ONLINE APPENDIX

I. List of Study Site Investigators

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Dr. Francis Agnone Phoenix AZ (9), Dr. Meera Amar Waco TX (13)

Dr. Corey Anderson Sun City AZ (65), Dr. Harold Bays Louisville KY (30)

Dr. Bruce Bowling Endwell NY (72), Dr. Paul Bristol Austin TX (16)

Dr. Dennis Buth Wichita KS (49), Dr. Jambur Chandrashekar Indio CA (15)

Dr. Teresa Coats Austin TX (5), Dr. Pankaj Desai Owings Mills MD (15)

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Dr. R. David Ferrera Sacramento CA (30), Dr. Jerome Fischer San Antonio TX (81), Dr. Steven Folkerth Las Vegas NV (10), Dr. Neil Fraser Troy MI (41)

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Dr. Kurt Lesh Colorado Springs CO (54), Dr. James Lieber Chandler AZ (9)

Dr. Timothy Linder Selmer TN (9), Dr. Thomas Littlejohn III Winston-Salem NC (152), Dr. N. Martin Lunde Brooklyn Center MN (37), Dr. Scott Meyers Wichita KS (77), Dr. Richard Mills Mt. Pleasant SC (66), Dr. Manuel Modiano Tucson AZ (33), Dr. David Morin Bristol TN (97), Dr. Julio Pagan Dyersberg TN (4)

Dr. James Payne Jackson TN (3), Dr. Geri Poss San Antonio TX (10)

Dr. George Raad Charlotte NC (103), Dr. Patrick Rask Portland OR (9)

Dr. Marc Rendell Omaha NE (53), Dr. L. Edward Roberts, Jr. Lexington KY (12)

Dr. Jeffrey Rosen Coral Gables FL (36), Dr. Eli Roth Cincinnati OH (28)

Dr. John Rubino Raleigh NC (21), Dr. Steven Russell Philadelphia PA (5)

Dr. Robert Schreiman Santa Ana CA (39), Dr. Sherwyn Schwartz San Antonio TX (23), Dr. William Seger Fort Worth TX (23), Dr. Danny Sugimoto Chicago IL (90), Dr. Allen Sussman Renton WA (33), Dr. Phillip Toth Indianapolis IN (61)

Dr. Sunil Verma Warwick RI (25), Dr. Aaron Vinik Norfolk VA (8), Dr. Ralph Wade Bountiful UT (14)

II. Key Study Personnel

Study Oversight

Randomization was conducted using a telephone-based system with fax-back confirmation. Subjects were randomly allocated using a 5 digit subject number by study center with blocks of 6 subject numbers per block (4 bromocriptine-QR and 2 placebo per block). All
study drug was bottled centrally with unique bottle numbers and distributed by the VA Clinical Research Pharmacy, Albuquerque, NM. First patient enrolled 23 August 2004 and last patient completed 25 January 2007.

An independent data safety and monitoring board (DSMB) met quarterly and reviewed unblinded data. An independent safety monitor and safety officer processed all serious adverse events. Overall study oversight was by a steering committee consisting of two academic principle study investigators (Drs. Scranton and Gaziano), members responsible for site management coordination (Clinical Research Management of Agawam, MA and Veterans Affairs Cooperative Studies Program center located in Boston, MA), and members of the data and statistical coordinating center (EVEREST Inc., Toronto, CA).

| Safety Study                  | Name                    | Affiliation/Contact Information |
|------------------------------|-------------------------|--------------------------------|
|                              | Dean Rutty, MSc         | Everest Clinical Research Services, Inc |
| Study Biostatistician        |                         | 675 Cochrane Drive, Suite 408, East Tower Markham, Ontario, Canada L3R 0B8 |

| Data Safety Monitoring Committee (DSMC) | Name                                      | Affiliation/Contact Information                  |
|---------------------------------------|-------------------------------------------|--------------------------------------------------|
|                                       | Jonathan Seltzer, MD, MBA, MA, FACC       | Applied Clinical Intelligence, LLC               |
| Cardiologist: DSMC Chair              | 212C Race Street                          | Philadelphia, PA 19106                           |
|                                       | Timothy Allan Shapiro, MD                 | Science for Organizations, Inc.                 |
| Cardiologist                          | 380 Lankenau Medical Science Building     | Wynnewood, PA 19096                             |
|                                       | 100 Lancaster Avenue West of City Line    |                                                  |
|                                       | Jerry Gardener, MD                        |                                                  |
| Endocrinologist                       | 156 Terrace Drive                         |                                                  |
|                                       | Lawrence Leiter, MD                       | Head, Division of Endocrinology & Metabolism     |
| Endocrinologist                       | St. Michael’s Hospital                    |                                                  |
|                                       | Irving Hwang, PhD                         | Irving Consulting Group                          |
| Biostatistician                       | P. O. Box 258                             | Pluckemin, New Jersey 07978-0258                 |
|                                       | Patricia Lynn Ruppel, PhD                 | Innovative Analytics                             |
| Unblinded Trial Biostatistician       | 161 East Michigan Ave.                    |                                                  |
|                                       |                                            | Kalamazoo, MI 49007                              |

| Event Adjudication Committee Members | Name/Role                                    | Affiliation/Contact Information                  |
|-------------------------------------|----------------------------------------------|--------------------------------------------------|
|                                    | Christopher O’Connor MD, FACP,                | Professor of Medicine                            |
|                                    | FACC                                         | Duke Clinical Research Institute                 |
|                                    | EAC Chair                                    |                                                  |
|                                    | Peter Carson MD                              | Washington D.C. VA Medical Center                |
|                                    | Jennifer Green, MD                           | Duke University Medical Center                   |
|                                    |                                              | Division of Endocrinology, Metabolism, and Nutrition |

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III. Disclosures
Dr. Gaziano reports that he currently or in the past two years has received investigator-initiated federal funding from National Institutes of Health (NCI, NHLBI, NIA, NEI) and the VA (CSP) and non-federal investigator initiated funding from Amgen and Pliva; has received research support in the form of pills and or packaging from Wyeth Pharmaceuticals; has received honoraria from Bayer and McNeil Consumer Products for speaking engagements. Dr. Scranton has served within in the past five years as consultant or advisor for Berlex, Sanofi-Aventis; a scientific investigator for Pfizer Inc, MERCK, Pliva, Berlex Pharmaceuticals, and received research funding from Pharmerit North America and VA (CSP), and currently serves as the Chief Medical Officer for VeroScience. Anthony Cincotta is the Chief Science Officer of VeroScience. Dean Rutty and Jonathon Ma report no conflicts of interest.
Appendix IV Figure A — Subject Disposition

4074 assessed for eligibility

879 ineligible
644 protocol ineligibility
184 Withdraw consent
2 Administrative
58 Lost to follow up
91 Other

2:1 bromocriptine-QR to placebo
Randomization
(n = 3095)

25 did not receive study drug
13 bromocriptine-QR and 12 placebo

2054 bromocriptine-QR

115 (5.6%) Lost to follow up
845 Stopped treatment
498 Adverse events
33 Protocol deviations
4 Deaths*
187 Withdrawal of consent
21 Investigator decision
102 Other

Completed Assessment
- 9 Died*
- 1838 had final visit
- 92 did not have final planned visit but were alive at study end

2054 Bromocriptine-QR and 1016 placebo included in the ITT analysis
2364 subjects completed the study accounting for a total person time of 2906 person years (92% of expected)
1921 person years bromocriptine-QR and 984 person years on placebo

1016 placebo

55 (5.4%) Lost to follow up
266 Stopped treatment
107 Adverse events
27 Protocol deviations
2 Deaths*
72 Withdrawal of consent
13 Investigator decision
45 Other

Completed Assessment
- 3 Died*
- 927 had final visit
- 31 did not have final planned visit but were alive at study end

*Deaths: Bromocriptine-QR - 9 deaths (4 deaths while on treatment and 5 after treatment had stopped);
Placebo- 3 deaths (2 deaths while on treatment and one death after treatment had stopped)
## Appendix IV Table B — Baseline and change from baseline laboratory and blood pressure data in patients with Type 2 Diabetes

|                          | Level at Baseline | Change from Baseline | p value |
|--------------------------|-------------------|----------------------|---------|
|                          | Bromocriptine-QR  % | Placebo 6.8 (6.2, 7.6) | Absolute change | Placebo 0.2 (-0.3, 0.7) |        |
| **HbA1c, median (IQR)**  | 6.7 (6.2, 7.5)    | 0.1 (-0.3, 0.5)      |         | 0.0002 |
| **Lipids**               |                   |                      |         |       |
| Triglycerides, median (IQR) | 1.6 (1.1, 2.4) 1.67 (1.2, 2.4) | -5 (-26.0, 23.2) -0.4 (-22.7, 23.6) | 0.0283 |
| LDL cholesterol, median (IQR) | 2.4 (1.9, 2.9) 2.36 (1.9, 2.9) | -1.6 (-17.0, 15.6) -1.2 (-16, 16.0) | 0.6312 |
| HDL cholesterol, median (IQR) | 1.1 (1.0, 1.3) 1.1 (0.9, 1.3) | -2.5 (-10.5, 6.4) -3.2 (-10.7, 5.9) | 0.1807 |
| Total cholesterol, median (IQR) | 4.4 (3.8, 5.0) 4.3 (3.8, 5.0) | -2.1 (-11.9, 8.9) -1.5 (-11.6, 9.6) | 0.4784 |
| Total cholesterol/HDL ratio, median (IQR) | 3.85 (3.2, 4.6) 3.8 (3.3, 4.5) | 0.44 (-10.4, 12.2) 1.8 (-8.6, 13.8) | 0.1211 |
| Blood pressure:†         |                   |                      |         |       |
| Systolic blood pressure, median (IQR) | 130 (120, 140) 130 (120, 139) | -2.0 (-13.0, 8.0) 0.0 (-10.0, 10.0) | 0.0182 |
| Diastolic blood pressure, median (IQR) | 78 (70, 82) 77 (70, 82) | -2.0 (-9.0, 5.0) -1.0 (-8.0, 5.0) | 0.0249 |

†blood pressure value at screening visit
p-value comparing the two treatment arms is calculated using Wilcoxon Rank Sum test
Hb = hemoglobin; HDL = high density lipoprotein; LDL = low density lipoprotein; IQR interquartile range
## Appendix V Consort Statement

| PAPER SECTION And topic | Item | Descriptor | Reported on Page # |
|------------------------|------|------------|-------------------|
| TITLE & ABSTRACT       | 1    | How participants were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned"). | 1 |
| INTRODUCTION Background| 2    | Scientific background and explanation of rationale. | 1 |
| METHODS Participants   | 3    | Eligibility criteria for participants and the settings and locations where the data were collected. | 1-2 |
| Interventions          | 4    | Precise details of the interventions intended for each group and how and when they were actually administered. | 2-3 |
| Objectives             | 5    | Specific objectives and hypotheses. | 3-4 |
| Outcomes               | 6    | Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors). | 4 |
| Sample size            | 7    | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules. | 4-5 |
| Randomization -- Sequence generation | 8 | Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification) | Appendix II |
| Randomization -- Allocation concealment | 9 | Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned. | Appendix II |
| Randomization -- Implementation | 10 | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups. | Appendix II |
| Blinding (masking)     | 11   | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated. | Appendix II |
| Statistical methods    | 12   | Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses. | 5 |
| RESULTS Participant flow| 13  | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons. | 5 appendix IV |
| Recruitment            | 14   | Dates defining the periods of recruitment and follow-up. | Appendix II |
| Baseline data          | 15   | Baseline demographic and clinical characteristics of each group. | Appendix II |
| Numbers analyzed       | 16   | Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%). | 5 |
| Outcomes and estimation| 17   | For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval). | 7, table 2 |
| Ancillary analyses     | 18   | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory. | 3-4; 6-7 |
| Adverse events         | 19   | All important adverse events or side effects in each intervention group. | 7-9 |
| DISCUSSION Interpretation | 20 | Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes. | 9-11 |
| Generalizability       | 21   | Generalizability (external validity) of the trial findings. | 10 |
| Overall evidence       | 22   | General interpretation of the results in the context of current evidence. | 11 |