Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kesselheim AS, Robertson CT, Myers JA, et al. A randomized study of how physicians interpret research funding disclosures. N Engl J Med 2012;367:1119-27. DOI: 10.1056/NEJMoa1202397

Supplementary Appendix

TABLE OF CONTENTS

Section 1. Additional Details on Methods

In this section of the Appendix, we present further specificity regarding our methodology for data analysis, and additional results not reported in the primary article.

Proportional Odds Model

For each question, we estimated a hierarchical proportional odds regression model using the appropriate Likert-scale response as the outcome. This model included a random intercept for each physician to account for within-physician correlation of responses across abstracts, as well as fixed effects for methodological strength (low, moderate, high), funding source (pharmaceutical industry, none, NIH), and drug. Models were estimated using the ordinal package in the R statistical environment.

Specifically, if Y_{ij} is the response on abstract j for physician i, then the regression model is given by

$$\log\left\{\frac{\Pr(Y_{ij} \geq k)}{\Pr(Y_{ij} < k)}\right\} = \beta_k + \beta_B B_{ij} + \beta_P P_{ij} + \beta_L L_{ij} + \beta_H H_{ij} + \beta_{ND} ND_{ij} + \beta_{NIH} NIH_{ij} + \delta_i$$

$$\delta_i \sim N(0, \sigma^2)$$

where B is the indicator of the drug "bondaglutaraz" and P is the indicator of "provasinab" ("lampytinib" is the reference), L is an indicator of low methodological strength and H is an indicator of high methodological strength (moderate is the reference), and ND indicates no disclosure of funding source while NIH indicates NIH funding (industry funding is the reference). Correlation among the responses within each physician is modeled via the random effect δ_i, and we assume that this effect is normally distributed across physicians with mean zero and variance that is estimated from the data.

The outcome is modeled as the log of the odds of a score of k or higher versus less than k. In this sense, the coefficients may be interpreted similar to coefficients from a logistic regression model where responses were dichotomized as being greater than or equal to k versus less than k. By definition, the proportional odds model assumes that model coefficients are the same for all potential cutoff scores, k in {2, 3, 4, 5, 6, 7}. Therefore, the regression coefficients may be interpreted as the log odds ratio of a higher score (versus lower score) for any potential score cutoff. For example, e^{β_H} is the odds ratio comparing the odds of a high score for abstracts with high methodological strength to the odds of a high score for abstracts with moderate methodological strength. The proportional odds assumption indicates that this odds ratio is the same regardless of which cutoff on the Likert-scale is used to define "high score."

Model Diagnostics

For the primary hypotheses, we evaluated the adequacy of the proportional odds assumption by estimating independent logistic regression models using each potential score cutoff to dichotomize responses. We then compared estimated coefficients and confidence intervals across models to determine if there was evidence that the proportional odds assumption was violated. **Figure S1** shows that, with the exception of very high or very low cutoffs that result in estimates with very poor precision, the coefficients from the proportional odds model (POM) are similar to those across the logistic regressions using varying score cutoffs, indicating that the proportional odds assumption is generally well supported.

Analysis of Physician Characteristics

To investigate potential confounding by physician characteristics, we focused on the three primary questions (perception of study rigor, confidence in the conclusions, and willingness to prescribe for an appropriate patient) and fit proportional odds models. These models included

random intercepts for physicians, indicators for the variables describing methodological strength, funding source, and drug, as well as terms for physician characteristics: age, gender, medical school location (US versus non-US), practice type (general internal medicine versus subspecialty), time in clinical care activities (≥80% versus <80%), hrs/mo in clinical care (≥80 versus <80), acceptance of gifts from industry (any versus none), and reported belief that industry funding influences the outcome of studies in favor of the drug being tested (≥6 versus ≤5 on the 7-point scale). **Table S1** shows the results from these models.

Characteristics of Respondents and Non-Respondents

We also compared the differences between survey respondents and non-respondents on these same physician characteristics. We made the comparisons using chi-square tests for categorical variables and t-tests for continuous variables. As seen in **Table S2**, there were no significant differences between respondents and non-respondents in any personal or professional demographic characteristic that we were able to observe.

Section 2. Survey

In this section of the Appendix, we present the hard-copy and email communications to the survey sample, the survey flow and questions pertaining to each abstract. The 27 versions of the abstracts are presented in the next section of the Appendix. Page formatting has not been preserved.

A. POSTCARDS

[introductory post card]

Check your email!

The American Board of Internal Medicine Foundation will be sending you a link for an important on-line survey to help us study clinical decisionmaking about medications.

We need your help!

We will offer you a $50 honorarium for just 15 minutes of your time.

This project has been organized by researchers at Brigham and Women's Hospital, Harvard University, and the University of Arizona, and is not associated with any pharmaceutical manufacturer. You will be receiving the email with the survey link in the next few weeks. If you do not hear from us, or have any questions, please contact:

Kathryn M. Ross, MBE
Research Coordinator for Quality Research
American Board of Internal Medicine
510 Walnut Street, Suite 1700
Philadelphia, PA 19106
(p) 215-399-4060
(f) 215-399-4085
kross@abim.org

[follow up post card]

We have not heard from you!

A few weeks ago, the American Board of Internal Medicine Foundation sent you a link for an important on-line survey to help us study how physicians make prescribing decisions.

We still need your help!

We are offering a $50 honorarium for just 15 minutes of your time.

This project has been organized by researchers at Brigham and Women's Hospital, Harvard University, and University of Arizona and is not associated with any pharmaceutical manufacturer. If you did not receive an email, please contact:

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B. INTRODUCTORY EMAIL/COVER PAGE TO PAPER VERSION

You have been randomly selected to participate in a study to investigate how physicians make prescribing decisions. The American Board of Internal Medicine (ABIM) is partnering with researchers at Brigham and Women's Hospital, Harvard University, and the University of Arizona to conduct this study. The study is funded by an independent research center at Harvard, and is not connected with any pharmaceutical company. This study has been approved by the Institutional Review Board at Brigham and Women's Hospital.

Your views are highly valuable and we greatly appreciate your willingness to participate. As a token of our appreciation, we will give you a full $50 honorarium after you return the completed survey. We will also send you a copy of the final report of this research, if you would like.

You may fill out this hard copy, or go to [URL]

Your responses will be kept confidential and shared only with the academic researchers working on this study, in a de-identified manner, along with anonymized information from the Practice Characteristics Study and other general information. We will exclude all personal data such as your name, mailing address, email address, or telephone number.

If you prefer not to receive future reminders regarding this study, please contact Kate Ross at kross@abim.org.

The survey begins on the next page. It contains THREE abstracts describing hypothetical new drugs, with a few questions pertaining to each, and then a short set of questions at the end.

C. ABSTRACT #1

The following abstract describes a hypothetical new drug for treatment of dyslipidemia. Please read the abstract and then answer the six questions related to the hypothetical drug. These questions will relate to the study described in the abstract and its impact on your prescribing practices.

For this abstract, please assume that:
The abstract and accompanying article were published in a high-impact biomedical journal, and the primary authors are academic physicians at established universities in the United States.

The drug was recently approved by the Food and Drug Administration to reduce LDL and raise HDL in patients with primary hypercholesterolemia and mixed dyslipidemia.

The drug is covered by your patient's insurance.

[LAMPYTINIB ABSTRACT]

QUESTIONS

A 60-year-old male patient comes to your office with a history of coronary heart disease (noted on previous coronary catheterization). He has an LDL cholesterol of 199 mg/dL and HDL cholesterol of 35 mg/dL. He cannot tolerate statins due to myopathy and cannot tolerate niacin-containing products due to severe flushing. How likely would you be to <u>prescribe</u> lampytinib?

Very unlikely to prescribe			Completely unsure whether would prescribe			Very likely to prescribe
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

How confident are you in the validity of the conclusion that the authors draw about lampytinib in this abstract?

Not confident at all						Very confident
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Rate the overall <u>rigor</u> of the study methodology:

Not at all rigorous						Very rigorous
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Rate the <u>importance</u> of the study:

Not at all important						Very important
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Are you interested in reading the full article for the study described in this abstract?

Not at all interested						Very interested
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

D. ABSTRACT #2

The following abstract describes a hypothetical new drug for the treatment of both diabetes and low HDL cholesterol. Please read the abstract and then answer the six questions related to the hypothetical drug. These questions will relate to the study described in the abstract and its impact on your prescribing practices.

For this abstract, please assume that:
The abstract and accompanying article were published in a high-impact biomedical journal, and the primary authors are academic physicians at established universities in the United States.

The drug was recently approved by the Food and Drug Administration to improve glycemic control and raise HDL cholesterol in patients with diabetes and mixed dyslipidemia.

The drug is covered by your patient's insurance.

[BONDAGLUTARAZ ABSTRACT]

QUESTIONS

A 60-year-old male patient comes to your office with a history of Type 2 diabetes and coronary heart disease (noted on previous coronary catheterization). He has a hemoglobin A1c of 8.5% and HDL level of 35 mg/dL despite maximal tolerated treatment with metformin and a sulfonylurea. How likely would you be to <u>prescribe</u> bondaglutaraz?

Very unlikely to prescribe			Completely unsure whether would prescribe			Very likely to prescribe
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

How confident are you in the validity of the conclusion that the authors draw about bondaglutaraz in this abstract?

Not confident at all						Very confident
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Rate the overall <u>rigor</u> of the study methodology:

Not at all rigorous						Very rigorous
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Rate the <u>importance</u> of the study:

Not at all important						Very important
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Are you interested in reading the full article for the study described in this abstract?

1	2	3	4	5	6	7

☐	☐	☐	☐	☐	☐	☐

E. ABSTRACT #3

The following abstract describes a hypothetical new drug for the treatment of coronary artery angina. Please read the abstract and then answer the six questions related to the hypothetical drug. These questions will relate to the study described in the abstract and its impact on your prescribing practices.

For this abstract, please assume that:
The abstract and accompanying article were published in a high-impact biomedical journal, and the primary authors are academic physicians at established universities in the United States.

The drug was recently approved by the Food and Drug Administration for treatment of angina pectoris.

The drug is covered by your patient's insurance.

[PROVASINAB ABSTRACT]

QUESTIONS

A 60-year-old male patient comes to your office with a history of multivessel coronary heart disease ineligible for percutaneous coronary intervention (PCI). He has daily angina associated with exercise despite maximal therapy with a beta blocker. How likely would you be to <u>prescribe</u> provasinab?

Very unlikely to prescribe			Completely unsure whether would prescribe			Very likely to prescribe
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

How confident are you in the validity of the conclusion that the authors draw about provasinab in this abstract?

Not confident at all						Very confident
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Rate the overall <u>rigor</u> of the study methodology:

Not at all rigorous						Very rigorous
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Rate the <u>importance</u> of the study:

Not at all important						Very important
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Are you interested in reading the full article for the study described in this abstract?

Not at all interested						Very interested
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

F. FINAL QUESTIONS

Over the last 30 days, about how many biomedical journal abstracts have you read describing trials related to prescription drugs?

_____

Do you think that pharmaceutical company funding is likely to influence the outcome of scientific studies about the efficacy and safety of pharmaceuticals <u>in favor of</u> the drug in question?

Not likely to influence			Completely unsure whether would influence			Very likely to influence
1	2	3	4	5	6	7
☐	☐	☐	☐	☐	☐	☐

Which of the following have you received in the last year from drug, device, or other medically related companies?

CHECK YES OR NO FOR EACH	Yes	No
a. Food or beverage in the workplace	☐	☐
b. Free drug samples	☐	☐
c. Honoraria for speaking	☐	☐
d. Payment for consulting services	☐	☐
e. Payment for service on a scientific advisory board or board of directors?	☐	☐
f. Payment in excess of costs for enrolling patients in industry-sponsored trials?	☐	☐
g. Costs of travel, time, meals, lodging, or other personal expenses for attending meetings?	☐	☐
h. Gifts received as a result of prescribing practices?	☐	☐
i. Free tickets to cultural or sporting events?	☐	☐
j. Free or subsidized admission to meetings or conferences for which Continuing Medical Education (CME) credits were awarded?	☐	☐

Important Note:
The drugs and funding attributions in this survey were completely hypothetical and for research purposes only. No such drugs exist and none of these studies were ever conducted. None of the pharmaceutical companies listed had any connection to any of these hypothetical studies.

Section 3. Full copies of each abstract version

Following are copies of each of the 27 versions of the abstract that we used in our randomized study. The title on each page—"1. XXX". "2. XXX", etc.—is provided for ease in interpretation. Each title describes which of the 3 different versions of each of the 3 different variables is represented in the abstract printed on that page.

1. Drug: Lampytinib; Methodological Strength: High; Disclosure statement: Industry

Efficacy and Safety of Lampytinib, a New Cholesteryl Ester Transfer Inhibitor, for Treatment of Patients with Lipid Disorders

BACKGROUND
Lampytinib is a cholesteryl ester transfer protein inhibitor that lowers low-density lipoprotein (LDL) cholesterol and raises high-density lipoprotein (HDL) cholesterol.

METHODS
We conducted a randomized, double-blind, active-comparator controlled trial in 12 centers across the US to assess the efficacy and safety profile of lampytinib in patients who had coronary heart disease (CHD) or at least 3 major risk factors for CHD. Eligible patients could not tolerate any statin, had an LDL cholesterol >160 mg/dL, and an HDL cholesterol <40 mg/dL. Patients were assigned to receive 10 mg of lampytinib or 10 mg of ezetimibe (Zetia) daily for 36 months. The primary end point was a combined cardiovascular disease endpoint (cardiovascular death, myocardial infarction, or stroke). We also assessed change from baseline in LDL and HDL cholesterol at 24 weeks, and the safety and side-effect profile of lampytinib.

RESULTS
A total of 5322 patients underwent 1:1 randomization. The combined cardiovascular disease endpoint occurred in 147 patients treated with lampytinib (5.5%) and 252 patients receiving ezetimibe (9.5%) (risk reduction (RR) 0.60, 95% confidence interval 0.51-0.73, P<0.001). By 24 weeks, the LDL cholesterol level was reduced from 181 mg/dL to 68 mg/dL in the lampytinib group, as compared with a reduction from 182 mg/dL to 127 mg/dL in the ezetimibe group (P<0.01) — a 32% reduction with lampytinib over ezetimibe. In addition, the HDL cholesterol level increased from 39 mg/dL to 56 mg/dL in the lampytinib group, as compared with an increase from 38 mg/dL to 40 mg/dL in the ezetimibe group (P<0.01) — a 38% increase with lampytinib beyond that seen with ezetimibe. Less than 9% of patients were lost to follow-up or withdrew from the study. Through 36 months, no significant changes were noted in blood pressure with lampytinib as compared with ezetimibe, and there were no episodes of abnormal liver function tests or myopathy among patients receiving lampytinib.

CONCLUSIONS
Treatment with lampytinib improved cardiovascular outcomes, had significant beneficial effects on HDL and LDL cholesterol, and had an acceptable side-effect profile. Lampytinib offers an effective therapeutic option for patients with dyslipidemia. (ClinicalTrials.gov #NCT31425812)

This study was funded by a grant from [company]. The lead author reports serving as a consultant to [company].

2. Drug: Lampytinib; Methodological Strength: Moderate; Disclosure statement: Industry

Efficacy and Safety of Lampytinib, a New Cholesteryl Ester Transfer Inhibitor, for Treatment of Patients with Lipid Disorders

BACKGROUND
Lampytinib is a cholesteryl ester transfer protein inhibitor that lowers low-density lipoprotein (LDL) cholesterol and raises high-density lipoprotein (HDL) cholesterol.

METHODS
We conducted a randomized, single-blind, active-comparator controlled trial to assess the efficacy and safety profile of lampytinib in patients who had known coronary heart disease (CHD) or who had at least 3 major risk factors for CHD. Eligible patients could not tolerate any statin, had an LDL cholesterol >160 mg/dL, and an HDL cholesterol <40 mg/dL. Patients were assigned to receive 10 mg of lampytinib or 10 mg of ezetimibe (Zetia) daily for 12 months. The primary end points were the change from baseline in LDL and HDL cholesterol at 16 weeks and the safety and side-effect profile of lampytinib over 12 months.

RESULTS
A total of 964 patients underwent 1:1 randomization. By 16 weeks, the LDL cholesterol level was reduced from 181 mg/dL to 68 mg/dL in the lampytinib group, as compared with a reduction from 182 mg/dL to 127 mg/dL in the ezetimibe group ($P<0.01$) — a 32% reduction with lampytinib over ezetimibe. In addition, the HDL cholesterol level increased from 39 mg/dL to 56 mg/dL in the lampytinib group, as compared with an increase from 38 mg/dL to 40 mg/dL in the ezetimibe group ($P<0.01$) — a 38% increase with lampytinib beyond that seen with ezetimibe. 13% of patients were lost to follow-up or withdrew from the study. Through 12 months, no significant changes were noted in blood pressure with lampytinib as compared with the ezetimibe group, and there were no episodes of abnormal liver function tests or myopathy among patients receiving lampytinib.

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Treatment with lampytinib had significant beneficial effects on LDL and HDL cholesterol, and had an acceptable side-effect profile. Lampytinib offers an effective therapeutic option for patients with dyslipidemia. (ClinicalTrials.gov #NCT31425812).

This study was funded by a grant from [company]. The lead author reports serving as a consultant to [company].

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BACKGROUND
Lampytinib is a cholesteryl ester transfer protein inhibitor that lowers low-density lipoprotein (LDL) cholesterol and raises high-density lipoprotein (HDL) cholesterol.

METHODS
We conducted a randomized, open-label controlled trial to assess the utility of lampytinib in men with a history of familial hypercholesterolemia and no other medical problems. Eligible patients could not tolerate any statin, had an LDL cholesterol >160 mg/dL, and had an HDL cholesterol <40 mg/dL. Patients were assigned to receive 10 mg of lampytinib or usual care for 4 months. The primary end points were the change from baseline in LDL and HDL cholesterol.

RESULTS
A total of 483 patients were randomized in a 1:1 fashion. By 16 weeks, the LDL cholesterol level was reduced from 181 mg/dL to 68 mg/dL in the lampytinib group, as compared with a reduction from 182 mg/dL to 127 mg/dL in the usual care group (P<0.01) — a 32% reduction with lampytinib over usual care. In addition, the HDL cholesterol level increased from 39 mg/dL to 56 mg/dL in the lampytinib group, as compared with an increase from 38 mg/dL to 40 mg/dL in the usual care group (P<0.01) — a 38% increase with lampytinib beyond that seen with usual care. 19% of patients were lost to follow-up or withdrew from the study.

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This study was funded by a grant from [company]. The lead author reports serving as a consultant to [company].

4. Drug: Lampytinib; Methodological Strength: High; Disclosure statement: NIH

Efficacy and Safety of Lampytinib, a New Cholesteryl Ester Transfer Inhibitor, for Treatment of Patients with Lipid Disorders

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Lampytinib is a cholesteryl ester transfer protein inhibitor that lowers low-density lipoprotein (LDL) cholesterol and raises high-density lipoprotein (HDL) cholesterol.

METHODS
We conducted a randomized, double-blind, active-comparator controlled trial in 12 centers across the US to assess the efficacy and safety profile of lampytinib in patients who had coronary heart disease (CHD) or at least 3 major risk factors for CHD. Eligible patients could not tolerate any statin, had an LDL cholesterol >160 mg/dL, and an HDL cholesterol <40 mg/dL. Patients were assigned to receive 10 mg of lampytinib or 10 mg of ezetimibe (Zetia) daily for 36 months. The primary end point was a combined cardiovascular disease endpoint (cardiovascular death, myocardial infarction, or stroke). We also assessed change from baseline in LDL and HDL cholesterol at 24 weeks, and the safety and side-effect profile of lampytinib.

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Treatment with lampytinib improved cardiovascular outcomes, had significant beneficial effects on HDL and LDL cholesterol, and had an acceptable side-effect profile. Lampytinib offers an effective therapeutic option for patients with dyslipidemia. (ClinicalTrials.gov #NCT31425812)

This study was funded by a grant from the National Institutes of Health.

5. Drug: Lampytinib; Methodological Strength: Moderate; Disclosure statement: NIH

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This study was funded by a grant from the National Institutes of Health.

6. Drug: Lampytinib; Methodological Strength: Low; Disclosure statement: NIH

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This study was funded by a grant from the National Institutes of Health.

7. Drug: Lampytinib; Methodological Strength: High; Disclosure statement: None

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Treatment with lampytinib improved cardiovascular outcomes, had significant beneficial effects on HDL and LDL cholesterol, and had an acceptable side-effect profile. Lampytinib offers an effective therapeutic option for patients with dyslipidemia. (ClinicalTrials.gov #NCT31425812)

8. Drug: Lampytinib; Methodological Strength: Moderate; Disclosure statement: None

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Lampytinib is a cholesteryl ester transfer protein inhibitor that lowers low-density lipoprotein (LDL) cholesterol and raises high-density lipoprotein (HDL) cholesterol.

METHODS
We conducted a randomized, single-blind, active-comparator controlled trial to assess the efficacy and safety profile of lampytinib in patients who had known coronary heart disease (CHD) or who had at least 3 major risk factors for CHD. Eligible patients could not tolerate any statin, had an LDL cholesterol >160 mg/dL, and an HDL cholesterol <40 mg/dL. Patients were assigned to receive 10 mg of lampytinib or 10 mg of ezetimibe (Zetia) daily for 12 months. The primary end points were the change from baseline in LDL and HDL cholesterol at 16 weeks and the safety and side-effect profile of lampytinib over 12 months.

RESULTS
A total of 964 patients underwent 1:1 randomization. By 16 weeks, the LDL cholesterol level was reduced from 181 mg/dL to 68 mg/dL in the lampytinib group, as compared with a reduction from 182 mg/dL to 127 mg/dL in the ezetimibe group (P<0.01) — a 32% reduction with lampytinib over ezetimibe. In addition, the HDL cholesterol level increased from 39 mg/dL to 56 mg/dL in the lampytinib group, as compared with an increase from 38 mg/dL to 40 mg/dL in the ezetimibe group (P<0.01) — a 38% increase with lampytinib beyond that seen with ezetimibe. 13% of patients were lost to follow-up or withdrew from the study. Through 12 months, no significant changes were noted in blood pressure with lampytinib as compared with the ezetimibe group, and there were no episodes of abnormal liver function tests or myopathy among patients receiving lampytinib.

CONCLUSIONS
Treatment with lampytinib had significant beneficial effects on LDL and HDL cholesterol, and had an acceptable side-effect profile. Lampytinib offers an effective therapeutic option for patients with dyslipidemia. (ClinicalTrials.gov #NCT31425812

9. Drug: Lampytinib; Methodological Strength: Low; Disclosure statement: None

Efficacy and Safety of Lampytinib, a New Cholesteryl Ester Transfer Inhibitor, for Treatment of Patients with Lipid Disorders

BACKGROUND
Lampytinib is a cholesteryl ester transfer protein inhibitor that lowers low-density lipoprotein (LDL) cholesterol and raises high-density lipoprotein (HDL) cholesterol.

METHODS
We conducted a randomized, open-label controlled trial to assess the utility of lampytinib in men with a history of familial hypercholesterolemia and no other medical problems. Eligible patients could not tolerate any statin, had an LDL cholesterol >160 mg/dL, and had an HDL cholesterol <40 mg/dL. Patients were assigned to receive 10 mg of lampytinib or usual care for 4 months. The primary end points were the change from baseline in LDL and HDL cholesterol.

RESULTS
A total of 483 patients were randomized in a 1:1 fashion. By 16 weeks, the LDL cholesterol level was reduced from 181 mg/dL to 68 mg/dL in the lampytinib group, as compared with a reduction from 182 mg/dL to 127 mg/dL in the usual care group (P<0.01) — a 32% reduction with lampytinib over usual care. In addition, the HDL cholesterol level increased from 39 mg/dL to 56 mg/dL in the lampytinib group, as compared with an increase from 38 mg/dL to 40 mg/dL in the usual care group (P<0.01) — a 38% increase with lampytinib beyond that seen with usual care. 19% of patients were lost to follow-up or withdrew from the study.

CONCLUSIONS
Treatment with lampytinib had significant beneficial effects on LDL and HDL cholesterol. Lampytinib offers an effective therapeutic option for patients with dyslipidemia. (ClinicalTrials.gov #NCT31425812)

10. Drug: Bondaglutaraz; Methodological Strength: High; Disclosure statement: Industry

Use of Bondaglutaraz, a New Dual Agonist of Peroxisome Proliferator–Activated Receptors (PPAR) Alpha and Gamma, for Treatment of Patients with Inadequately Controlled Diabetes

BACKGROUND
Patients with diabetes frequently have elevated cholesterol, further increasing their cardiovascular risk. Bondaglutaraz is a dual agonist of alpha and gamma peroxisome proliferator–activated receptors (PPAR) that increases insulin sensitivity and modulates lipid metabolism.

METHODS
We conducted a randomized, double-blind, active-comparator controlled trial in 12 centers in the US to assess the efficacy and safety of bondaglutaraz in patients aged 55 and older who had Type 2 diabetes, hypercholesterolemia, and a history of coronary heart disease (CHD) or at least one other CHD risk factor. Eligible patients had a hemoglobin A1c between 8.0% and 9.0% and an HDL cholesterol <40 mg/dL while receiving maximal tolerated doses of metformin and a sulfonylurea, and were unwilling or unable to add insulin to their regimen. Participants were assigned to receive 100 mg of bondaglutaraz or 100 mg of sitagliptin (Januvia) for 36 months. The primary end point was a combined cardiovascular disease endpoint (cardiovascular death, myocardial infarction, or stroke). We also assessed the change from baseline in hemoglobin A1c at 24 weeks, effect on HDL cholesterol, and the safety and side-effect profile of bondaglutaraz.

RESULTS
A total of 5322 patients underwent randomization in a 1:1 fashion. The combined cardiovascular disease endpoint occurred in 147 patients treated with bondaglutaraz (5.5%) and 252 patients receiving sitagliptin (9.5%) (risk reduction (RR) 0.60, 95% confidence interval 0.51-0.73, P<0.01). By 24 weeks, the hemoglobin A1c decreased from 8.8% to 6.4% in the bondaglutaraz group, as compared with a decrease from 8.7% to 7.8% in the sitagliptin group (P<0.01) — a 17% decrease with bondaglutaraz beyond that seen with sitagliptin. In addition, the HDL cholesterol level increased from 39 mg per deciliter to 59 mg per deciliter in the bondaglutaraz group, as compared with an increase from 38 mg per deciliter to 44 mg per deciliter in the sitagliptin group (P<0.01) — a 36% increase with bondaglutaraz beyond that seen with sitagliptin. Less than 9% of patients were lost to follow up or withdrew from the study. Through 36 months, no significant changes were noted in blood pressure, kidney function or hypoglycemic episodes with bondaglutaraz as compared with placebo.

CONCLUSIONS
Treatment with bondaglutaraz improved cardiovascular outcomes, had significant beneficial effects on hemoglobin A1c and HDL cholesterol, and had an acceptable side-effect profile. Bondaglutaraz offers an effective therapeutic option for patients with diabetes. (ClinicalTrials.gov #NCT87212354)

This study was funded by a grant from [company]. The lead author reports serving as a consultant to [company].

11. Drug: Bondaglutaraz; Methodological Strength: Moderate; Disclosure statement: Industry

Use of Bondaglutaraz, a New Dual Agonist of Peroxisome Proliferator–Activated Receptors (PPAR) Alpha and Gamma, for Treatment of Patients with Inadequately Controlled Diabetes

BACKGROUND
Patients with diabetes frequently have elevated cholesterol, further increasing their cardiovascular risk. Bondaglutaraz is a dual agonist of alpha and gamma peroxisome proliferator–activated receptors (PPAR) that increases insulin sensitivity and modulates lipid metabolism.

METHODS
We conducted a randomized, single-blind, active-comparator controlled trial to assess the efficacy and safety profile of bondaglutaraz in patients aged 55 and older with Type 2 diabetes, hypercholesterolemia, and a history of coronary heart disease (CHD) or at least one other CHD risk factor. Eligible patients had a hemoglobin A1c between 8.0% and 9.0% and an HDL cholesterol <40 mg/dL while receiving maximal tolerated doses of metformin and a sulfonylurea, and were unwilling or unable to add insulin to their regimen. Participants were assigned to receive 100 mg of bondaglutaraz or 100 mg of sitagliptin (Januvia) for 12 months. The primary end points were change from baseline in hemoglobin A1c at 16 weeks, the effect on HDL cholesterol, and the safety and side-effect profile of bondaglutaraz.

RESULTS
A total of 964 patients underwent randomization in a 1:1 fashion. By 16 weeks, the hemoglobin A1c decreased from 8.8% to 6.4% in the bondaglutaraz group, as compared with a decrease from 8.7% to 7.8% in the sitagliptin group (P<0.01) — a 17% decrease with bondaglutaraz beyond that seen with sitagliptin. In addition, the HDL cholesterol level increased from 39 mg per deciliter to 59 mg per deciliter in the bondaglutaraz group, as compared with an increase from 38 mg per deciliter to 44 mg per deciliter in the sitagliptin group (P<0.01) — a 36% increase with bondaglutaraz beyond that seen with sitagliptin. 13% of patients were lost to follow up or withdrew from the study. Through 12 months, no significant changes were noted in blood pressure, kidney function or hypoglycemic episodes with bondaglutaraz as compared with placebo.

CONCLUSIONS
Treatment with bondaglutaraz had significant beneficial effects on hemoglobin A1c and HDL cholesterol, and had an acceptable side-effect profile. Bondaglutaraz offers an effective therapeutic option for patients with diabetes. (ClinicalTrials.gov #NCT87212354)

This study was funded by a grant from [company]. The lead author reports serving as a consultant to [company].

12. Drug: Bondaglutaraz; Methodological Strength: Low; Disclosure statement: Industry

Use of Bondaglutaraz, a New Dual Agonist of Peroxisome Proliferator–Activated Receptors (PPAR) Alpha and Gamma, for Treatment of Patients with Inadequately Controlled Diabetes

BACKGROUND
Patients with diabetes frequently have elevated cholesterol, further increasing their cardiovascular risk. Bondaglutaraz is a dual agonist of alpha and gamma peroxisome proliferator–activated receptors (PPAR) that increases insulin sensitivity and modulates lipid metabolism.

METHODS
We conducted a randomized, open-label, controlled trial to assess the utility of bondaglutaraz in people with diabetes. Eligible patients had been treated with chronic steroid therapy for at least 6 months and developed diabetes uncontrolled by maximal tolerated doses of metformin and a sulfonylurea, and were unwilling or unable to add insulin to their regimen. Patients were required to have a hemoglobin A1c between 8.0% and 9.0% and an HDL cholesterol <40 mg/dL. Patients were randomized to receive 100 mg of bondaglutaraz for 4 months or usual care. The primary end points were the change from baseline in hemoglobin A1c and the effect on HDL cholesterol.

RESULTS
A total of 483 patients were randomized in a 1:1 fashion. By 16 weeks, the hemoglobin A1c decreased from 8.8% to 6.4% in the bondaglutaraz group, as compared with a decrease from 8.7% to 7.8% in the usual care group (P<0.01) — a 17% decrease with bondaglutaraz beyond that seen with usual care. In addition, the HDL cholesterol level increased from 39 mg per deciliter to 59 mg per deciliter in the bondaglutaraz group, as compared with an increase from 38 mg per deciliter to 44 mg per deciliter in the usual care group (P<0.01) — a 36% increase with bondaglutaraz beyond that seen with usual care. 19% of patients were lost to follow-up or withdrew from the study.

CONCLUSIONS
Treatment with bondaglutaraz had significant beneficial effects on hemoglobin A1c and HDL cholesterol levels. Bondaglutaraz offers an effective therapeutic option for patients with diabetes. (ClinicalTrials.gov #NCT87212354)

This study was funded by a grant from [company]. The lead author reports serving as a consultant to [company].

13. Drug: Bondaglutaraz; Methodological Strength: High; Disclosure statement: NIH

Use of Bondaglutaraz, a New Dual Agonist of Peroxisome Proliferator–Activated Receptors (PPAR) Alpha and Gamma, for Treatment of Patients with Inadequately Controlled Diabetes

BACKGROUND
Patients with diabetes frequently have elevated cholesterol, further increasing their cardiovascular risk. Bondaglutaraz is a dual agonist of alpha and gamma peroxisome proliferator–activated receptors (PPAR) that increases insulin sensitivity and modulates lipid metabolism.

METHODS
We conducted a randomized, double-blind, active-comparator controlled trial in 12 centers in the US to assess the efficacy and safety of bondaglutaraz in patients aged 55 and older who had Type 2 diabetes, hypercholesterolemia, and a history of coronary heart disease (CHD) or at least one other CHD risk factor. Eligible patients had a hemoglobin A1c between 8.0% and 9.0% and an HDL cholesterol <40 mg/dL while receiving maximal tolerated doses of metformin and a sulfonylurea, and were unwilling or unable to add insulin to their regimen. Participants were assigned to receive 100 mg of bondaglutaraz or 100 mg of sitagliptin (Januvia) for 36 months. The primary end point was a combined cardiovascular disease endpoint (cardiovascular death, myocardial infarction, or stroke). We also assessed the change from baseline in hemoglobin A1c at 24 weeks, effect on HDL cholesterol, and the safety and side-effect profile of bondaglutaraz.

RESULTS
A total of 5322 patients underwent randomization in a 1:1 fashion. The combined cardiovascular disease endpoint occurred in 147 patients treated with bondaglutaraz (5.5%) and 252 patients receiving sitagliptin (9.5%) (risk reduction (RR) 0.60, 95% confidence interval 0.51-0.73, P<0.01). By 24 weeks, the hemoglobin A1c decreased from 8.8% to 6.4% in the bondaglutaraz group, as compared with a decrease from 8.7% to 7.8% in the sitagliptin group (P<0.01) — a 17% decrease with bondaglutaraz beyond that seen with sitagliptin. In addition, the HDL cholesterol level increased from 39 mg per deciliter to 59 mg per deciliter in the bondaglutaraz group, as compared with an increase from 38 mg per deciliter to 44 mg per deciliter in the sitagliptin group (P<0.01) — a 36% increase with bondaglutaraz beyond that seen with sitagliptin. Less than 9% of patients were lost to follow up or withdrew from the study. Through 36 months, no significant changes were noted in blood pressure, kidney function or hypoglycemic episodes with bondaglutaraz as compared with placebo.

CONCLUSIONS
Treatment with bondaglutaraz improved cardiovascular outcomes, had significant beneficial effects on hemoglobin A1c and HDL cholesterol, and had an acceptable side-effect profile. Bondaglutaraz offers an effective therapeutic option for patients with diabetes. (ClinicalTrials.gov #NCT87212354)

This study was funded by a grant from the National Institutes of Health.

14. Drug: Bondaglutaraz; Methodological Strength: Moderate; Disclosure statement: NIH

Use of Bondaglutaraz, a New Dual Agonist of Peroxisome Proliferator–Activated Receptors (PPAR) Alpha and Gamma, for Treatment of Patients with Inadequately Controlled Diabetes

BACKGROUND
Patients with diabetes frequently have elevated cholesterol, further increasing their cardiovascular risk. Bondaglutaraz is a dual agonist of alpha and gamma peroxisome proliferator–activated receptors (PPAR) that increases insulin sensitivity and modulates lipid metabolism.

METHODS
We conducted a randomized, single-blind, active-comparator controlled trial to assess the efficacy and safety profile of bondaglutaraz in patients aged 55 and older with Type 2 diabetes, hypercholesterolemia, and a history of coronary heart disease (CHD) or at least one other CHD risk factor. Eligible patients had a hemoglobin A1c between 8.0% and 9.0% and an HDL cholesterol <40 mg/dL while receiving maximal tolerated doses of metformin and a sulfonylurea, and were unwilling or unable to add insulin to their regimen. Participants were assigned to receive 100 mg of bondaglutaraz or 100 mg of sitagliptin (Januvia) for 12 months. The primary end points were change from baseline in hemoglobin A1c at 16 weeks, the effect on HDL cholesterol, and the safety and side-effect profile of bondaglutaraz.

RESULTS
A total of 964 patients underwent randomization in a 1:1 fashion. By 16 weeks, the hemoglobin A1c decreased from 8.8% to 6.4% in the bondaglutaraz group, as compared with a decrease from 8.7% to 7.8% in the sitagliptin group (P<0.01) — a 17% decrease with bondaglutaraz beyond that seen with sitagliptin. In addition, the HDL cholesterol level increased from 39 mg per deciliter to 59 mg per deciliter in the bondaglutaraz group, as compared with an increase from 38 mg per deciliter to 44 mg per deciliter in the sitagliptin group (P<0.01) — a 36% increase with bondaglutaraz beyond that seen with sitagliptin. 13% of patients were lost to follow up or withdrew from the study. Through 12 months, no significant changes were noted in blood pressure, kidney function or hypoglycemic episodes with bondaglutaraz as compared with placebo.

CONCLUSIONS
Treatment with bondaglutaraz had significant beneficial effects on hemoglobin A1c and HDL cholesterol, and had an acceptable side-effect profile. Bondaglutaraz offers an effective therapeutic option for patients with diabetes. (ClinicalTrials.gov #NCT87212354)

This study was funded by a grant from the National Institutes of Health.

15. Drug: Bondaglutaraz; Methodological Strength: Low; Disclosure statement: NIH

Use of Bondaglutaraz, a New Dual Agonist of Peroxisome Proliferator–Activated Receptors (PPAR) Alpha and Gamma, for Treatment of Patients with Inadequately Controlled Diabetes

BACKGROUND
Patients with diabetes frequently have elevated cholesterol, further increasing their cardiovascular risk. Bondaglutaraz is a dual agonist of alpha and gamma peroxisome proliferator–activated receptors (PPAR) that increases insulin sensitivity and modulates lipid metabolism.

METHODS
We conducted a randomized, open-label, controlled trial to assess the utility of bondaglutaraz in people with diabetes. Eligible patients had been treated with chronic steroid therapy for at least 6 months and developed diabetes uncontrolled by maximal tolerated doses of metformin and a sulfonylurea, and were unwilling or unable to add insulin to their regimen. Patients were required to have a hemoglobin A1c between 8.0% and 9.0% and an HDL cholesterol <40 mg/dL. Patients were randomized to receive 100 mg of bondaglutaraz for 4 months or usual care. The primary end points were the change from baseline in hemoglobin A1c and the effect on HDL cholesterol.

RESULTS
A total of 483 patients were randomized in a 1:1 fashion. By 16 weeks, the hemoglobin A1c decreased from 8.8% to 6.4% in the bondaglutaraz group, as compared with a decrease from 8.7% to 7.8% in the usual care group (P<0.01) — a 17% decrease with bondaglutaraz beyond that seen with usual care. In addition, the HDL cholesterol level increased from 39 mg per deciliter to 59 mg per deciliter in the bondaglutaraz group, as compared with an increase from 38 mg per deciliter to 44 mg per deciliter in the usual care group (P<0.01) — a 36% increase with bondaglutaraz beyond that seen with usual care. 19% of patients were lost to follow-up or withdrew from the study.

CONCLUSIONS
Treatment with bondaglutaraz had significant beneficial effects on hemoglobin A1c and HDL cholesterol levels. Bondaglutaraz offers an effective therapeutic option for patients with diabetes. (ClinicalTrials.gov #NCT87212354)

This study was funded by a grant from the National Institutes of Health.

16. Drug: Bondaglutaraz; Methodological Strength: High; Disclosure statement: None

Use of Bondaglutaraz, a New Dual Agonist of Peroxisome Proliferator–Activated Receptors (PPAR) Alpha and Gamma, for Treatment of Patients with Inadequately Controlled Diabetes

BACKGROUND
Patients with diabetes frequently have elevated cholesterol, further increasing their cardiovascular risk. Bondaglutaraz is a dual agonist of alpha and gamma peroxisome proliferator–activated receptors (PPAR) that increases insulin sensitivity and modulates lipid metabolism.

METHODS
We conducted a randomized, double-blind, active-comparator controlled trial in 12 centers in the US to assess the efficacy and safety of bondaglutaraz in patients aged 55 and older who had Type 2 diabetes, hypercholesterolemia, and a history of coronary heart disease (CHD) or at least one other CHD risk factor. Eligible patients had a hemoglobin A1c between 8.0% and 9.0% and an HDL cholesterol <40 mg/dL while receiving maximal tolerated doses of metformin and a sulfonylurea, and were unwilling or unable to add insulin to their regimen. Participants were assigned to receive 100 mg of bondaglutaraz or 100 mg of sitagliptin (Januvia) for 36 months. The primary end point was a combined cardiovascular disease endpoint (cardiovascular death, myocardial infarction, or stroke). We also assessed the change from baseline in hemoglobin A1c at 24 weeks, effect on HDL cholesterol, and the safety and side-effect profile of bondaglutaraz.

RESULTS
A total of 5322 patients underwent randomization in a 1:1 fashion. The combined cardiovascular disease endpoint occurred in 147 patients treated with bondaglutaraz (5.5%) and 252 patients receiving sitagliptin (9.5%) (risk reduction (RR) 0.60, 95% confidence interval 0.51-0.73, P<0.01). By 24 weeks, the hemoglobin A1c decreased from 8.8% to 6.4% in the bondaglutaraz group, as compared with a decrease from 8.7% to 7.8% in the sitagliptin group (P<0.01) — a 17% decrease with bondaglutaraz beyond that seen with sitagliptin. In addition, the HDL cholesterol level increased from 39 mg per deciliter to 59 mg per deciliter in the bondaglutaraz group, as compared with an increase from 38 mg per deciliter to 44 mg per deciliter in the sitagliptin group (P<0.01) — a 36% increase with bondaglutaraz beyond that seen with sitagliptin. Less than 9% of patients were lost to follow up or withdrew from the study. Through 36 months, no significant changes were noted in blood pressure, kidney function or hypoglycemic episodes with bondaglutaraz as compared with placebo.

CONCLUSIONS
Treatment with bondaglutaraz improved cardiovascular outcomes, had significant beneficial effects on hemoglobin A1c and HDL cholesterol, and had an acceptable side-effect profile. Bondaglutaraz offers an effective therapeutic option for patients with diabetes. (ClinicalTrials.gov #NCT87212354)

17. Drug: Bondaglutaraz; Methodological Strength: Moderate; Disclosure statement: None

Use of Bondaglutaraz, a New Dual Agonist of Peroxisome Proliferator–Activated Receptors (PPAR) Alpha and Gamma, for Treatment of Patients with Inadequately Controlled Diabetes

BACKGROUND
Patients with diabetes frequently have elevated cholesterol, further increasing their cardiovascular risk. Bondaglutaraz is a dual agonist of alpha and gamma peroxisome proliferator–activated receptors (PPAR) that increases insulin sensitivity and modulates lipid metabolism.

METHODS
We conducted a randomized, single-blind, active-comparator controlled trial to assess the efficacy and safety profile of bondaglutaraz in patients aged 55 and older with Type 2 diabetes, hypercholesterolemia, and a history of coronary heart disease (CHD) or at least one other CHD risk factor. Eligible patients had a hemoglobin A1c between 8.0% and 9.0% and an HDL cholesterol <40 mg/dL while receiving maximal tolerated doses of metformin and a sulfonylurea, and were unwilling or unable to add insulin to their regimen. Participants were assigned to receive 100 mg of bondaglutaraz or 100 mg of sitagliptin (Januvia) for 12 months. The primary end points were change from baseline in hemoglobin A1c at 16 weeks, the effect on HDL cholesterol, and the safety and side-effect profile of bondaglutaraz.

RESULTS
A total of 964 patients underwent randomization in a 1:1 fashion. By 16 weeks, the hemoglobin A1c decreased from 8.8% to 6.4% in the bondaglutaraz group, as compared with a decrease from 8.7% to 7.8% in the sitagliptin group (P<0.01) — a 17% decrease with bondaglutaraz beyond that seen with sitagliptin. In addition, the HDL cholesterol level increased from 39 mg per deciliter to 59 mg per deciliter in the bondaglutaraz group, as compared with an increase from 38 mg per deciliter to 44 mg per deciliter in the sitagliptin group (P<0.01) — a 36% increase with bondaglutaraz beyond that seen with sitagliptin. 13% of patients were lost to follow up or withdrew from the study. Through 12 months, no significant changes were noted in blood pressure, kidney function or hypoglycemic episodes with bondaglutaraz as compared with placebo.

CONCLUSIONS
Treatment with bondaglutaraz had significant beneficial effects on hemoglobin A1c and HDL cholesterol, and had an acceptable side-effect profile. Bondaglutaraz offers an effective therapeutic option for patients with diabetes. (ClinicalTrials.gov #NCT87212354)

18. Drug: Bondaglutaraz; Methodological Strength: Low; Disclosure statement: None

Use of Bondaglutaraz, a New Dual Agonist of Peroxisome Proliferator–Activated Receptors (PPAR) Alpha and Gamma, for Treatment of Patients with Inadequately Controlled Diabetes

BACKGROUND
Patients with diabetes frequently have elevated cholesterol, further increasing their cardiovascular risk. Bondaglutaraz is a dual agonist of alpha and gamma peroxisome proliferator–activated receptors (PPAR) that increases insulin sensitivity and modulates lipid metabolism.

METHODS
We conducted a randomized, open-label, controlled trial to assess the utility of bondaglutaraz in people with diabetes. Eligible patients had been treated with chronic steroid therapy for at least 6 months and developed diabetes uncontrolled by maximal tolerated doses of metformin and a sulfonylurea, and were unwilling or unable to add insulin to their regimen. Patients were required to have a hemoglobin A1c between 8.0% and 9.0% and an HDL cholesterol <40 mg/dL. Patients were randomized to receive 100 mg of bondaglutaraz for 4 months or usual care. The primary end points were the change from baseline in hemoglobin A1c and the effect on HDL cholesterol.

RESULTS
A total of 483 patients were randomized in a 1:1 fashion. By 16 weeks, the hemoglobin A1c decreased from 8.8% to 6.4% in the bondaglutaraz group, as compared with a decrease from 8.7% to 7.8% in the usual care group (P<0.01) — a 17% decrease with bondaglutaraz beyond that seen with usual care. In addition, the HDL cholesterol level increased from 39 mg per deciliter to 59 mg per deciliter in the bondaglutaraz group, as compared with an increase from 38 mg per deciliter to 44 mg per deciliter in the usual care group (P<0.01) — a 36% increase with bondaglutaraz beyond that seen with usual care. 19% of patients were lost to follow-up or withdrew from the study.

CONCLUSIONS
Treatment with bondaglutaraz had significant beneficial effects on hemoglobin A1c and HDL cholesterol levels. Bondaglutaraz offers an effective therapeutic option for patients with diabetes. (ClinicalTrials.gov #NCT87212354)

19. Drug: Provasinab; Methodological Strength: High; Disclosure statement: Industry

Use of Provasinab, a New Smooth Muscle Surface Protein Inhibitor, for Treatment of Patients with Exercise-Related Coronary Artery Angina

BACKGROUND
Provasinab is a smooth muscle surface protein inhibitor that affects coronary arterial blood flow and provides relief from angina.

METHODS
We conducted a randomized, double-blind, active-comparator controlled trial in 12 centers in the US to assess the efficacy and safety of provasinab in patients aged 55 and older who had a history of coronary heart disease (CHD), as well as exercise-related angina. Eligible patients experienced at least three episodes of angina per week, were on maximal doses of a beta blocker, and had multivessel coronary artery disease untreatable by percutaneous coronary intervention (PCI). Patients were assigned to receive 60 mg of provasinab or 60 mg of isosorbide mononitrate (Imdur) daily for 36 months. The primary end point was a combined cardiovascular disease endpoint (cardiovascular death and myocardial infarction). We also assessed the number of anginal episodes per week, the change from baseline in exercise tolerance on a standard Bruce treadmill test at 24 weeks, and the safety and side-effect profile of provasinab.

RESULTS
A total of 5322 patients underwent 1:1 randomization. The combined cardiovascular disease endpoint occurred in 147 patients treated with provasinab (5.5%) and 252 patients receiving isosorbide mononitrate (9.5%) (risk reduction (RR) 0.60, 95% confidence interval 0.51-0.73, P<0.01). By 24 weeks, the number of anginal episodes per week decreased from 8 to 3 in the provasinab group, as compared with a reduction from 9 to 6 in the isosorbide group (P<0.01) — a 29% reduction with provasinab beyond that seen with isosorbide. In addition, exercise tolerance increased from 2.5 minutes to 4.1 minutes in the provasinab group, as compared with an increase from 2.3 minutes to 3.1 minutes in the isosorbide group (P<0.01) — a 30% increase with provasinab beyond that seen with isosorbide. Less than 9% of patients were lost to follow up or withdrew from the trial. Through 36 months, no significant changes were noted in episodes of postural hypotension or symptomatic bradycardia with provasinab as compared with isosorbide.

CONCLUSIONS
Treatment with provasinab improved cardiovascular outcomes, had significant beneficial effects on anginal events and exercise tolerance, and had an acceptable side-effect profile. Provasinab offers an effective therapeutic option for patients with symptomatic angina who are ineligible for PCI. (ClinicalTrials.gov #NCT91256122)

This study was funded by a grant from [company]. The lead author reports serving as a consultant to [company].

20. Drug: Provasinab; Methodological Strength: Moderate; Disclosure statement: Industry

Use of Provasinab, a New Smooth Muscle Surface Protein Inhibitor, for Treatment of Patients with Exercise-Related Coronary Artery Angina

BACKGROUND
Provasinab is a smooth muscle surface protein inhibitor that affects coronary arterial blood flow and provides relief from angina.

METHODS
We conducted a randomized, single-blind, active-comparator controlled trial to assess the efficacy and safety of provasinab in patients aged 55 and older who had a history of coronary heart disease (CHD), as well as exercise-related coronary angina. Eligible patients experienced at least three episodes of angina per week, were on maximal doses of a beta blocker, and had multivessel coronary artery disease untreatable by percutaneous coronary intervention (PCI). Patients were assigned to receive 60 mg of provasinab or 60 mg of isosorbide mononitrate (Imdur) daily for 12 months. The primary end point was the change from baseline in number of anginal events, exercise tolerance on a standard Bruce treadmill test at 16 weeks, and the safety and side-effect profile of provasinab.

RESULTS
A total of 964 patients underwent randomization in a 1:1 fashion. By 16 weeks, the number of anginal episodes per week decreased from 8 to 3 in the provasinab group, as compared with a reduction from 9 to 6 in the isosorbide group ($P<0.01$) — a 29% reduction with provasinab beyond that seen with isosorbide. In addition, exercise tolerance increased from 2.5 minutes to 4.1 minutes in the provasinab group, as compared with an increase from 2.3 minutes to 3.1 minutes in the isosorbide group ($P<0.01$) — a 30% increase with provasinab beyond that seen with isosorbide. 13% of patients were lost to follow up or withdrew from the trial. Through 12 months, no changes were noted in episodes of postural hypotension or syptomamtic bradycardia with provasinab as compared with isosorbide.

CONCLUSIONS
Treatment with provasinab had significant beneficial effects on anginal events and exercise tolerance, and had an acceptable side-effect profile. Provasinab offers an effective therapeutic option for patients with symptomatic angina ineligible for PCI. (ClinicalTrials.gov #NCT91256122)

This study was funded by a grant from [company]. The lead author reports serving as a consultant to [company].

21. Drug: Provasinab; Methodological Strength: Low; Disclosure statement: Industry

Use of Provasinab, a New Smooth Muscle Surface Protein Inhibitor, for Treatment of Patients with Exercise-Related Coronary Artery Angina

BACKGROUND
Provasinab is a smooth muscle surface protein inhibitor that affects coronary arterial blood flow and provides relief from angina.

METHODS
We conducted a randomized, open-label, controlled trial to assess the utility of provasinab in people with a history of Prinzmetal's angina. Eligible patients experienced at least three episodes of angina per week and were on maximal doses of a beta blocker. Patients were assigned to receive 60 mg of provasinab or usual care for 4 months. The primary end point was the change from baseline in number of anginal events and exercise tolerance on a standard Bruce treadmill test.

RESULTS
A total of 483 patients were randomized in a 1:1 fashion. By 16 weeks, the number of anginal episodes per week decreased from 8 to 3 in the provasinab group, as compared with a reduction from 9 to 6 in the usual care group ($P<0.01$) — a 29% reduction with provasinab beyond that seen with usual care. In addition, exercise tolerance increased from 2.5 minutes to 4.1 minutes in the provasinab group, as compared with an increase from 2.3 minutes to 3.1 minutes in the usual care group ($P<0.01$) — a 30% increase with provasinab beyond that seen with usual care. 19% of patients were lost to follow-up or withdrew from the study.

CONCLUSIONS
Treatment with provasinab had significant beneficial effects on anginal events and exercise tolerance. Provasinab offers an effective therapeutic option for patients with symptomatic angina. (ClinicalTrials.gov #NCT91256122)

This study was funded by a grant from [company]. The lead author reports serving as a consultant to [company].

22. Drug: Provasinab; Methodological Strength: High; Disclosure statement: NIH

Use of Provasinab, a New Smooth Muscle Surface Protein Inhibitor, for Treatment of Patients with Exercise-Related Coronary Artery Angina

BACKGROUND
Provasinab is a smooth muscle surface protein inhibitor that affects coronary arterial blood flow and provides relief from angina.

METHODS
We conducted a randomized, double-blind, active-comparator controlled trial in 12 centers in the US to assess the efficacy and safety of provasinab in patients aged 55 and older who had a history of coronary heart disease (CHD), as well as exercise-related angina. Eligible patients experienced at least three episodes of angina per week, were on maximal doses of a beta blocker, and had multivessel coronary artery disease untreatable by percutaneous coronary intervention (PCI). Patients were assigned to receive 60 mg of provasinab or 60 mg of isosorbide mononitrate (Imdur) daily for 36 months. The primary end point was a combined cardiovascular disease endpoint (cardiovascular death and myocardial infarction). We also assessed the number of anginal episodes per week, the change from baseline in exercise tolerance on a standard Bruce treadmill test at 24 weeks, and the safety and side-effect profile of provasinab.

RESULTS
A total of 5322 patients underwent 1:1 randomization. The combined cardiovascular disease endpoint occurred in 147 patients treated with provasinab (5.5%) and 252 patients receiving isosorbide mononitrate (9.5%) (risk reduction (RR) 0.60, 95% confidence interval 0.51-0.73, P<0.01). By 24 weeks, the number of anginal episodes per week decreased from 8 to 3 in the provasinab group, as compared with a reduction from 9 to 6 in the isosorbide group (P<0.01) — a 29% reduction with provasinab beyond that seen with isosorbide. In addition, exercise tolerance increased from 2.5 minutes to 4.1 minutes in the provasinab group, as compared with an increase from 2.3 minutes to 3.1 minutes in the isosorbide group (P<0.01) — a 30% increase with provasinab beyond that seen with isosorbide. Less than 9% of patients were lost to follow up or withdrew from the trial. Through 36 months, no significant changes were noted in episodes of postural hypotension or symptomatic bradycardia with provasinab as compared with isosorbide.

CONCLUSIONS
Treatment with provasinab improved cardiovascular outcomes, had significant beneficial effects on anginal events and exercise tolerance, and had an acceptable side-effect profile. Provasinab offers an effective therapeutic option for patients with symptomatic angina who are ineligible for PCI. (ClinicalTrials.gov #NCT91256122)

This study was funded by a grant from the National Institutes of Health.

23. Drug: Provasinab; Methodological Strength: Moderate; Disclosure statement: NIH

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RESULTS
A total of 964 patients underwent randomization in a 1:1 fashion. By 16 weeks, the number of anginal episodes per week decreased from 8 to 3 in the provasinab group, as compared with a reduction from 9 to 6 in the isosorbide group ($P<0.01$) — a 29% reduction with provasinab beyond that seen with isosorbide. In addition, exercise tolerance increased from 2.5 minutes to 4.1 minutes in the provasinab group, as compared with an increase from 2.3 minutes to 3.1 minutes in the isosorbide group ($P<0.01$) — a 30% increase with provasinab beyond that seen with isosorbide. 13% of patients were lost to follow up or withdrew from the trial. Through 12 months, no changes were noted in episodes of postural hypotension or syptomamtic bradycardia with provasinab as compared with isosorbide.

CONCLUSIONS
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This study was funded by a grant from the National Institutes of Health.

24. Drug: Provasinab; Methodological Strength: Low; Disclosure statement: NIH

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RESULTS
A total of 483 patients were randomized in a 1:1 fashion. By 16 weeks, the number of anginal episodes per week decreased from 8 to 3 in the provasinab group, as compared with a reduction from 9 to 6 in the usual care group ($P<0.01$) — a 29% reduction with provasinab beyond that seen with usual care. In addition, exercise tolerance increased from 2.5 minutes to 4.1 minutes in the provasinab group, as compared with an increase from 2.3 minutes to 3.1 minutes in the usual care group ($P<0.01$) — a 30% increase with provasinab beyond that seen with usual care. 19% of patients were lost to follow-up or withdrew from the study.

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This study was funded by a grant from the National Institutes of Health.

25. Drug: Provasinab; Methodological Strength: High; Disclosure statement: None

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26. Drug: Provasinab; Methodological Strength: Moderate; Disclosure statement: None

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CONCLUSIONS
Treatment with provasinab had significant beneficial effects on anginal events and exercise tolerance, and had an acceptable side-effect profile. Provasinab offers an effective therapeutic option for patients with symptomatic angina ineligible for PCI. (ClinicalTrials.gov #NCT91256122)

27. Drug: Provasinab; Methodological Strength: Low; Disclosure statement: None

Use of Provasinab, a New Smooth Muscle Surface Protein Inhibitor, for Treatment of Patients with Exercise-Related Coronary Artery Angina

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Treatment with provasinab had significant beneficial effects on anginal events and exercise tolerance. Provasinab offers an effective therapeutic option for patients with symptomatic angina. (ClinicalTrials.gov #NCT91256122)

Section 4. Results on responses to abstract-specific questions

In this section of the Appendix, we present the raw data for responses on the Likert scale for each of the abstract-specific questions.

How likely would you be to <u>prescribe</u> [drug name]? [Question presented after clinical scenario describing patient where drug would be useful for approved indication.]

Funding Source:	**Methodological rigor** Mean score out of 7 (95% confidence interval)		
	Low	Moderate	High
Pharmaceutical company	4.47 (4.08, 4.86)	4.78 (4.45, 5.12)	5.48 (5.19, 5.78)
None listed	4.79 (4.44, 5.14)	4.98 (4.66, 5.30)	5.61 (5.28, 5.94)
NIH	4.8 (4.4, 5.21)	5.25 (4.90, 5.60)	5.9 (5.68, 6.13)

How confident are you in the validity of the conclusion that the authors draw about [drug name] in this abstract?

Funding Source:	**Methodological rigor** Mean score out of 7 (95% confidence interval)		
	Low	Moderate	High
Pharmaceutical company	3.98 (3.63, 4.32)	4.42 (4.09, 4.76)	5.08 (4.81, 5.34)
None listed	4.29 (3.97, 4.62)	4.58 (4.29, 4.86)	5.19 (4.90, 5.47)
NIH	4.32 (3.99, 4.64)	5.05 (4.79, 5.31)	5.41 (5.17, 5.66)

Rate the overall <u>rigor</u> of the study methodology:

Funding Source:	**Methodological rigor** Mean score out of 7 (95% confidence interval)		
	Low	Moderate	High
Pharmaceutical company	3.85 (3.53, 4.18)	4.18 (3.90, 4.46)	5.12 (4.91, 5.33)
None listed	4.25 (3.95, 4.55)	4.41 (4.15, 4.67)	5.20 (4.91, 5.49)
NIH	4.12 (3.82, 4.42)	4.86 (4.59, 5.12)	5.33 (5.08, 5.58)

Rate the <u>importance</u> of the study:

Funding Source:	**Methodological rigor** Mean score out of 7 (95% confidence interval)		
	Low	Moderate	High
Pharmaceutical company	4.64 (4.29, 5.00)	5.00 (4.72, 5.28)	5.67 (5.45, 5.89)
None listed	4.96 (4.67, 5.24)	5.12 (4.83, 5.42)	5.40 (5.13, 5.67)
NIH	4.80 (4.47, 5.13)	5.39 (5.14, 5.63)	5.91 (5.70, 6.12)

Are you interested in reading the full article for the study described in this abstract?

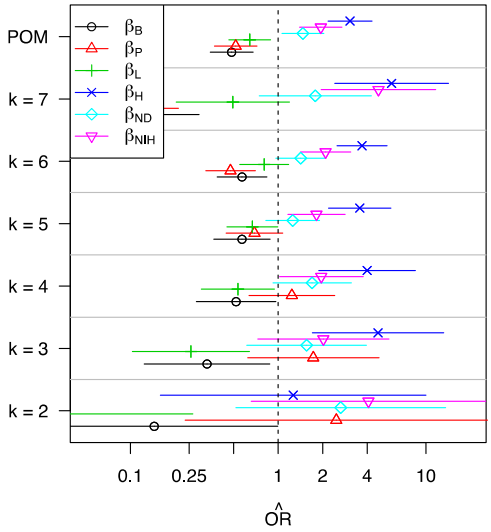
Funding Source:	**Methodological rigor** Mean score out of 7 (95% confidence interval)		
	Low	Moderate	High
Pharmaceutical company	4.90 (4.51, 5.29)	5.05 (4.64, 5.46)	5.73 (5.42, 6.03)
None listed	5.24 (4.89, 5.60)	5.30 (4.93, 5.66)	5.40 (5.02, 5.78)
NIH	4.91 (4.47, 5.35)	5.43 (5.09, 5.78)	6.02 (5.77, 6.27)

Section 5. Appendix Tables and Figures

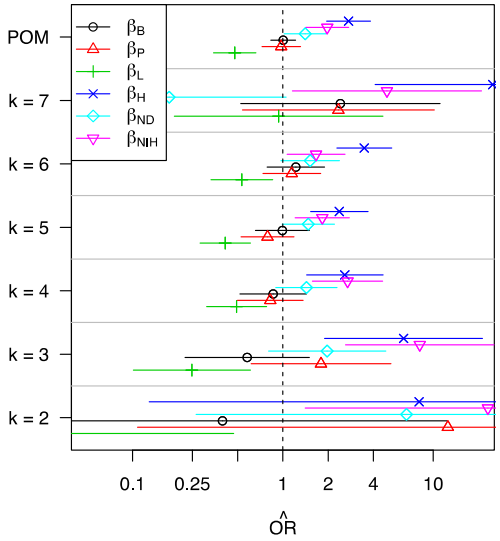
In this section of the Appendix, we present Tables and Figures referred to earlier in the Appendix.

Figure S1. Comparison of the coefficients from the proportional odds model (POM) across the logistic regressions

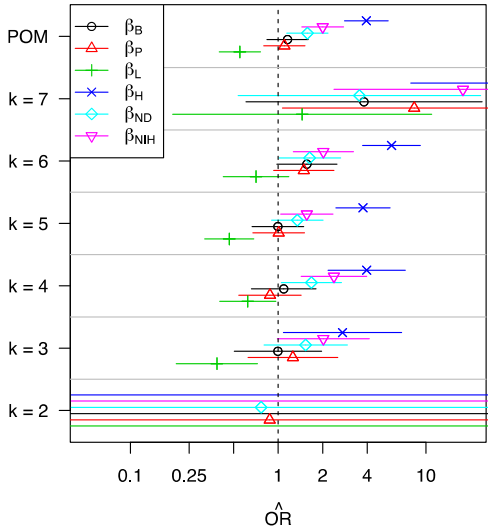
A) Physician willingness to prescribe drug



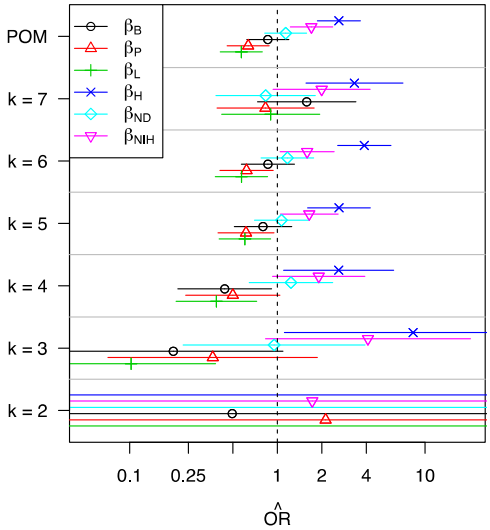
B) Confidence in results



C) Interpretation of study's rigor



D) Interpretation of study's importance



Fixed effect estimates model coefficients from the proportional odds model (POM) and logistic regression models that dichotomized the response as $\geq k$ versus $< k$. Coefficients (log ORs) are plotted with axes on the OR scale for four survey questions.

Table S1. Results after adjusting for physician characteristics

	Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
Physician willingness to prescribe drug				
Low vs Mod	0.61	0.44	0.86	0.005
High vs Mod	3.35	2.34	4.8	<.001
None vs Pharma	1.35	0.96	1.89	0.087
NIH vs Pharma	1.91	1.35	2.7	<.001
Confidence in results				
Low vs Mod	0.48	0.34	0.68	<.001
High vs Mod	2.87	2.01	4.1	<.001
None vs Pharma	1.31	0.93	1.84	0.126
NIH vs Pharma	2.04	1.44	2.89	<.001
Interpretation of study's rigor				
Low vs Mod	0.57	0.4	0.79	0.001
High vs Mod	4.04	2.82	5.79	<.001
None vs Pharma	1.51	1.07	2.12	0.018
NIH vs Pharma	1.89	1.34	2.65	<.001

Table S2. Characteristics of respondents and non-respondents in sample

Personal characteristics	Respondents **Total N=241***	Nonrespondents **Total N=262***	**P-value**
Age, median (IQR)	48 (45-53)	48 (45-53)	0.82
Sex			
Male, n (%)	162 (67.2)	183 (69.8)	0.53
Female, n (%)	79 (32.8)	79 (30.2)	
Birth country†			
US, n (%)	121 (50.2)	123 (46.9)	0.41
Non-US, n (%)	118 (49.0)	139 (53.1)	
Professional characteristics			
Medical school location			
US, n (%)	136 (56.4)	140 (53.4)	0.50
Non-US, n (%)	105 (43.6)	122 (46.6)	
Board Certification			
Internal medicine only, n (%)	203 (84.2)	--	--
Internal medicine with subspecialty, n (%)	38 (15.4)	--	
Percentage of time spent in clinical care overall, median (IQR)	80 (70-90)	80 (70-88)	0.63
Hours per month in clinical care activities‡			
≤ 80, n (%)	78 (32.4)	86 (32.8)	0.94
> 80, n (%)	162 (67.2)	176 (67.2)	
Of clinical time, percentage devoted to primary care, median (IQR)	80 (20-91)	70 (6-95)	0.35
Of clinical time, percentage spent in each setting:			
Office/ambulatory, median (IQR)	75 (50-90)	70 (50-90)	0.47
Hospital, median (IQR)	18 (8-30)	20 (8-30)	0.78
Intensive care, median (IQR)	2 (0-5)	1 (0-5)	0.71
Other, median (IQR)	0 (0-5)	0 (0-10)	0.19
Practice type§			
Solo/group private practice, n (%)	136 (56.4)	157 (59.9)	0.42
Group/staff model HMO, n (%)	26 (10.8)	21 (8.0)	0.62
Academic faculty practice, n (%)	33 (13.7)	32 (12.2)	0.62
Hospital inpatient practice, n (%)	34 (14.1)	28 (10.7)	0.24
Other, n (%)	58 (24.1)	63 (24.0)	0.99
Journal abstracts read in last month relating to prescription drugs, median (IQR)‖	4 (2-8)	--	--
Types of industry support received¶			
Any of the following:	188 (75.5)	--	--
Free drug samples, n (%)	153 (61.4)	--	--
Food or beverages in the workplace, n (%)	128 (51.4)	--	--
Free or subsidized admission to meetings or	18 (7.2)	--	--

conferences for which CME credits were awarded, n (%)			
Honoraria for speaking, n (%)	10 (4.0)	--	--
Costs of travel, time, meals, lodging, or other personal expenses for attending meetings, n (%)	10 (4.1)	--	--
Other, n (%)	8 (3.2)	--	--
None of the above	61 (24.5)	--	--

Because data on the journal abstracts read and types of industry support received were obtained from the survey, these data are not available for non-respondents. P-value calculated using chi-square tests for categorical variables and t-tests for continuous variables.

* Demographic data could not be matched for 22/263 (8.4%) respondents. These data therefore remain in the non-respondents column.

† Data missing for 1 physician.

‡ Data missing for 2 physicians.

§ Multiple responses per physician permitted.

‖ Based on data from 248 physicians

¶ Based on data from 249 physicians