBP (mm Hg)	Maximum SBP (mm Hg)	Change from Base to Max (mm Hg)	Time from Start to Max SBP (min:sec)
0.05 [8]	115.9 ± 12.6	133.5. ± 9.2	17.6 ± 5.2	6:30 ± 2:43
0.10 [8]	115.9 ± 12.6	143.6 ± 9.3	27.8 ± 11.8	5:32 ± 1:22
0.20 [8]	115.9 ± 12.6	152.6 ± 12.2	36.8 ± 12.5	6:49 ± 1:06

Table 4
Change from Baseline in Diastolic Blood Pressure (DBP) and Time to Maximum Change
Mean (± SD)

Dose [N] (ug/kg/min)	Baseline DBP (mm Hg)	Minimum DBP (mm Hg)	Change from Base to Min (mm Hg)	Time from Start to Min DBP (min:sec)
0.05 [8]	63.5 ± 4.4	57.4 ± 6.4	-6.1 ± 5.2	11:26 ± 6:32
0.10 [8]	63.5 ± 4.4	54.5 ± 6.1	-9.0 ± 3.7	9:51 ± 7:12
0.20 [8]	63.5 ± 4.4	51.3 ± 10.8	-12.3 ± 7.6	5:41 ± 4:19

COMMENT: As will be discussed in the "COMMENTS" section, the sponsor has assumed one baseline HR, SBP, DBP from which to measure the effects of the three infusions. However, given that the half-life of the drug is 8 to 8.5 minutes, presumably a 20 minute washout period would be insufficient. In fact, upon inspecting graphical representations of the HR, SBP and DBP data during the three infusions (or the three TD regimens), it is clear that using one baseline from which to measure effect is inappropriate since the baseline shifted throughout. Thus, the sponsor's data should be evaluated qualitatively, not quantitatively. Witness (e.g.) the sponsor's own statement that "Mean SBP at 11-20 minutes post infusion was within ± 13 mm Hg of baseline, for all infusions, and within ± 10 mm Hg of baseline for 87% (21/24) of infusions, at 11-20 minutes post infusion."

RESULTS - 2. ARBUTAMINE TRANSDERMAL (TD)

Since there were no apparent differences between Group 1 (sustained) and Group 2 (pulsed) in the effect on HR and BP after TD arbutamine,the data from the two groups are combined

TABLE 5
Maximum Change From Baseline in HR, SBP, and DBP
Following TD Administration
(Mean ± SD)

Current (mA/cm^2)	n	HR (bpm)	SBP (mmHg)	DBP (mmHg)
0.8	8	20.7 ± 12.1	25.9 ± 10.6	-8.6 ± 3.2
1.0	8	22.4 ± 17.8	26.3 ± 13.8	-9.9 ± 4.7
1.2	8	22.5 ± 18.9	22.9 ± 15.4	-10.1 ± 3.0

TABLE 6
Time to Maximum HR and Time From End of TD Administration To A Percent Decrease in HR Change
Mean (± SD)

Dose [N] (mA/cm^2)	T_{max} to Max HR (min:sec)	10% (min:sec)	20% (min:sec)	50% (min:sec)
0.8 [8]	14:02 ± 6:26	10:53 ± 5:11	17:33 ± 6:06	32:10 ± 17:48
1.0 [8]	16:45 ± 8:19	10:32 ± 8:47	16:16 ± 8:32	23:23 ± 6:27
1.2 [8]	17:28 ± 11:43	8:31 ± 9:12	11:26 ± 9:05	20:30 ± 12:06

Safety Data for IV/TD Administration:

TABLE 7
Summary of Adverse Events With IV Administration

Adverse Event (Who Preferred Term)(n=8)	n	%
Palpitation	8	100
Headache	3	38
Flushing	2	25
Pain	1	13
Paresthesia (skin)	1	13
Chest pain precordial	1	13
Hypesthesia	1	13
Abdominal pain	1	13
Nausea	1	13

TABLE 8
Summary of Adverse Events with TD Administration

Adverse Event (Who Preferred Term)(n=8)	n	%
Palpitation	6	75
Application site reaction	6	75
Back pain	2	25
Malaise	2	25
Dizziness	1	13
Twitching	1	13
Nausea	1	13

Of the 8 subjects studied, 7 subjects exhibited at least one LDH value during the course of the study which was below the normal range. None of these levels was considered to be clinically relevant.

No trends in the plasma potassium level over the course of the study were detected.

Erythema, minimal edema or papules with no significant damage to superficial skin at the electrode sites was present 2 hours after sustained or pulsed administration of drug. Erythema was still evident and the superficial skin layers remained slightly glazed 24 hours after treatment. Less irritation was observed
for the indifferent electrode site and was resolved in most cases by 24 hours.

Device Results:

The HR and infusion rate data following IV arbutamine administration was used to calculate the auto-regressive, exogenous input (ARX) model parameters under nonsteady-state conditions. The nonsteady-state, investigator controlled infusion was designed to create a HR response under dynamic conditions that better approximates a closed loop infusion regimen.

The parameter definitions and estimates calculated in this study are as follows:

Model Parameters and Definitions:

Mgain = Model gain is an index that relates the change in HR to the change in infusion rate during the infusion period.

onDelay = time from start of infusion to initial HR response (onset delay)

$t_{1/2}$ = the onset time constant is an index which describes the exponential rate at which the heart rate increases after the initial onset delay

offDelay = time from end of infusion before HR starts to decrease (offset delay)

$t_{1/2}d$ = the offset time constant is an index of the exponential rate at which the heart rate decreases after the offset delay

Noise = standard deviation of the difference between filtered and measured HR during the infusion period (HR variability)

Parameter Estimates From Infusion Data:

n = 16 * infusions	Mgain (b p m • μ g $^{-1}$•kg•min)	onDelay (sec)	$t_{1/2}$ (min)	offDelay (sec)	$t_{1/2}d$ (min)	Noise (bpm)
mean	289	88	1.89	58	3.11	7.84
std dev	147	36	1.19	39	2.22	3.68

COMMENTS:

1. Data Integrity Questions:

Assumption of Stable Baseline: The sponsor has assumed one numerical baseline for HR, SBP, and DBP from which to quantify the effects of various IV/TD regimens of arbutamine. However, given the 8 to 8.5 minute half-life of arbutamine, drug could still be exerting a pharmacologic effect after only a 20 minute washout period (especially the TD dosage form since this route often results in a delayed Tmax and a delayed resolution of effect). Upon examining graphical representations of the effects of arbutamine infusions on HR, SBP, and DBP, one often sees a different baseline for all three parameters immediately before initiation of the next infusion. Thus, use of a singular baseline to quantify the effects of differing arbutamine regimens is inappropriate. The sponsor's data should be viewed as qualitative representations of the effects of differing doses of arbutamine.

No Placebo group: There was no placebo group in this study. Although not critical for this type of study, its inclusion could have assisted in better quantifying the effects of the differing arbutamine regimens, especially given the choice of an inappropriate baseline.

2. Heart Rate (HR)/Systolic Blood Pressure (SBP)/Diastolic Blood Pressure (DBP) Data: IV Data: In all cases, only qualitative observations can be made as per reasons referred to in Comment #1 above. In general, as the IV dose of Arbutamine increased, the HR and SBP increased while the DBP decreased. In previous studies (0102 and 0104), the effects of arbutamine on HR, SBP, and DBP did not mimic those effects produced by ETT.

TD Data: The effects of the TD arbutamine regimens on HR, SBP, and DBP were nearly indistinguishable (and in the absence of placebo, it could be argued whether there was any effect). As seen previously with TD administration, the Tmax and offset of HR/SBP response was delayed as compared to the IV route.

3 Safety Data:

A. Adverse Reactions: The most frequently occurring adverse event with both IV and TD arbutamine was palpitations (100% and 75%, respectively, of subjects studied). As seen in previous TD studies, subjects experienced erythema (often accompanied by papules) at the application site, most cases lasting up to 24 hours.

No trends in the potassium level over the course of the study were detected: This could possibly be due to the fact that the doses administered in the present study were lower and of shorter duration than in the previous studies.

No ECG data was provided; thus, the effects of arbutamine on the QTc interval could not be assessed. However, given the lower doses of arbutamine studied, even if ECG data had been collected, it may have been of debatable value.

APPEARS THIS WAY
ON ORIGINAL

PROTOCOL 0110: CLINICAL STUDY REPORT CS0110

DESIGN SUMMARY:

This study's purpose was to assess the pharmacodynamics and pharmacokinetics of intravenous (IV) arbutamine in normal male subject pre-treated with saline, **metoprolol**, or**propranolol**. The study was designed as an open-label, randomized, balanced three-way crossover study. Seven subjects participated with none completing all three treatment periods due to **paradoxical hypotensive reactions** observed in three of the subjects receiving arbutamine (when pre-treated with saline).

PROTOCOL

• Enrollment Criteria

The Inclusions and Exclusions were as per PROTOCOLs 0102, 0104, and 0105.

• Qualifying Criteria

As per the three previous protocols, subjects performed a symptom limited exercise tolerance test (ETT) to determine if they could achieve their predicted maximal heart rate (HR) of 220-age.

• Treatment Regimen

Three treatments **were** to be administered:

1. Treatment 1: **Normal saline** 5 ml IV injection over 3 minutes. Five minutes after pre-treatment, arbutamine was infused in 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, and 1.1 ug/kg/min **(9.75 ug/kg total dose)**for 3 minutes at each rate.

2. Treatment 2: **Propranolol** 0.075 mg/kg (total dose not to exceed 6 mg) IV injection not to exceed a rate of 1 mg/min. Five minutes after pre-treatment, arbutamine was infused as described above.

3. Treatment 3: **Metoprolol,** as three 5 mg IV injections, each infused over one minute with two minutes between each dose (total of 15 mg). Five minutes after pre-treatment, arbutamine was infused as described above.

The infusions of arbutamine were chosen to achieve an approximately 50 bpm increase in HR over 12 to 21 minutes. Infusions were administered until: 1)HR reach 85% of maximal (predicted from the ETT); SBP >220 mm Hg; the infusion rate was completed; or an intolerable adverse event occurred. Arbutamine was administered using an IVAC Model

560 volumetric infusion pump. All drug solutions were prepared within 2 hours of drug administration.

- **Endpoints/Equipment used**

HR, systolic blood pressures (SBP), and diastolic blood pressures (DBP) were measured at the screening visits using methods routinely used by the investigator. On treatment days, HR, SBP, and DBP were measured using a Clinical Research Prototype ESA System. HR was measured every 5 seconds and SBP/DBP were measured at -10, -5, and 0 minutes during a 10 minute baseline period, every 2 minutes during drug administration, and every 2 minutes for at least 30 minutes during each recovery period.

All ECGS were obtained using a Marquette Case 12 Model ECG Monitor. Twelve lead ECGs were obtained at "predetermined times" or when clinically indicated.

- **Statistical Procedures**

- **Data Set Analyzed**

Seven subjects completed the trial. Due to **paradoxical hypotensive reactions** in 3/4 people receiving normal saline pre-treatment, the study was terminated early and following subjects received these treatments:

Subject #	Saline + Arbutamine	Propranolol + Arbutamine	Metoprolol + Arbutamine
1	YES (0.6)**		
2	YES (0.4)***		YES
3		YES	YES
4	YES		
5		YES	YES
6	YES	YES	
7*		YES	

*subject 7 was a replacement for subject 1
**subject 1: arbutamine stopped at 0.6 ug/kg/min due to hypotension
***subject 2: arbutamine infusion stooped at 0.4 ug/kg/min due to hypotension

Thus a total of seven subjects received twelve treatments (4 with saline, 4 with metoprolol, and 4 with propranolol).

- **Handling of Missing Data**

HR and SBP/DBP data were not recorded for subject #1 during the recovery period due to an operator error after stopping the infusion. However, subject #1's data are included in the pharmacodynamic analysis.

- **Analyses performed**

None described.

- **Subject Characteristics**

Eight adult male caucasian subjects aged 29.7 ± 7.4 years (mean ± SD), of average height (185.2 ± 4.8 cm, mean ± SD) and weight (80.4 ± 7.1 Kg, mean ± SD) .

RESULTS:

None of the subjects demonstrated cardiovascular abnormalities during ETT.

All subjects in the propranolol and metoprolol groups received the complete arbutamine regimen (i.e., arbutamine up to 1.1 ug/kg/min). **However, in the placebo group, the infusions for subjects #1 and #2 were stopped at 0.6 ug/kg/min and 0.4 ug/kg/min, respectively.**

TABLE 1
Maximum Change from Baseline in Heart Rate (HR)
Mean (± SD)

Pre-Treatment	N	Baseline HR (bpm)	Maximum HR (bpm)	HR CHANGE (bpm)
Saline	4	61.9 ± 5.2	120.2 ± 9.1	58.3 ± 13.9
Metoprolol	4	65.8 ± 7.9	126.3 ± 7.7	60.5 ± 7.8
Propranolol	4	61.2 ± 7.0	82.5 ± 18.0	21.3 ± 13.0

TABLE 2
Time to Maximum HR and Time From End of Infusion To A Percent Decrease in HR
Mean (± SD) (N=4)

Pre-Treatment	T_{max} to Max HR (min:sec)	10% (min:sec)	20% (min:sec)	50% (min:sec)
Saline	17:04 ± 5:24	3:31 ± 4:33	6:53 ± 6:11	13:55 ± 1:55
Metoprolol	21:54 ± 0:48	1:39 ± 0:42	2:28 ± 1:16	12:08 ± 5:16
Propranolol	21:50 ± 0:39	1:00 ± 0:39	1:08 ± 0:40	7:24 ± 3:49

Table 3

Maximum POSITIVE Change from Baseline in Systolic Blood Pressure (SBP) and Time to Maximum Change
Mean (± SD)

Pre-Treatment Dose (N)	Baseline SBP (mm Hg)	Maximum SBP (mm Hg)	Change from Base to Max (mm Hg)	Time from Start to Max SBP (min)
Saline (4)	119 ± 10	148 ± 23	29 ± 18	12 ± 9
Metoprolol (4)	118 ± 8	162 ± 15	44 ± 13	20 ± 3
Propranolol (4)	107 ± 6	146 ± 13	39 ± 7	22 ± 0.5

Table 4

Change from Baseline in Diastolic Blood Pressure (DBP) and Time to Maximum Change
Mean (± SD)

Pre-Treatment Dose (N)	Baseline DBP (mm Hg)	Minimum DBP (mm Hg)	Change from Base to Min (mm Hg)	Time from Start to Min DBP (min:sec)
Saline (4)	64 ± 6	41 ± 6	-23 ± 4	14 ± 3
Metoprolol (4)	62 ± 6	51 ± 7	-11 ± 6	13 ± 6
Propranolol (4)	67 ± 8	63 ± 5	-4 ± 4	26 ± 8

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TABLE 5

Arbutamine Plasma Concentrations (ng/ml) at the End of the Three Treatments

Subject	Pre-TX	End of Infus	+2 minutes	+ 6 minutes
1	placebo	5.50	2.93	1.71
2	placebo	2.58	2.39	0.92
4	placebo	10.99	8.93	4.02
7	placebo	11.97	8.91	3.90
mean ± SD		**7.8 ± 4.5**	**5.8 ± 3.6**	**2.6 ± 1.6**
2	metoprolol	SNA*	6.97	SNA*
3	metoprolol	8.72	8.02	3.70
4	metoprolol	10.41	5.75	3.15
6	metoprolol	9.92	7.10	4.27
mean ± SD		**9.7 ± 0.9**	**7.0 ± 0.9**	**3.7 ± 0.6**
3	propranolol	SNA*	8.79	4.93
5	propranolol	9.72	7.64	3.79
6	propranolol	7.39	9.33	4.25
7	propranolol	5.80	5.82	7.26
mean ± SD		**7.6 ± 2.0**	**7.9 ± 1.6**	**5.0 ± 1.5**

*SNA = sample not available for analysis

Safety Data:

Given that 3/4 placebo subjects suffered a hypotensive event, the quantification of only POSITIVE SBP changes obviously is insufficient. Since the firm did not provide the complete numerical raw data, Table 4 below contains an approximation of the magnitude of the hypotensive effects of arbutamine in these three subjects. The estimations are based upon the firm's graphical representations:

Table 6

Maximum NEGATIVE Change from Baseline in SBP and Time to Maximum Change for the three subjects with HYPOTENSIVE episodes
Mean (± SD)

Pre-Treatment Dose (N)	Baseline SBP (mm Hg)	Minimum SBP (mm Hg)	Change from Base to MIN (mm Hg)	Time from Start to Min SBP (min:sec)
Saline (3)	120.7 ± 12	95.3 ± 12	-25.3 ± 3	11:24 ± 1:42

DESCRIPTION OF HYPOTENSIVE EPISODES:

Subject #1: (19 years old) when pre-treated with saline, subject experienced hypotension (BP=84/38) with ST segment depression upsloping <0.5 mm with flushing, dizziness, chest pain. Infusion stopped at 0.6 ug/kg/min. HR peaked during this decrease. BP returned to baseline within 5 min of stopping arbutamine infusion.

Subject #2: (23 years old) also pre-treated with saline, one minute into an 0.4 ug/kg/hr arbutamine infusion, BP dropped to 98/45 with ST segment depression but no overt symptoms (upsloping and <0.5 mm) 3 minutes prior to the BP decrease. As with subject #1, HR peaked during this episode. Subject recovered 2 minutes after stopping the arbutamine infusion.

Subject #4: (27 years old)also pre-treated with saline, while at the 0.4 ug/kg/hr infusion of arbutamine, BP dropped to 91/38 with horizontal ST segment depression of 1-2 mm noted just prior to and during the hypotensive episode. Subject experienced lightheadedness, pallor, and diaphoresis. BP then rose to 144/54 when the arbutamine dose was increased to 1.1 ug/kg/hr. Sponsor felt the ST segment depression was either ischemia or an anomalous finding.

APPEARS THIS WAY
ON ORIGINAL

Table 7

Number of Adverse Events by Pre-Treatment Group (N=4 for all groups)

ADVERSE EVENT	PLACEBO	METOPROLOL	PROPRANO
palpitation	2	2	3
ECG abnormalities	4	4	2
sinus bradycardia	0	0	1
junctional tachycardia	0	0	1
first degree AV block	0	0	1
sinus arrhythmia	0	0	1
sinus tachycardia	2	4	0
tachycardia	1	2	0
premature junctional contractions	1	2	0
junctional rhythm	1	1	0
premature atrial contractions	0	0	0
hypotension	3	0	0
chest pain	1	0	0
dizziness	2	0	0
flushing	2	0	0
diaphoresis	1	0	0
pallor	1	0	0
headache	1	0	0
nausea	1	0	0
tremor	0	0	0

Serum Potassium:

Table 8

Mean (± SD) Changes in Plasma Potassium Concentrations (mEq/L)

Pre-treatment	Baseline	End of Infusion	2 hr after Inf.
Placebo (N=4)	4.8 ± 0.6	3.4 ± 0.4	4.6 ± 0.3
Metoprolol (N=4)	4.8 ± 0.2	3.5 ± 0.5	4.4 ± 0.2
Propranolol (N=4)	5.1 ± 0.8	4.7 ± 0.2	4.7 ± 0.8

COMMENTS:

1. Heart Rate (HR) effects: It is difficult to quantitatively assess the effects of the two beta-blockers on HR as compared with placebo since 3/4 patients in the placebo group suffered hypotensive episodes; thus in those subjects, it is not clear how much a change in HR is due to a reflex reaction versus drug effect. In the one subject (#7) who did not have a hypotensive episode from saline pre-treatment, HR raised 79 bpm from baseline at the maximal 1.1 ug/kg/min dose, an increase comparable to the 70 and 72 bpm increase seen with the maximal doses in protocol 0102 and 0104, respectively.

   Qualitatively, the non-selective beta-blocker propranolol dampened HR increase whereas the effects of the selective beta-blocker metoprolol were indistinguishable from saline pre-treatment. Both beta-blockers pushed the dose-response curve to the rights since the time to maximal HR was delayed by almost 5 minutes (17 versus almost 22 minutes). This time to maximal HR (with saline pre-treatment) compares to the 16 minute figure seen in Protocol 0104. As in protocols 0101 and 0102, the arbutamine (+ saline) subjects required 14 minutes to drop their HR increase by 50%. The time needed for a 50% decrease in HR was decreased slightly by metoprolol (12 minutes) and markedly by propranolol (7.4 minutes). However, one could argue that since the baseline HR on saline was no different the baseline HR observed with either beta-blocker, was beta-blockade truly achieved?

2. Systolic Blood Pressure (SBP) effects: As with the HR data, the hypotensive episodes suffered by 3/4 patients make interpretation of SBP data extremely difficult. Given this important limitation, the data indicates that both beta-blockers result in increases in SBP more than saline (44 and 39 versus 29). However, it should be noted that max doses of arbutamine in Protocols 0102 and 0104 increased SBP by 47 and 42, respectively. As with the HR data, both beta-blockers appeared to push the response curve to the right, since maximal SBP effects occurred at 20 and 22 minutes for metoprolol and propranolol, respectively versus 12 minutes for saline pre-treatment.

3. Diastolic Blood Pressure (DBP) effects: Again, due to the hypotensive episodes, assessment of the DBP effects is difficult. While saline pre-treatment lowered DBP by 23 mm Hg, metoprolol pre-treatment decreased DBP by 11 mm Hg, while propranolol appeared to cause the greatest attenuation, decreasing DBP by only 4 mm Hg. In Protocol 0102, DBP was decreased by 11 mm Hg (at the highest arbutamine dose), whereas the DBP decrease was 18 mm Hg in Protocol 0104 (placebo effect in that protocol was -9.5 mm Hg).

4. SAFETY DATA:

A. Hypotensive reactions: The sponsor did not quantify the NEGATIVE effects of arbutamine on SBP. At times, data indicating a hypotensive episode was even missing from the raw data tabulations. Thus this reviewer was forced to, at times, read numbers off of graphs in an attempt to describe the nature of the hypotensive episodes (NOTE: The sponsor committed to reviewing the Phase II/III studies to insure that these data omissions were not occurring in that database as well). In general, the three episodes occurred during the 0.4-0.6 ug/kg/min infusions, around 11 minutes into the arbutamine infusion, with an average drop of 25 mm Hg.

The reasons for the hypotensive reactions observed in this study are unclear. There were no obvious differences in the affected subjects in terms of weight, performance on the ETT, effect on lab values (including potassium), or even plasma arbutamine concentrations. However ALL of the study subjects, including those pre-treated with beta-blockers, demonstrated either little or even a slight decrease in SBP until the 0.4-0.6 ug/kg/min dose. Afterwards, increasing the arbutamine infusion caused a dramatic increase in SBP.

B. ECG data: The sponsor states that none were retained for comparative analyses, thus the effects noted previously on the QTc interval cannot be assessed. However, all three subjects with hypotensive episodes showed ST segment depression. While this depression was <0.5 mm in 2 of the 3 subjects, the third subject demonstrated a 1-2 mm depression. This raises several (unanswerable?) questions which deserve follow-up: Is this arbutamine inducing true ischemic events? Are these events as a result of a combination of arbutamine and a hypotensive event? Are these events artifactual as the sponsor speculates and thus producing a false positive for ischemia?

C. Potassium Effects: While both saline and metoprolol pre-treatment groups demonstrated 30% "end-of-infusion" decreases in plasma potassium, propranolol decreased potassium by only 7.5%. Thus, the non-selective beta-blocker appeared to attenuate the effects of the non-selective beta-agonist arbutamine. However, unlike previous protocols, the sponsor measured plasma potassium two hours after the end of infusion. This data indicated a normalization of potassium 2 hours after arbutamine infusion.

5. Efficacy Questions: In previous protocols, the effects of arbutamine on HR, SBP, and DBP were not as dramatic as those induced by ETT. The effects noted in this study (now including the hypotensive episodes) do nothing to allay that potential concern. In addition, there is yet another potential concern: that arbutamine could cause false positive indications of ischemic heart disease.

PROTOCOL 0116: CLINICAL STUDY REPORT CS0116

DESIGN SUMMARY:

This study's purpose was to determine the infusion rates of intravenous (IV) arbutamine required to achieve a HR rise of 50 bpm in the presence of steady-state trough levels of **atenolol** and **propranolol** in normal male subjects. A secondary purpose was to determine the safety of IV arbutamine given concomitantly with beta-blockers. This study was designed as an open-label study with half the subjects receiving propranolol pre-treatment and the other half atenolol. However, due to the adverse events of **severe tremors** in two subjects and **PVCs** in another, instead of the planned 18 subjects, only 7 subjects participated in this study.

PROTOCOL

- **Enrollment Criteria:**

The Inclusions and Exclusions were as in previous protocols: male subjects between 18 and 40 years of age.

- **Qualifying Criteria**

As in previous protocols.

- **Treatment Regimen**

The following treatments **WERE** to be administered :

Group 1 (subjects 1-3): pre-treatment with propranolol 160 mg (Inderal LA) QD x 4 doses, followed by an arbutamine regimen of 0.4, 0.56, and 0.8 (all ug/kg/min x 10 minutes).
Group 2 (subjects 4-6): pre-treatment with atenolol 100 mg (Tenormin) QD x 3 doses, followed by an arbutamine regimen of 0.28, 0.40, and 0.56 (all ug/kg/min x 10 minutes).
Group 3 (subjects 7-12): first, no pre-treatment, followed by arbutamine 0.20, 0.28, and 0.40 (all ug/kg/min x 10 minutes, all doses separated by a 20 minute washout); then all subjects would receive propranolol 160 mg QD x 4 days, then arbutamine 0.40, 0.56, and 0.80 (all ug/kg/min x 10 minutes).
Group 4 (subjects 13-18): first, no pre-treatment, followed by arbutamine 0.20, 0.28, and 0.40 (all ug/kg/min x 10 minutes, all doses separated by a 20 minute washout); then all subjects would receive atenolol 100 mg (Tenormin) QD x 3 doses, followed by an

arbutamine regimen of 0.28, 0.40, and 0.56 (all ug/kg/min x 10 minutes).

Arbutamine was administered into an arm vein using an IVAC model 560 volumetric pump. Additionally, arbutamine was administered 24 hours after the last dose of beta-blocker (at trough).

However, due to the severe tremors encountered in two subjects (#1 and #13) and pre-mature ventricular contractions (PVCs) in another (#5), the study was pre-maturely terminated.

Thus, the following subjects actually participated in the study:

Subject	Pre-treatment	Arbutamine Regimen (ug/kg/min x min)
1	propranolol 160 mg every 24 hours x 4 days	0.40 x 10 0.56 x 10 0.80 x 10
2	propranolol 160 mg every 24 hours x 4 days	none*
3	propranolol 160 mg every 24 hours x 4 days	0.40 x 10 0.56 x 10 0.80 x 10
4	atenolol 100 mg every 24 hours x 3 days	0.28 x 10 0.40 x 10 0.56 x 10
5	atenolol 100 mg every 24 hours x 3 days	0.28 x 10 0.40 x 6
6	atenolol 100 mg every 24 hours x 3 days	0.28 x 10
13	no pre-treatment	0.20 x 5

* subject asked to be excused from the study for personal reasons

- **Endpoints/Equipment used**

HR, systolic blood pressures (SBP), and diastolic blood pressures (DBP) were measured at the screening visits using methods routinely used by the investigator. On treatment-days, HR, SBP, and DBP were measured using a Clinical Research Prototype ESA System. HR was measured every 5 seconds and SBP/DBP were measured at -10, -5, and 0

minutes during a 10 minute baseline period, every 2 minutes during drug administration, and at 2,4,6,8,10,20 and 30 minutes during each recovery period. ECGS were monitored continuously.

- **Statistical Procedures**

- **Data Set Analyzed/Handling of Missing Data**

Seven subjects participated in the trial. Three received atenolol pre-treatment, two received propranolol pre-treatment, one subject received no pre-treatment, and another subject asked to be dismissed from the trial after receiving propranolol pre-treatment but prior to arbutamine treatment (this subject's data are included in the safety analysis but not the evaluation of pharmacodynamic response).

- **Analyses performed**

None described.

- **Subject Characteristics**

Seven adult male subjects, six caucasian and one American Indian (subject #13) aged 25.6 ± 6.3 years (mean ± SD), of average height (180.7 ± 6.4 cm, mean ± SD) and weight (79.1 ± 9.2 Kg, mean ± SD) .

RESULTS:

None of the subjects demonstrated cardiovascular abnormalities during the ETT. Maximum HR achieved during ETT averaged 194 ± 6.3 bpm (mean ± SD).

The sponsor states that plasma samples for the Beta-blockers were drawn but not analyzed due to the early termination of the trial.

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

Maximum Change from Baseline in Heart Rate (HR) per subject, pretreatment, and arbutamine infusion and duration

SUBJECT	Pre-treatment	Maximal Dose of Arbutamine (ug/kg/hr) x (min)	Baseline to Maximum HR (bpm)	HR_{CHANGE} (bpm)
1				
3				
4				
5				
6				
13				

TABLE 2

Maximum Change from Baseline in Systolic Blood Pressure (SBP) per subject, pretreatment, and arbutamine infusion and duration

SUBJECT	Pre-treatment	Maximal Dose of Arbutamine (ug/kg/hr) x (min)	Maximum SBP (mm Hg)	Max Positive change from Baseline (SBP) (mm Hg)
1				
3				
4				
5				
6				
13				

TABLE 3

Maximum Change from Baseline in Diastolic Blood Pressure (DBP) per subject, pretreatment, and arbutamine infusion and duration

SUBJECT	Pre-treatment	Maximal Dose of Arbutamine (ug/kg/hr) x (min)	Minimum DBP (mm Hg)	Max change from Baseline (DBP) (mm Hg)
1				
3				
4				
5				
6				
13				

Safety Data:

INDIVIDUAL SUBJECT DESCRIPTIONS:

Subject #1: (33 years old) pre-treated with **propranolol**: three minutes into the 0.8 ug/kg/min infusion of arbutamine, the subject experienced **tremors of the extremities**. Intensity of the tremors increased and the infusion was stopped after 4.5 minutes.

Subject #3: (22 years old) pre-treated with **propranolol**: uneventful; all arbutamine infusions completed.

Subject #4: (23 years old) pre-treated with **atenolol**: infusions completed as planned. Subject's SBP increased slightly, then **BPs dropped to 90/28** accompanied by **chest pain** noted at the highest (0.56) infusion rate.

Subject #5: (20 years old) pre-treated with **atenolol**: five minutes into the 0.4 infusion, **several PVCs** were observed on the monitor. PVCs increased in frequency over the next minute and the infusion stopped. Subject experienced bigeminy, trigeminy, and quadrigeminy over the next 10-15 minutes which resolved after **180 mg of lidocaine IV**.

Subject #6: (24 years old) pre-treated with **atenolol**: HR hit target (>50 bpm increase) with the lowest arbutamine infusion (0.28). However, at this time, BP dropped from 112/60 to 110/43 and the subject noted **chest pain**.

Subject #7: (36 years old) no pre-treatment: Subject experienced **dizziness and nausea** three minutes into the 0.2 infusion; one minute later he experienced **tremors of the lower extremities** and the infusion was terminated one minute later. At one point during the infusion the SBP dropped 30 mm Hg back to baseline (145 ->115).

Table 4
Arbutamine plasma concentrations at end of infusion and adverse events (P=propranolol, A-Atenolol, and N=None)

SUBJECT (+ tx)	CONCENTRATION (ng/ml)	Adverse Event(s)
1 P		tremors
3 P		---
4 A		hypotension, chest pain
5 A		PVCs
6 A		drop in DBP, chest pain
13 N		dizziness, nausea, tremors

The table above discloses no obvious relationship between adverse events and arbutamine plasma concentration. Analysis of plasma levels of the two beta-blockers may have provided further insight, although the sponsor chose not to perform this determination.

Table 5
Serum Potassium concentrations per subject and pre-treatment (P=propranolol, A-Atenolol, and N=None)

Subject + Tx	Pre-study Potassium (mEq/L)	Post-study Potassium (mEq/L)
1 P		
3 P		
4 A		
5 A		
6 A		
13 N		

As in Protocol 0110, the non-selective beta-blocker propranolol caused the least change in serum potassium.

COMMENTS:

1. Heart Rate (HR) effects: With five of six subjects experiencing adverse events (such as hypotension, PVCs, tremors) some of which led to infusion termination, it is difficult to quantitatively assess the effects of the two beta-blockers on HR as compared with placebo. One can say that as a general trend, pre-treatment with the non-selective beta-blocker **propranolol** resulted in less of a HR increase than either **atenolol** or no pre-treatment. The effects of latter two treatments on HR appeared indistinguishable (as seen in Protocol 0110). It was not possible to assess the effects on the beta-blockers on the dose-response curve (recall that in Protocol 0110, both beta-blockers appeared to push the dose-response curve to the right).

2. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) effects: As with the HR data, the early infusion terminations make assessments of the effects of the beta-blockers on SBP/DBP very difficult. Propranolol seemed to cause a slightly increased effect on SBP as compared to the other two treatments whereas atenolol caused the greatest effect (negative) on DBP.

   AGAIN, the sponsor did not descriptively quantify the NEGATIVE effects of arbutamine on BP. At times, data indicating a hypotensive episode was even missing from the raw data tabulations. Thus this reviewer was forced to read numbers off of graphs in an attempt to describe the nature of the hypotensive episodes. Again, the sponsor has committed to reviewing the Phase II/III studies to insure that these types of data omissions were not occurring in that database as well.

3. SAFETY DATA:

   A. Hypotensive reactions/tremors/PVCs/chest pain: The reasons for these adverse reactions observed in this study are unclear. The only subject of the six studied without adverse events (#3, pre-treated with propranolol) had the highest observed arbutamine plasma concentration. All non-propranolol treated subjects demonstrated hypokalemia after arbutamine treatment (in fact, subject #3, with no adverse events had the highest pre and post-treatment serum potassium). In addition, subject #3 was clearly beta-blocked (post-propranolol HR = 48.7), whereas it was not clear that the other subjects were so. Again, plasma levels of the beta-blockers may have been beneficial.

   B. ECG data: The sponsor states that ECG data was observed from a monitor but that otherwise none were recorded.

C. Potassium Effects: As a general trend, both subjects pre-treated with propranolol had blunted responses to arbutamine-induced hypokalemia as compared to atenolol alone

4. Efficacy Questions: In Protocol 0110, it was noted that arbutamine induced ST segment depression. In this study, two subjects reported chest pain during hypotensive episode. Is arbutamine causing ischemic events? Could it result in false positives for ischemic heart disease?

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PROTOCOL 0118: CLINICAL STUDY REPORT CS0118

DESIGN SUMMARY:

This study's purpose was to determine the pharmacodynamic effects of varying doses of intravenous (IV) **atropine** pre-treatments given prior to an arbutamine infusion. The study was designed as a single-blind (subject), randomized, two period crossover incomplete block design, single dose study in 21 normal volunteers (average age of 53).

PROTOCOL

- **Enrollment Criteria:**

The Inclusions and Exclusions were as in previous protocols except that FEMALES were included and subjects between 50 and 61 years of age were studied. In addition blacks as well hispanics were included in this study.

- **Qualifying Criteria**

As in previous protocols: subjects must be able to complete the symptom limited ETT (Bruce protocol) without incident.

- **Treatment Regimen**

Twenty subjects were scheduled to receive two of the following five pretreatments followed by IV arbutamine. However, due to **supraventricular tachycardia (SVT)** in two subjects and **multifocal PVCs** in another, twenty-one subjects received one or more of the scheduled pre-treatments, followed six minutes later by arbutamine:

IV placebo [normal saline]	n = 7
IV atropine 6 µg/kg	n = 8
IV atropine 8 µg/kg	n = 7
IV atropine 11 µg/kg	n = 9
IV atropine 15 µg/kg	n = 8

Arbutamine regimen: 0.05, 0.1, and 0.2 µg/kg/min for ten minutes at each infusion rate **(3.5 ug/kg total dose)**

The first treatment was administered the day after admission into the testing unit (Day 1); approximately 24 hours later the second treatment was administered (Day 2).

- **Endpoints/Equipment used**

HR, systolic blood pressures (SBP), and diastolic blood pressures (DBP) were measured at the screening visits using methods routinely used by the investigator. On treatment days, HR, SBP, and DBP were measured using a Clinical Research Prototype ESA System. HR was measured every 5 seconds and SBP/DBP were measured at -10, -5, and 0 minutes during a 10 minute baseline period, every 2 minutes during drug administration, and at 2,4,6,8,10,20 and 30 minutes during each recovery period. ECGS were monitored continuously.

- **Statistical Procedures**

- **Data Set Analyzed/Handling of Missing Data**

Baseline was defined as the resting HR or BP observed just prior to starting atropine pretreatment. The pharmacodynamic data for subjects #5, 17, and 18 was not included (these subjects were dropped due to adverse events).

- **Analyses performed**

The mean HR at baseline and the mean of the maximum HR during the different infusion phases were compared between the five pretreatment groups using Analysis of Variance (ANOVA). This was a crossover design so terms included in the ANOVA were patient, period and pretreatment. A preliminary run indicated the period by pretreatment interaction term was not statistically significant and it was removed from the model to maximize the error degrees of freedom. The same comparisons of mean values was made for maximum SBP and minimum DBP.

Dose response was investigated with a general linear model including patient and period as classes and pretreatment dose as the independent predictor variable.

Mean changes in HR, SBP and DBP were compared within and between pretreatment groups using the same ANOVA model. Within group mean changes were statistically compared to zero using the pooled estimate of error from all five pretreatment groups. The changes inspected were: from baseline to the maximum during pretreatment; from pretreatment to the end of the arbutamine infusion; and from baseline to the end of the arbutamine infusion.

- **Subject Characteristics**

Twenty-one healthy middle-aged subjects (7 female, 14 male, 17 white, 2 black, 2 hispanic) aged 52.8 $\pm$ 3.1 (mean $\pm$ SD), of average height (176.1 $\pm$ 8.9 cm, mean $\pm$ SD) and weight (76.9 $\pm$ 12.2 kg, mean $\pm$ SD).

RESULTS:

None of the subjects demonstrated cardiovascular abnormalities during the ETT. Maximum HR achieved during ETT averaged 168 ± 4.2 bpm (mean ± SD).

TABLE 1
Maximum Change in Heart Rate (HR) from baseline after pre-treatment and after arbutamine (mean ± SD)

HR changes (bpm)	Placebo (N = 7)	Atropine 6 ug/kg (N = 7)	Atropine 8 ug/kg (N = 7)	Atropine 11 ug/kg (N = 7)	Atropine 15 ug/kg (N = 8)
Baseline	60.8 ± 12.6	58.4 ± 6.9	58.4 ± 9.7	60.9 ± 6.6	64.1 ± 9.2
Pre-treat	64.2 ± 12.0	70.3 ± 6.0	78.1 ± 10.1	84.6 ± 7.4	92.7 ± 8.6
Change from Base	3.3 ± 1.9	11.9 ± 7.5	19.7 ± 8.0	23.7 ± 5.0	28.7 ± 2.3
Arbut 0.2	124.2 ± 6.4	133.8 ± 8.5	134.3 ± 5.9	147.6 ± 7.9	152.1 ± 5.6
Change from Base	63.4 ± 12.5	75.4 ± 11.7	75.9 ± 13.2	86.7 ± 8.1	86.5 ± 11.4
Change from Pre-tx	60.0 ± 12.3	63.5 ± 12.4	56.2 ± 9.9	63.0 ± 4.6	58.3 ± 10.2

The baseline HRs for each treatment group were similar (p=0.6599). Following pretreatment with atropine and placebo there was a statistically significant (p<0.015), dose-dependent (linear, R^2 = 0.93) increase in mean maximum HR for all groups. Pairwise comparisons revealed that the mean maximum changes from baseline in pretreatment with placebo or atropine 6 µg/kg were not statistically different; mean changes for atropine 8 and 11 µg/kg were not statistically different but were larger than placebo and atropine 6 µg/kg; and the mean change for atropine 15 µg/kg was significantly larger than all other doses.

The mean maximum changes in HR, measured from baseline to the end of the arbutamine infusion, were significantly greater in the atropine 8, 11, and 15 µg/kg groups when compared to the placebo group (p = 0.0033). However, when measured from the end of the pretreatment period the mean maximum changes in HR response to arbutamine infusion were not statistically different between all pretreatment groups (p = 0.7059). Therefore, the primary effect of atropine pretreatment appeared to be to increase the HR prior to arbutamine administration.

TABLE 2
Mean (± SD) Time for H R to Decrease by 10, 20 and 50%
After Termination of Arbutamine Infusion

Atropine Pretreatment (µg/kg)	n	Time for 10% Decrease (min:sec)	Time for 20% Decrease (min:sec)	Time for 50% Decrease (min:sec)
Placebo	7	1:59 ± 0:41	3:45 ± 1:11	14:26 ± 3:36
6	7	0:51 ± 2:39	4:50 ± 3:26	16:45 ± 2:29*
8	7	1:13 ± 2:15	3:29 ± 2:59	19:24 ± 6:06
11	7	3:04 ± 0:30	5:39 ± 1:27	18:57 ± 5:43
15	8	2:28 ± 1:09	5:09 ± 1:44	18:46 ± 2:34

* n=6 for Atropine 6 µg/kg group for $T_{50\%}$.

Although atropine pretreatment appears to increase the HR offset time after arbutamine, the mean difference is not statistically significant. In addition, atropine pre-treatment appeared to exert little effect on the HR Tmax.

TABLE 3
Mean (± SD) Maximum **POSITIVE** SBP and Maximum **POSITIVE** Change in SBP from Baseline

SBP (mmHg)	Placebo (n = 7)	Atropine 6 µg/kg (n = 7)	Atropine 8 µg/kg (n = 7)	Atropine 11 µg/kg (n = 7)	Atropine 15 µg/kg (n = 8)
Baseline	112.3±8.9	112.3±14.0	113.6±16.9	108.6±13.0	110.1±12.8
PreTx max/Δ	118.9±13.9 6.6±7.4	118.9±14.6 6.6±4.9	119.1±15.6 5.6±3.3	115.0±7.2 6.4±6.8	121.4±13.9 11.3±5.8
Arb 0.2 max/Δ	157.4±25.6 45.1±21.2	151.1±18.3 38.9±8.6	144.9±17.7 31.3±7.8	143.4±6.7 34.9±12.8	143.7±21.6 34.7±15.2

Placebo and atropine pretreatments caused similar increases in mean SBP (approximately 6-11 mmHg above baseline, p=0.3920 for ANOVA comparisons). Atropine pretreatment had no consistent effect on the mean SBP response to each arbutamine infusion rate and the maximum SBP for each treatment group (p=ns for all comparisons).

TABLE 4
Mean (± SD) Minimum DBP and Minimum Change in DBP from Baseline

DBP (mmHg)	Placebo (n = 7)	Atropine 6 µg/kg/min (n = 7)	Atropine 8 µg/kg/min (n = 7)	Atropine 11 µg/kg/min (n = 7)	Atropine 15 µg/kg/min (n = 8)
Baseline	68.4±5.8	65.7±9.2	71.7±9.8	63.7±8.8	67.8±7.2
PreTx max/Δ	66.0±8.3 -2.4±3.4	65.7±5.1 0.0±3.4	68.6±7.6 -3.1±8.0	65.9±7.0 2.1±2.7	67.0±7.5 -0.8±3.4
Arb 0.2 max/Δ	57.6±8.1 -10.9±4.7	49.9±5.9 -15.9±7.6	48.9±5.9 -22.9±10.5	53.9±8.9 -9.9±6.5	56.3±8.6 -11.2±10.4

Placebo and atropine pretreatments had little effect on mean DBP (p=ns for all comparisons). Atropine pretreatment had no consistent effect on the decrease in DBP caused by arbutamine.

Safety Data:

Again, the sponsor has poorly documented the hypotensive responses seen in many of the subjects. These data are not available from the raw data tables but can only be obtained from graphical representations. The sponsor states that arbutamine infusions for subjects #10 and #19 were stopped due to hypotension, whereas subjects #6, 9, 12, 13, and 20 experienced hypotensive episodes of varying, albeit lesser, severity. This report is true; however, a number of other subjects experienced hypotensive episodes of varying severity as well. Table 5 includes the subjects noted above, as well as others, and outlines the nature and time course of these events (again, recall that most of the readings below are estimations obtained from graphical representations):

Table 5

Description of Hypotensive episodes, including the time it took the event to develop (unless otherwise stated, event took 2 minutes or less to develop)
(all SBP/DBP readings in mm Hg)

Subject	Pre-TX	Baseline SBP/DBP	SBP/DBP preceding hypotension	SBP/DBP during hypotension	Time course of hypotension
2					
3					
"					
3					
"					
6					
"					
9					
"					
9					
10*					
12					
13					
14					
16					
"					
17					
18					
19*					
19					
20					
20					
21					

*Infusion terminated due to hypotension

The drop in SBP ranged from 12 to 55 mm Hg (mean $\pm$ SD = 28.4 $\pm$ 11.9).

TABLE 6
Number of Adverse Events by Dosing Group
(# of Treatments)

Adverse Event (WHO Preferred Term)	Placebo (n=7)	Atropine 6 µg/kg (n=8)	Atropine 8 µg/kg (n=7)	Atropine 11 µg/kg (n=9)	Atropine 15 µg/kg (n=8)
Tachycardia	2(28.6%)	2(25.0%)	4(57.1%)	5(55.6%)	4(50.0%)
Palpitations	4(57.1%)	4(50.0%)	2(28.6%)	1(11.1%)	1(12.5%)
Dry Mouth	0(0.0%)	3(37.5%)	2(28.6%)	2(22.2%)	4(50.0%)
Headache	1(14.3%)	0(0.0%)	1(14.3%)	2(22.2%)	1(12.5%)
PVC	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**1(11.1%)**	**1(12.5%)**
PC Origin Unknown	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**2(22.2%)**	**0(0.0%)**
PVC, Multifocal	**0(0.0%)**	**1(12.5%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**
Dyspnea	0(0.0%)	0(0.0%)	1(14.3%)	1(11.1%)	1(12.5%)
Paresthesia	0(0.0%)	0(0.0%)	0(0.0%)	1(11.1%)	2(25.0%)*
Chest Pain	**0(0.0%)**	**0(0.0%)**	**1(14.3%)**	**1(11.1%)**	**0(0.0%)**
Severe Hypotension	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**2(25.0%)**
Nausea	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2(25.0%)
Supraventricular Tachycardia	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**2(22.2%)**	**0(0.0%)**
Asthenia	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(12.5%)
Rigors	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(12.5%)
Tremor	0(0.0%)	0(0.0%)	1(14.3%)	0(0.0%)	0(0.0%)
Euphoria	1(14.3%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Somnolence	0(0.0%)	0(0.0%)	0(0.0%)	1(11.1%)*	0(0.0%)

*One episode of somnolence and one episode of paresthesia were reported in the pretreatment groups.

As can be seen from table 6, most of the more serious adverse events occurred in the 11 ug/kg to 15 ug/kg atropine groups.

Arrhythmias occurred in six subjects. All had received atropine (6, 11 or 15 µg/kg) pretreatment prior to arbutamine. **Premature Contractions** occurred in five subjects (#'s 3, 5, 14, 17 and 18). In subject 18, the arbutamine infusion was stopped due to multifocal PVCs which resolved without adverse sequelae. In subject 5, **premature contractions** and **SVT** occurred in the recovery period and resolved after administration of IV propranolol 1 mg (NOTE: It is not clear why the sponsor did not include this subject's data in the pharmacodynamic analysis since this adverse event took place after the full amount of arbutamine had been infused). In subject 17, **SVT** occurred during

arbutamine infusion and resolved after termination of arbutamine and administration of IV propranolol 1 mg.

Plasma Arbutamine samples were collected just prior to arbutamine infusion termination. As in previous studies, there appeared to be no correlation between those subjects who experienced adverse events and those that did not based on plasma arbutamine concentrations. For example, subjects #15, who did not report a significant adverse event had an end of arbutamine plasma level of 4.96 ng/ml. However, subject #5, who terminated because of premature contractions and SVT was noted to have a plasma arbutamine level of 3.94. Both subjects who experienced hypotensive episodes that led to termination of their arbutamine infusions actually had higher plasma concentrations of arbutamine during the infusions in which they did not experience (as severe) adverse reactions. While subject #3 had lower plasma arbutamine concentrations during an episode of PVCs (as opposed to the treatment arm where she did not have an adverse event), subject #21 had higher plasma arbutamine concentrations during the treatment arm where he did experience PVCs.

Subjects 11, 12 and 20 had normal **creatine kinase enzyme** levels with slight elevations in the **MB fraction**. None of these subjects demonstrated other signs or symptoms of myocardial ischemia or damage (none of the two reports of chest pain occurred in these subjects). The sponsor attributes these findings to assay variability (highest abnormal reading was 12 (normal range 0 - 9)).

Plasma Potassium:

TABLE 7
Mean (± SD) Plasma Potassium Concentrations (mEq/mL)

	Placebo (n = 7)	Atr 6 µg/kg (n = 7)	Atr 8 µg/kg (n = 7)	Atr 11 µg/kg (n = 7)	Atr 15 µg/kg (n = 8)
Pre-arb	4.43±0.33	4.37±0.53	4.24±0.44	4.29±0.35	4.63±0.51
Immed. Post-Arb	3.67±0.44	3.43±0.23	3.56±0.32	3.93±1.68	3.44±0.44
30 min Post-Arb	3.64±0.24	3.91±0.58	3.99±0.50	3.73±0.35	3.89±0.61
60 min Post- Arb	4.11±0.15	4.20±0.47	4.23±0.43	4.30±0.64	4.24±0.60
120 min Post-Arb	4.39±0.52	4.37±0.45	4.56±0.37	4.21±0.25	4.49±0.56*

* N=7 for the atropine 15 µg/kg pretreatment group.

The effects on plasma potassium of the various pretreatment groups were similar (p=0.9868 for all ANOVA comparisons). Mean potassium concentration measured immediately, 30 and 60 minutes after stopping arbutamine was significantly less than the pre-arbutamine concentration ($p < 0.05$). Potassium concentration measured 120 minutes after stopping arbutamine was similar to the pre-arbutamine level.

COMMENTS:

1. Heart Rate (HR) effects: As seen in previous studies, a number of hypotensive episodes of varying severity occurred. The majority of these subjects are included in the sponsor's calculations for HR effects. Thus, it is not clear whether the net HR increases are due to arbutamine's desired effects, or the result of hypotensive reactions (conversely, it is not known if the hypotensive effects are in compensation for the effects on HR?). With this in mind, pretreatment with atropine and placebo significantly increased ($p<0.015$) in a dose-dependent (linear, $R^2 = 0.93$) manner, the mean maximum HR for all groups. The mean maximum changes in HR, measured from baseline to the end of the arbutamine infusion, were significantly greater in the atropine 8, 11, and 15 µg/kg groups when compared to the placebo group ($p = 0.0033$). However, when measured from the end of the pretreatment period the mean maximum changes in HR response to arbutamine infusion were not statistically different between all pretreatment groups ($p = 0.7059$). Therefore, the primary effect of atropine pretreatment appeared to be to increase the HR prior to arbutamine administration.

   Although atropine pretreatment appears to slightly increase the HR offset time after arbutamine, the mean difference is not statistically significant.

2. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) effects: As with the HR data, the assessment of arbutamine effects on SBP is complicated due to the number of hypotensive events. AGAIN, the sponsor did not descriptively quantify the NEGATIVE effects of arbutamine on SBP. In most cases, data indicating a hypotensive episode was even missing from the raw data tabulations. Thus, this reviewer often read numbers from graphs in order to describe the nature of the hypotensive episodes. The sponsor has committed to reviewing the Phase II/III studies to insure that these types of data omissions were not occurring in that database as well.

   The sponsor's data regarding INCREASES in SBP indicate that placebo and atropine pretreatments caused similar increases in mean SBP (approximately 6-11 mmHg above baseline, p=0.3920 for ANOVA comparisons). Atropine pretreatment had no consistent effect on the mean SBP response to each arbutamine infusion rate and the maximum SBP for each treatment group (p=ns for all comparisons). Placebo and atropine pretreatments had no effect on mean DBP (p=ns for all comparisons). Atropine pretreatment had no consistent effect on the decrease in DBP caused by arbutamine.

3. SAFETY DATA:

A. Severe Hypotensive reactions/SVT/PVCs: The majority of subjects experiencing these adverse events had been administered either atropine 11 ug/kg or 15 ug/kg as pre-treatments. However, 13 of 21 subjects experienced some reductions in SBP during arbutamine infusion, although only 2 reactions necessitated infusion termination. Although the majority of these events would probably not constitute safety concerns, this reviewer is concerned that these episodes may compromise arbutamine's ability to screen for perfusion deficits (see Comment #4 below).

The SVT events were treated with propranolol and resolved without sequelae as did the episodes of PVCs. None of the following factors appeared to correlate with these adverse events: plasma arbutamine concentrations; subject age, race, sex, weight; plasma potassium concentrations.

B. ECG data: The sponsor states that ECG data was observed from a monitor but that otherwise none were recorded.

C. Potassium Effects: Almost all subjects demonstrated hypokalemia following termination of arbutamine infusion. However, the hypokalemia returned to baseline within 2 hours.

4. Efficacy Questions: As has been noted in the Comments sections for the preceding protocols, this reviewer continues to have questions regarding arbutamine's efficacy. Given the submaximal HR increases, the hypotensive episodes, and the lowering of DBP (separate from hypotensive episodes), this reviewer wonders if this agent could reliably produce sufficient cardiac work during a non-invasive test.

Additionally, in this study, two subjects reported chest pain - unaccompanied by hypotensive episodes. Three other subjects has very slight increases in the MB band fractions of their creatinine kinase enzymes, albeit unaccompanied by any other signs and symptoms of ischemia. Arbutamine induced ST segment depression in three subjects in Protocol 0110, and two subjects reported chest pain while their BP was lowered in Protocol 0116. Again are these events ischemia, or false positives?

PROTOCOL 0119: CLINICAL STUDY REPORT CS0119

DESIGN SUMMARY:

This study's purpose was to determine the safety and efficacy of arbutamine given alone and 24 hours after administration of steady-state **atenolol** and **propranolol**. The study was designed as an open-label, randomized, crossover design in 20 males patients with **Coronary Artery disease (CAD)**.

PROTOCOL

• Enrollment/Qualifying Criteria:

Inclusion Criteria:
- males or females;
- minimum age of age 30 years with no upper limit;
- **patients with coronary artery disease (CAD), having a positive diagnostic exercise test (> 1 mm ST segment depression 80 msec after the J point) within 3 months of entry** (if a positive exercise test had not been performed within 3 months of study commencement, one was to be performed at least 7 days before arbutamine administration).

Exclusion Criteria:
- women who are pregnant or at risk of pregnancy or breast feeding;
- patients with respiratory disease, heart failure, or second or third degree heart block;
- clinically significant renal or hepatic disease;
- history of chronic arrhythmias
- unstable angina pectoris or myocardial infarction within 6 months of study entry;
- hypertension (systolic blood pressure >160 mm Hg;
- idiopathic hypertrophic subaortic stenosis or aortic stenosis;
- thyroid disease, glaucoma, cerebrovascular disease.
- patients taking digoxin, theophylline, and any anti-hypertensive agents.

• Treatment Regimen

Thirty subjects were screened for entry into the study 7-21 days before first arbutamine treatment. Patients meeting study criteria were allocated a randomization number from a pre-assigned randomization schedule to one of the following two-treatment groups:

Group 1 : Arbutamine alone/ arbutamine with propranolol;
Group 2 : Arbutamine with propranolol/ arbutamine alone;
Group 3 : Arbutamine alone/ arbutamine with atenolol;
Group 3 : Arbutamine with atenolol/ Arbutamine alone.

The beta-blocker treatment was administered by pre-treatment as a single daily dose taken for 7-10 days prior to arbutamine administration. The second arbutamine infusion was performed 7-10 days after the first infusion. Inderal LA 160 mg and Tenormin 50/100 mg (choice based on dose needed to achieve beta-blockade, defined by the investigators as a HR at least 10 bpm below baseline)were the products/doses used. The following arbutamine infusions (at trough beta-blockade) were performed:

Arbutamine alone: 0.15, 0.21, and 0.3 ug/kg/min (x 10 min. each dose, total dose = 6.6 ug/kg).
Arbutamine + atenolol: 0.28, 0.4, 0.56 ug/kg/min (x 10 min. each dose, total dose = 12.4 ug/kg).
Arbutamine + propranolol: 0.4, 0.56, 0.8 ug/kg/min(x 10 min each dose, total = 17.6 ug/kg).

Each 10 minute arbutamine infusion was separated by 20 minutes of no drug administration.

Subjects were to suspend all co-medications at least two weeks before the start of the study. Nitrates could be used anytime; however, details of their usage were recorded.

- **Endpoints/Equipment used**

Heart Rate (HR), systolic blood pressures (SBP), and diastolic blood pressures (DBP) were measured at the screening visits using methods routinely used by the investigator. On treatment days, HR, SBP, and DBP were measured using a Siemens SIrecust 402 ECG monitor, a Wyse computer,a Harvard infusion pump, a Critkon Dynamap blood pressure monitor, and a computer interface box and printer. The data obtained by these instruments was stored by the Gen ESA (open-loop) system prototype automatically. HR was measured every 5 seconds and SBP/DBP were measured at -10, -5, and 0 minutes during a 10 minute baseline period, every 2 minutes during drug administration and at 5 minute intervals during each recovery period (patients were monitored until HR returned to $\pm$ 15 bpm of baseline HR).

Twelve-lead ECGs were obtained during all tests using Marquette equipment. The time of onset, duration, and leads in which changes occurred were noted. Transthoracic two-dimensional echocardiograms were recorded, but due to technical difficulties in processing this data, were not available.

Infusion of arbutamine was to be completed unless angina and/or ECG changes diagnostic of ischemia (ST segment depression of > 1 mm [0.1 mV] 80 msec after the J point) or any other serious event occurred.

- **Statistical Procedures**

- **Data Set Analyzed/Handling of Missing Data**

All 20 patients randomized completed both arms of the study according to protocol (8 patients with propranolol pre-treatment, 12 patients with atenolol pre-treatment). Of the randomized patients, there were no violations of inclusion/exclusion criteria and no major protocol deviations that necessitated removal of any patients from the study.

- **Analyses performed**

The study was analyzed as a two-period crossover to account for residual effects between treatments and to take advantage of each subjects acting as his own control using an appropriate Analysis of Variance (ANOVA) test. Analyses of residuals were carried out in connection with the repeated measure model in order to assess whether normality assumptions were reasonable for these data. If the Shapiro-Wilk test for normality failed, then parametric analyses were replaced by appropriate non-parametric analyses.

The differences between baseline efficacy parameters and treatment means were compared by specifying orthogonal contrasts in the model and the use of suitable multiple comparison procedures where appropriate. Inferential statistical analysis was carried out twice, once to compare arbutamine with arbutamine/atenolol, and once to compare arbutamine with arbutamine/propranolol. For those response variables measured repeatedly, a repeated measures ANOVA was constructed (using intrapatient sums and differences). The effect of each treatment was determined statistically by comparing the baseline values of each parameter to the values recorded at the peak effect of treatment (using normal theory methods).

- **Subject Characteristics**

Twenty male subjects (19 white, one oriental) aged 52.3 ±1.6 (mean ± SE [standard error of the mean]) with a height of 173.9 ± 1.8 cm (mean ± SE) and weight 79.4 ± 2.2 kg (mean ± SE) participated in the study. In the 12 subjects randomized to the atenolol group, prior to the study, 6 subjects had been on calcium antagonists, four on beta-blockers, and one subject was on both. Of the 8 propranolol subjects, 4 had previously been on calcium antagonists, whereas one subject had been on both calcium antagonists and beta-blockers.

RESULTS:

Table 1

Mean (±SE) Baseline, Maximum, and Change in HR and Time to Max HR

Arbutamine + Treatment	Baseline HR (bpm ± S.E.)	Maximum HR (bpm ± S.E.)	Max HR change (base - max) (bpm ± S.E.)	Time to Max (min:sec)
Arbut alone: + atenolol: (N=12)	69.77 ± 3.77 57.16 ± 2.41 (P=0.007)	124.45 ± 4.88 115.91 ± 3.64 (p=0.086)	54.69 ± 4.29 58.77 ± 3.50 (p=0.500)	43:45 ± 6:19 50:07 ± 6:39 (p=0.381)
Arbut alone: + propran.: (N=8)	70.78 ± 4.74 59.50 ± 2.68 (p=0.020)	125.01 ± 6.05 96.56 ± 7.29 (p=0.006)	54.23 ± 3.28 37.06 ± 5.12 (p=0.020)	39:19 ± 8:17 64:56 ± 7:02 (p=0.005)

Table 2
TIme for 50% decrease in HR after end of Arbutamine Infusion per dose and treatment group (N = number of readings available)

Treatment Group	Dose (in (ug/kg/min)	Time for 50% Decrease in HR (in mins ± S.D.)
Arbutamine alone	0.15	11.8 + 6.1 (N = 4)
Arbutamine alone	0.21	13.4 + 6.8 (N = 3)
Arbutamine alone	0.3	19.2 + 8.8 (N = 8)
Arbutamine + atenolol	0.28	17.2 + 4.7 (N = 11)
Arbutamine + atenolol	0.40	17.1 + 4.1 (N = 9)
Arbutamine + atenolol	0.56	20.8 + 10.0 (N =6)
Arbutamine + propranolol	0.15	12.5 + 6.1 (N =18)
Arbutamine + propranolol	0.21	12.7 + 4.8 (N =15)
Arbutamine + propranolol	0.30	15.6 + 7.5 (N =7)

Both beta-blockers significantly reduced baseline HR prior to arbutamine infusion. As seen in previous studies (0110 and 0116), propranolol pre-treatment reduced the mean maximum and the maximum change in HR. Atenolol's effects were not readily distinguished from no treatment regarding these two parameters.

The firm's calculation of the Tmax data included the 20 minute washout between infusions, thus explaining the relatively large numbers seen with this data. Although both beta-blockers pushed the dose response cure to the right, propranolol's effects reached statistical significance.

The sponsor did not provide data regarding follow-up of the subjects after arbutamine testing. Only the time to 50% decrease of HR was provided. That value was not readily distinguishable between the three groups. However, the range of 12.7 to 20.8 minutes is reasonably consistent with the 13-14 minute figure seen in earlier studies (see, e.g., Protocol 0102, 0104). Also, these figures bring into question the adequacy of a 20 minute "washout period" between arbutamine infusions.

Table 3
Mean (±SE) Baseline, Maximum, and Change in SBP and Time to Max SBP

Arbutamine + Treatment	Baseline SBP (mmHg±S.E.)	Maximum SBP (mmHg±S.E.)	Max SBP change (base - max) (mmHg±S.E.)	Time to Max (min:sec)
Arbut alone:	128.25 ± 5.29	162.75 ± 4.02	34.50 ± 3.41	30:58 ± 7:33
+ atenolol:	122.00 ± 5.41	157.00 ± 4.42	35.00 ± 4.06	37:35 ± 7:48
(N=12)	(P=0.184)	(p=0.050)	(p=0.475)	(p=0.522)
Arbut alone:	118.00 ± 6.35	153.00 ± 8.19	35.00 ± 4.16	31:41 ± 8:19
+ propran.:	120.63 ± 7.84	156.25 ± 6.24	35.63 ± 6.15	37:59 ± 8:21
(N=8)	(p=0.594)	(p=0.534)	(p=0.942)	(p=0.557)

Table 4
Mean (±SE) Baseline, Minimum, and Change in DBP and Time to Min DBP

Arbutamine + Treatment	Baseline DBP (mmHg±S.E.)	Minimum DBP (mmHg±S.E.)	Min DBP change (base - min) (mmHg±S.E.)	Time to Min (min:sec)
Arbut alone:	77.75 ± 2.34	62.50 ± 2.14	-15.25 ± 0.79	19:52 ± 6:03
+ atenolol:	75.17 ± 3.19	54.83 ± 2.80	-20.33 ± 2.81	29:46 ± 6:46
(N=12)	(P=0.082)	(p=0.005)	(p=0.041)	(p=0.263)
Arbut alone:	74.13 ± 3.45	57.38 ± 4.87	-16.75 ± 3.73	14:48 ± 6:10
+ propran.:	76.13 ± 3.42	63.50 ± 3.70	-12.63 ± 2.22	12:06 ± 5:11
(N=8)	(p=0.521)	(p=0.218)	(p=0.511)	(p=0.797)

The effects of beta-blocker pre-treatment on BPs were minimal. While propranolol had little effect on either SBP or DBP, atenolol slightly but significantly decreased SBP, and had an even more dramatic effect to lower DBP over arbutamine treatment alone. Neither beta-blocker significantly altered the time to achieve maximum SBP or minimum DBP (again, these time calculations included the 20 minute infusion period).

Table 5
Mean (±SE) Baseline, Maximum, and Change in Pressure Rate Product (PRP) and Time to Max PRP

Arbutamine + Treatment	Baseline PRP (mmHg x bpm ±S.E.)	Maximum PRP (mmHg x bpm ±S.E.)	(base - max) PRP change (mmHg x bpm ±S.E.)	Time to Max (min:sec)
Arbut alone: + atenolol: (N=12)	8992 ± 747 6964 ± 399 (P=0.004)	18302 ± 853 16329 ± 790 (p=0.008)	9311 ± 685 9365 ± 648 (p=0.828)	41:13 ± 6:54 45:24 ± 7:23 (p=0.564)
Arbut alone: + propran.: (N=8)	8223 ± 616 7329 ± 539 (p=0.272)	17139 ± 1208 13979 ± 1166 (p=0.078)	8916 ± 780 6649 ± 1177 (p=0.116)	37:03 ± 7:27 63:33 ± 7:27 (p=0.162)

Atenolol pre-treatment significantly reduced PRP at baseline and the mean maximum PRP observed. Propranolol did not induce any significant changes in PRP.

In assessing efficacy, arbutamine infusion (alone) elicited a diagnosis of ischemia via ECG in 8/20 or 40% of patients. Beta-blocker pre-treatment elicited the diagnosis in 4/20 subjects (20%), of which 1/8 (12.5%) occurred on propranolol treatment, and 3/12 (25%) on atenolol.

DEVICE RESULTS:

In assessing the HR responses to varying doses of arbutamine ± beta-blockade, patient sensitivity (gain) was reduced in the presence of beta-blockade even at trough levels. With the control algorithm used in this study, the effects of the reduced gain are likely to trigger alarms during an ESA test, especially in the presence of propranolol. There was no difference in the onset delay between arbutamine alone group and the beta-blocker pre-treatment group. The onset time was constant was different in the presence of propranolol. The sponsor recommends that HR response in the presence of trough propranolol levels with longer washout periods (24, 36 hours) be further investigated.

APPEARS THIS WAY
ON ORIGINAL

SAFETY:

Table 6

Adverse Events by Treatment Group

ADVERSE EVENT (WHO preferred term)	Arbutamine alone (N=20)	Arbutamine + atenolol (N=12)	Arbutamine + propranolol (N=8)
Patients with Events	14 (70%)	7 (58%)	2 (25%)
Angina Pectoris	12 (60%)	5 (42%)	0 (0%)
Severe Hypotension	2 (10%)	1 (8%)	0 (0%)
Bradycardia	2 (10%)	0 (0%)	0 (0%)
Nausea	1 (5%)	0 (0%)	0 (0%)
Headache	1 (5%)	1 (8%)	1 (13%)
Dizziness	0 (0%)	1 (8%)	0 (0%)
Paresthesia	0 (0%)	1 (8%)	0 (0%)
IDIOVENTRICULAR RHYTHM	0 (0%)	1 (8%)	0 (0%)
dyspnea	0 (0%)	1 (8%)	0 (0%)
hot flushes	0 (0%)	1 (8%)	0 (0%)
malaise	0 (0%)	1 (8%)	0 (0%)
sweating	0 (0%)	1 (8%)	0 (0%)
VENTRICULAR TACHYCARDIA	0 (0%)	0 (0%)	1 (13%)
Chest Pain	0 (0%)	0 (0%)	1 (13%)

As can be seen from Table 6 above, both beta-blockers blunted the emergence of angina pectoris during arbutamine, propranolol completely suppressing its symptomatic emergence. Severe hypotension occurred in 10% of patients on arbutamine alone, 8% with atenolol pre-treatment, and 0% on propranolol pre-treatment. In this study, unlike previous studies, the sponsor much more fully documented the effects of arbutamine to lower SBP (see Table 7 below):

Table 7

Number of Patients with SBP drops categorized by level of drop from baseline SBP and by treatment

Level of SBP decrease (in mm Hg)	Arbutamine alone (# of patients) (N = 20)	Arbutamine + propranolol (# of patients) (N = 8)	Arbutamine + atenolol (# of patients) (N = 12)
10 - 19	3	3	2
20 - 29	1	0	3
30 - 39	1	0	1
≥ 40	1	0	1
Total 10 - ≥40	5	3	7

Twenty percent **(20%)** of patients receiving arbutamine infusions experienced some degree of hypotension. Thirty-eight percent **(38%)** of patients pre-treated with propranolol experienced hypotension during their arbutamine infusion (all mild episodes), whereas **58%** of atenolol pre-treated patients experienced hypotensive episodes. Although the magnitude of most of the decreases would pose a safety concern for only a few patients, a concern remains as to how adequately would subjects be stressed for their non-invasive test - that is, could there be underdiagnosis? The fact that arbutamine was able to identify only 40% of these study patients with known CAD adds weight to this potential concern.

Table 8
Arrhythmias by Treatment Group

ARRHYTHMIA	Arbutamine (N = 20)	Arbutamine + atenolol (N = 12)	Arbutamine + propranolol (N = 12)
Patients with Arrhythmias	20 (100%)	11 (92%)	8 (100%)
Premature Ventric Contract	19 (95%)	8 (67%)	8 (100%)
Premature Atrial Contract	13 (65%)	6 (50%)	3 (38%)
Sinus Arrhythmias	9 (45%)	1 (8%)	2 (25%)
Atrial Arrhythmia	4 (20%)	1 (8%)	1 (13%)
Ventricular Bigeminy	3 (15%)	2 (17%)	2 (25%)
Prem Vent Contr, Couplets	2 (10%)	3 (25%)	1 (13%)
Sinus Tachycardia	2 (10%)	0 (0%)	0 (0%)
Atrial Bigeminy	2 (10%)	0 (0%)	0 (0%)
Paroxys Atrial Fibrillation	1 (5%)	0 (0%)	1 (13%)
Sinus Bradycardia	1 (5%)	0 (0%)	0 (0%)
Sinoatrial Block	1 (5%)	0 (0%)	0 (0%)
Supraventricular Tachy	1 (5%)	1 (8%)	0 (0%)
Prem Vent Cont, triplets	1 (5%)	1 (8%)	0 (0%)
Ventricular Tachycardia	0 (0%)	0 (0%)	1 (13%)
Prem Contr Vent, multifocal	0 (0%)	0 (0%)	1 (13%)
Idioventricular rhythm	0 (0%)	1 (8%)	0 (0%)
Junctional rhythm	0 (0%)	1 (8%)	0 (0%)

As noted in Table 8 above, arrhythmias were very common in this population, although serious arrhythmias were not so. The episode of idioventricular rhythm and ventricular tachycardia (one 5-beat run) resolved uneventfully after discontinuance of arbutamine infusion.

Table 9
Arbutamine Infusion Duration, Dose, and Reasons (Adverse Event) for Stopping Infusion

Group	Events Causing Infusion Termination	% of Infusions Stopped due to Event	Duration of Arbutamine Infusion (mins) (mean ± SE)	Mean Arbutamine Dose (ug/kg ± SE)
Arbut alone (atenolol group) (N = 12)	Angina Pectoris Regimen Completed ECG changes Adverse Events	58 33 33 8	4.2 ± 0.6	21.2 ± 2.2
Arbut + atenolol: (N=12)	Angina Pectoris Regimen Completed ECG changes Adverse Events	42 33 17 25	8.7 ± 1.1 (p=0.002 as compared to arbut alone)	23.0 ± 2.1 (p=0.530 as compared to arbut alone)
Arbut alone (propran. group) (N = 8)	Angina Pectoris Regimen Completed ECG changes Adverse Events	63 25 50 13	3.9 ± 0.7	19.1 ± 2.5
Arbut + propran (N=8)	Regimen Completed ECG changes	100 13	16.4 ± 1.2 (p=0.005 as compared to arbut alone)	27.4 ± 2.3 (p=0.027 as compared to arbut alone)

As mentioned previously, Table 9 indicates that propranolol pretreatment produced a blunting effect on the emergence of symptomatic angina pectoris, much more so than atenolol. All of the arbutamine infusions were completed with propranolol pre-treatment as opposed to 25-33% percent with either arbutamine alone or atenolol pre-treatment. In addition, although both beta-blockers enabled arbutamine to be infused for a significantly longer time that no pre-treatment, only propranolol pre-treatment allowed for a significantly higher dose of arbutamine to be infused.

Table 10
Serum Potassium (in mEq/L) per treatment group at specified times

Draw Times for Serum Potassium	Arbutamine alone (N = 20)	Arbutamine + atenolol (N = 12)	Arbutamine + propranolol (N = 8)
Pre-arbut Infusion	4.3 ± 0.3	4.4 ± 0.2	4.3 ± 0.2
Immediately after	3.7 ± 0.3	3.6 ± 0.3	4.3 ± 0.6
30 minutes after	3.9 ± 0.3	3.8 ± 0.3	4.3 ± 0.6

Table 11

Beta-blocker* and arbutamine** plasma levels compared to adverse reactions experienced

Pt #	Propran. level (ng/ml)	Atenolol level (ng.ml)	Arbut level (alone) (ng/ml)	Arbut level (on Beta) (ng/ml)	Adverse Reaction Arbut alone	Adverse Reaction Arbut + Beta Blocker
1						
2						
3						
4						
5						
6						
8						
10						
11						
14						
15						
18						
19						
20						
21						
22						
23						
24						
25						
26						

* - beta-blocker levels drawn just prior to the series of arbutamine infusions

** - arbutamine levels drawn at the end of the last completed arbutamine infusion

*** - confirmed

As seen in Table 10, propranolol pre-treatment blunted the hypokalemic response to arbutamine. The effects of atenolol pre-treatment were indistinguishable from no pre-treatment as both caused serum potassium to drop 14-18% during arbutamine infusion. Recovery from arbutamine-

C ECG data: No QT or QTc data were available from the sponsor. The sponsor states that these data were not recorded.

D. Potassium Effects: As noted in Protocols 0110 and 0116, propranolol pre-treatment blunted the hypokalemic response to arbutamine. The effects of atenolol pre-treatment were indistinguishable from no pre-treatment as both caused serum potassium to drop 14-18% during arbutamine infusion. Recovery from arbutamine-induced hypokalemia was not completed in 30 minutes. As seen in protocols 0110 and 0118, two hours may be required before serum potassium levels returned to baseline.

4. Efficacy Questions: In assessing efficacy, arbutamine infusion (alone) elicited a diagnosis of ischemia via ECG in 8/20 or 40% of patients with known CAD and positive exercise tests. As has been noted in the Comments sections for the preceding protocols, this reviewer continues to have questions regarding arbutamine's efficacy, given the submaximal HR increases, the hypotensive episodes, and the lowering of DBP (separate from hypotensive episodes). However, the small number of patients in this study (N = 20), and the fact that arbutamine was infused using the open-loop option of the genESA system may limit the generalizability of these concerns

5. Effects of Beta-blockade: Beta-blocker pre-treatment elicited the diagnosis of ischemia in 4/20 subjects (20%), of which 1/8 (12.5%) occurred on propranolol treatment, and 3/12 (25%) on atenolol. Thus, it appears that more than a 24 hour interval between a beta-blocker dose (given during steady-state) and an arbutamine infusion is necessary for more accurate diagnosis (especially if the beta-blocker is propranolol). How much longer than 24 hours is not clear from the results of this study. Of note is that plasma arbutamine levels were much higher in subjects pre-treated with beta-blockers as opposed to no pre-treatment. This may be because beta-blocker pre-treatment allowed longer infusion times/higher doses of arbutamine to be infused. However, this reviewer can not rule out a pharmacokinetic interaction.

APPEARS THIS WAY
ON ORIGINAL

14 pages

PURGED

Confidential

Commercial

Information

OVERALL COMMENTS

1. Pharmacodynamic Effects, Heart Rate (HR), Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP): In healthy normal subjects, the highest infusion rates of arbutamine raised HR 60 to 70 bpm, raised SBP 42 to 47 mm Hg, and lowered DBP 11 to 18 mm Hg from baseline readings. In the one study of 20 coronary artery disease (CAD) patients, arbutamine raised HR 55 bpm, raised SBP 35 mm Hg, and lowered DBP 16 mm Hg from baseline. However, arbutamine infusions were never able to raise HR to 85% of normal subjects' s exercise tolerance test (ETT) HR. Other than HR data, the sponsor has provided little SBP/DBP data from ETTs. However, from the data provided, SBP increases from arbutamine infusions never attained the levels achieved with ETT, and DBPs were consistently lowered by arbutamine as opposed to ETT which raised DBP.

2. Safety Concerns:

   A. Hypotension: There were a number of hypotensive episodes with arbutamine. With diverse regimens and small numbers of subjects, it is difficult to accurately describe the incidence and severity of these episodes. In addition, although graphical representations of arbutamine infusions often demonstrated sudden drops in blood pressure, data quantitating these episodes was often missing from data tables. Thus, for the most part, these events were described by this reviewer by estimating data from a graph. The sponsor was made aware of this missing information and has committed to insuring that any missing data from phase II/III trials are brought to our attention. Although the severity of most of the hypotensive episodes reported was mild, there were a few cases of DBP readings below 45 mm Hg and/or SBP readings below 95 mm Hg. Even if the vast majority of these episodes do not pose safety concerns, this reviewer is concerned that these events may decrease cardiac work/stress, possibly resulting in underdiagnosis of CAD (see Comment #3).

   B. ST segment depression/chest pain: In Protocol 0110, 3 subjects with hypotensive episodes demonstrated some degree of ST segment depression. Although depressions less than 0.5 mm occurred in 2 of the 3 subjects, the third subject (an otherwise healthy 27 year old white male) demonstrated 1-2 mm ST segment depression during an arbutamine-induced hypotensive episode. Other studies have contained occasional reports of poorly characterized chest pain. Clearly, if DBP is lowered beyond the point of maintaining coronary blood flow, ischemic symptoms could result, even in healthy normal subjects. Thus, it is possible that arbutamine possesses a unique property that induces/causes ischemia even in healthy normal subjects. However, it seems more likely that these ischemic events are resultant from hypotensive events. This reviewer also believes that these albeit infrequent arbutamine-induced hypotensive episodes could be problematic in select patients with serious CAD. In addition, this reviewer is concerned that arbutamine could result in a false positive or obscure result during a non-invasive test for CAD that could prompt additional (unnecessary) diagnostic measures.

   C. Arrhythmogenesis: Arbutamine induced a variety of arrhythmias. The vast majority of these were not serious, and the very few arrhythmias that were serious (bigeminy, idioventricular rhythm, 5-beat ventricular tachycardia) resolved quickly, either by

discontinuance of arbutamine infusion, or a single-dose of IV lidocaine or propranolol.

However, arbutamine infusions are associated with two phenomena that could potentially facilitate arrhythmia induction. The first of these phenomena is hypokalemia. Plasma potassium levels measured immediately following an arbutamine infusion ranged 12-30% lower than pre-infusion levels. However, plasma potassium had generally returned to baseline within 2 hours after the end of the arbutamine infusion.

The second potentially arrhythmogenic phenomenon is prolongation of the QTc interval. This data is quite preliminary (data from two studies, Protocols 0102 and 0103), but merits verification from Phase II/III data. In Protocol 0102, subjects' ETT HR averaged 189.9 bpm (N=34), and their QT_c interval was prolonged a maximum of 32.1 milliseconds (msec). However, arbutamine doses that raised HR over 100 bpm resulted in maximal QTc intervals ranging from 55 to 67 msec over baseline. Transdermal arbutamine treatments produced similar prolongations. While 20% of subjects undergoing ETT experienced QTc interval prolongations $\geq$ 440 msec, maximal QTc $\geq$440 msec occurred in 9/11 subjects (82%) receiving arbutamine starting with the 0.0448 ug/kg/min dose and up. These are preliminary observations based on limited data, but merit further investigation.

3. Sensitivity/Specificity Questions: Arbutamine did not raise HR and SBP to levels achieved in ETT and actually lowered DBP (opposite the effect seen in ETT). Although serious hypotensive episodes were rarely induced by arbutamine, milder episodes were more frequent. Thus, this reviewer is concerned that in select patients, arbutamine may produce a suboptimal level of cardiac work, leading to underdiagnosis of CAD. This potential concern is fueled further by the results of Protocol 0119 where in 20 patients with a positive ETT for CAD, arbutamine was able to diagnose CAD in only 40% of these subjects. It is important to emphasize again that only 20 patients were studied, and that all infusions were administered using the open-loop format; thus, larger studies using the closed-loop system could generate more favorable results. Phase II/III data should be carefully examined to assess arbutamine's sensitivity.

In addition, Phase II/III data should be investigated to assess arbutamine's specificity given that 3 healthy normal subjects demonstrated ST segment depression during arbutamine infusions (all three were during hypotensive episodes, and only one "diagnostic" of CAD).

4. Effects of Atropine pre-treatment: During dobutamine stress tests, patients are often given atropine to increase their HR response. Protocol 0118 studied the use of atropine combined with arbutamine in 21 normal volunteers of average age 53 years. The effects of arbutamine and atropine were additive, atropine's predominant effect being to increase the HR prior to arbutamine infusion. However, the use of atropine was associated with an increased incidence of arrhythmias, severe hypotension, and chest pain as compared to subjects without atropine pre-treatment. Given the possibility that atropine may be used with arbutamine (especially in light of arbutamine's suboptimal HR effects), the sponsor should either modify the labeling to include mention of these adverse events, or perform a study of this combination in a larger series of patients.

5. Effects of Beta-blocker pre-treatment: Given the likelihood that many patients undergoing a stress test may already be on beta-blockers, this is an important interaction to study. As might be expected, the non-selective beta-blocker propranolol blunted the effects of the non-selective beta-adrenergic agonist arbutamine much more effectively than either metoprolol or atenolol, both selective $beta_1$-blockers. Two of the three beta-blocker studies involved infusion of arbutamine 23-24 hours after the last dose of beta-blocker (at trough). In these studies, the maximal HR response with the selective beta-blockers was similar to arbutamine alone, although the selective beta-blocker did push the dose-response cure to the right. However, pre-treatment with propranolol significantly reduced the maximal HR response to arbutamine and significantly pushed the dose-response curve to the right. Additionally, the selective beta-blockers appeared to result in slightly lower DBP than arbutamine alone.

Adverse events appeared to be attenuated somewhat by propranolol, whereas adverse events appeared comparable between the selective beta-blockers and arbutamine alone. Of note was that in the 20 ETT positive CAD patients from protocol 0119, while arbutamine diagnosed CAD in 8/20 subjects, atenolol elicited this diagnosis in 3/12 patients (25%) and propranolol 1/8 (12.5%). Thus it appears that more than a 24 hours are needed between a beta-blocker dose (given during steady-state) and an arbutamine infusion to be free of beta-blocker effects (especially if the beta-blocker is propranolol). Apparently , the sponsor has conducted beta-blocker washout studies determining that a minimum of 48 hours is needed between arbutamine infusion and the last dose of beta-blocker.

Another question involving beta-blockers: could they be used as "antidotes" for arbutamine-induced adverse reactions? Given the data in this portion of the NDA, the answer is unclear. Certainly, it would seem logical to use a non-selective beta-blocker such as propranolol over a selective one. Intravenous propranolol has been used to treat arbutamine-induced PVCs in one subject, but as has lidocaine - with no apparent difference in efficacy between the two treatments. In Protocol 0103, pre-treatment with propranolol blunted the ECG effects of transdermal arbutamine (including prolongation of the QTc interval) These are hardly the type of data that would justify the use of propranolol over other antiarrhythmics. In Protocol 0104, one subject's SBP rose to 193 mm Hg during an arbutamine infusion, and this was treated with discontinuance of infusion and a single-dose of IV propranolol. Again, this is hardly data that positions propranolol above other therapies. Also, given the lack of hypotensive episodes in propranolol pre-treated subjects, one could make a theoretical case for use of propranolol to treat arbutamine-induced *hypotension*. Once again, this issue has not been studied. Thus overall, there is no convincing data in this portion of the NDA that places non-selective beta-blockers over other therapies for arbutamine-induced adverse events.

Lastly, in Protocol 0119, higher plasma arbutamine levels were observed in patients pre-treated with beta-blockers. Although beta-blocker pre-treated subject received longer infusions and higher doses of arbutamine than un-pre-treated subjects, this reviewer cannot rule-out a pharmacokinetic interaction between beta-blockers and arbutamine.

RECOMMENDATIONS

1. Phase II/III studies should be carefully assessed (with both ECG and radionuclide imaging data) to confirm arbutamine's **sensitivity and specificity** in diagnosing CAD. Preliminary data raise concerns regarding arbutamine's ability to provide for an optimal stress test.

2. Regarding **QTc interval prolongation,** phase II/III studies should be assessed to confirm the sponsor's statement in the PRECAUTIONS section that "*This effect did not appear to be associated with an increased incidence of arrhythmias.*"

3. Regarding **atropine,** the WARNINGS section states: "*...arbutamine should not be administered to patients receiving...atropine...The use of atropine to enhance the chronotropic response to arbutamine is not recommended, given that the dosing of arbutamine is based on the HR response of the patient.*" Nonetheless, the possibility exists that atropine may eventually be used with arbutamine (as is done with dobutamine). Given the increase in adverse reactions observed in Protocol 0118 when these two agents were combined, this reviewer recommends adding this statement to this section: "*In a study of 21 healthy normal subjects (mean age of 53 years), the use of atropine combined with arbutamine was associated with an increased incidence of arrhythmias, hypotension, and chest pain.*" Alternatively, the sponsor could perform a study in a much larger group of actual patients comparing the incidence of adverse events between atropine/arbutamine and arbutamine alone.

4. The ADVERSE EVENTS section of the label states: "*If considered clinically appropriate, signs of symptoms including angina, tachyarrhythmias, ST segment deviation, and hypertension may be successfully treated with intravenous **beta-blockers,** such as metoprolol, esmolol or propranolol.*" In this portion of the NDA, the sponsor has not presented convincing data that would suggest beta-blockers be used over other existing therapies to treat arbutamine-induced adverse events. If this statement is based more on logic and mechanism of action arguments, then the use of non-selective beta-blockers such as propranolol would seem preferable to selective agents such as esmolol, atenolol, or metoprolol. The sponsor's labeling should be confirmed by data from phase II/III studies.

   Also, the DRUG INTERACTIONS section states: "*Beta-adrenergic antagonists may attenuate the response to arbutamine and should be withdrawn...at least 48 hours before conducting a GenSEA test.*" Similarly, the CLINICAL PHARMACOLOGY section reads: "*The effects of arbutamine on HR and systolic blood pressure are attenuated by concurrent administration of selective and non-selective beta-blockers.*" If the differential effects of selective and non-selective beta-blockade (observed in Protocol 0110, 0116, and 0119) are confirmed by phase II/III studies, this labeling should mention that this attenuation is especially the case for non-selective agents.

5. The PRECAUTIONS section of the label states: "*GenESA...can produce a transient reduction in serum potassium concentration, rarely to* ***hypokalemic*** *levels.*" This statement should be confirmed by data from phase II/III studies, since a number of hypokalemic (<3.5 mEq/L) readings were observed in subjects upon termination of arbutamine infusion.

6. The labeling discusses the effects of arbutamine on HR and SBP, but does not mention that arbutamine (in this database) routinely lowered DBP (as opposed to ETT which increased DBP). Once confirmed by phase II/III studies, a statement regarding arbutamine's effects on DBP should be included in the labeling for this product.

10/11/94

Igor Cerny, Pharm.D.
Interdisciplinary Scientist

cc: Fenichel
Buehler
NDA 20-420 (file)
Cerny
Stockbridge

Addendum #1 to Arbutamine (NDA 20-420) CLINICAL PHARMACOLOGY REVIEW

Sponsor: **Gensia**

Submission Date: **December 23, 1993**

Reviewer: **Igor Cerny, Pharm.D.**

Date of Addendum: October 24, 1994

Throughout the Clinical Pharmacology studies, arbutamine appeared to exhibit a somewhat linear dose response with regards to heart rate (HR). However, analysis of this dose-response was difficult to assess since doses of arbutamine infusion were quite variable: arbutamine was infused in doses ranging from 0.05 ug/kg/min to 1.1 ug/kg/min for anywhere from 5 minutes to 32 minutes. Also, sometimes these doses were separated by washout periods whose duration may have been insufficient.

The sponsor attempted to address the variable infusion dose/time issue by characterizing response in terms of **total dose** infused (e.g., 0.1 ug/kg/min x 20 minutes = **2 ug/kg** total dose). However, since arbutamine has an estimated half-life of 8 minutes, this total dose consideration is inadequate (e.g., referring to the above example, a 0.2 ug/kg/min infusion lasting 10 minutes would also give a total dose of **2 ug/kg**, yet the two regimens may have dramatically different effects).

This inability to more precisely characterize the dose-response of arbutamine has concerned this reviewer. However, in discussions with the Division's biopharmaceutics group, a method was suggested. This method generates a simulated plasma concentration based on a mean estimation of arbutamine's elimination rate constant (Ke) and volume of distribution (Vd):

$$C_T = C_{ss}(1 - e^{-KeT}) \quad \text{and} \quad C_{ss} = Ko/Ke \times Vd.$$

Where:
- C_T = the concentration at (pre-determined) time T
- C_{ss} = the steady-state/plateau plasma concentration
- Ko = infusion rate
- Ke = the elimination rate constant (= 0.086 min^{-1})
- Vd = volume of distribution (= 0.74 L/kg)
- T = a pre-specified time (in this case the time of maximal HR)

Population values were used for Vd and Ke, while T was the time of maximal HR. Thus the C_T represents simulated arbutamine concentration at the time of maximal HR. Data to generate this analysis was gathered from studies where Tmax data was available for all infusions (0102, 0104, 0105, 0118). This data was then cataloged (attachment 1) and plotted (Chart 1).

The data reveals a classic dose-response curve, somewhat linear in the early stages, then as maximal HR is achieved, increasing drug concentrations have little effect and the curve tapers-off (binomial plot, $R^2 = 0.806$). Tapering of the curve begins at the 50-60 bpm range (for HR) and between (simulated) arbutamine plasma concentrations of 1.5 and 2.0 ng/ml. Thus the HR response to an increase in the amount of arbutamine infused depends on the part of the dose-response curve the subject is on.

10/24/94
Igor Cerny, Pharm.D.

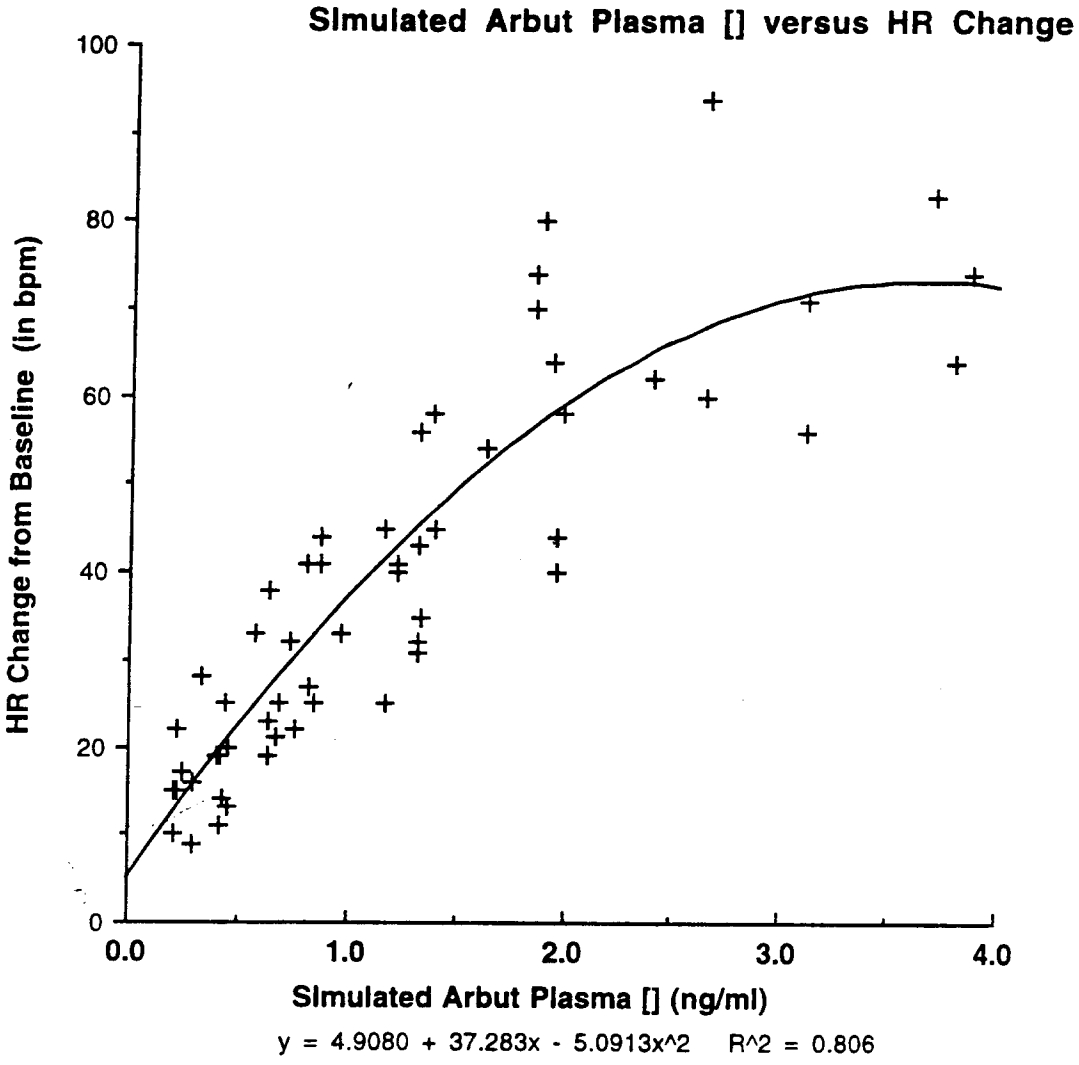
APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 20-420
Fenichel
Buehler
Cerny

CHART 1


Simulated Arbut Plasma [] versus HR Change
HR Change from Baseline (in bpm)
100
80
60
40
20
0
0.0
1.0
2.0
3.0
4.0
Simulated Arbut Plasma [] (ng/ml)
y = 4.9080 + 37.283x - 5.0913x^2 R^2 = 0.806

Arbut Conc vs HR change

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Study	SUbj #	Weight (kg)	Rate (ug/kg/m)	Ko (ug/min)	Tmax	CT	T of 50% drop	Css	Inf Dur.	kT	CT	HR max delta
2	102	29											
3	102	30											
4	102	31											
5	102	32											
6	102	33											
7	102	34											
8	102	35											
9	104	1											
10	104	2											
11	104	3											
12	104	4											
13	104	5											
14	104	6											
15	105	1											
16	105	1											
17	105	1											
18	105	2											
19	105	2											
20	105	2											
21	105	3											
22	105	3											
23	105	3											
24	105	4											
25	105	4											
26	105	4											
27	105	5											
28	105	5											
29	105	5											
30	105	6											
31	105	6											
32	105	6											
33	105	7											
34	105	7											
35	105	7											
36	105	8											
37	105	8											
38	105	8											
39	118	1											
40	118	1											
41	118	1											
42	118	2											
43	118	2											
44	118	2											
45	118	4											
46	118	4											
47	118	4											
48	118	7											
49	118	7											
50	118	7											
51	118	9											
52	118	9											
53	118	9											
54	118	10											
55	118	10											
56	118	10											
57	118	20											
58	118	20											
59	118	20											