Hoss

MEDICAL/CLINICAL REVIEW
OF
STUDY PROTOCOLS

IND#: [redacted]

AUG 28 1998

SPONSOR: ROCHE

DRUG: ORLISTAT

SUBMISSION: PHASE 3B PROTOCOLS

DATE SUBMITTED: 8/20/98

DATE OF REVIEW: 8/27/98

This submission includes 4 phase 3b protocols. One study proposes to examine the effects of orlistat on cardiovascular risk factors in 750 peri- or post-menopausal women; two studies propose to study male and female patients with NIDDM inadequately controlled by insulin and metformin; and one study proposes to study males and females with hypertension inadequately controlled with antihypertensive medications. The latter 3 studies will enroll nearly 500 patients each. All studies will be 12 months in duration and will be placebo controlled.

The data in the NDA for this drug indicate that orlistat consistently reduces the serum levels of beta-carotene and vitamin D; its effects on the levels of vitamins K and A are less clear cut. Only one of the 7 phase 3a studies required all patients to take a vitamin supplement. And while the data from this study suggested that supplementation improves the vitamin status of the patients taking orlistat, we still have no placebo-controlled data examining this issue.

I would suggest that the sponsor, at some point, examine the effect of vitamin supplementation in a placebo-controlled manner.

The other issue that needs to be addressed is the wording in the consent form of the breast cancer findings from the phase 3a studies. More than one rendition is provided in the submission and none are appropriate by this Reviewer's standards. I would suggest the following language, or a reasonable alternative:

During previously conducted studies with Xenical involving nearly 2700 patients, a total of 11 cases of breast cancer were detected. All 11 cases occurred in women 45 years of age or older. During the studies, there were 10 women out of a total of 1063 assigned to Xenical who received a diagnosis of breast cancer and there was one woman out of a total of 579 assigned to placebo (sugar pill) who received a diagnosis of breast cancer. Reviews of these cases suggested that some of the breast cancers were apparent prior to study participation. Cancer studies in rats and mice showed no evidence that Xenical has any cancer-causing effects. There is currently no definite reason(s) to explain the greater number of breast cancer cases in the women treated with Xenical.

To be conveyed to the sponsor:

1. Please provide the rationale for not measuring plasma levels of fat-soluble vitamins (excluding vitamin D in study 46) and beta-carotene in the proposed studies.
2 Regarding the consent form, we request that the following language, or a reasonable alternative, be used to describe the phase 3a breast cancer data:

During previously conducted studies with Xenical involving nearly 2700 patients, a total of 11 cases of breast cancer were detected. All 11 cases occurred in women 45 years of age or older. During the studies, there were 10 women out of a total of 1063 assigned to Xenical who received a diagnosis of breast cancer and there was one woman out of a total of 579 assigned to placebo (sugar pill) who received a diagnosis of breast cancer. Reviews of these cases suggested that some of the breast cancers were apparent prior to study participation. Cancer studies in rats and mice showed no evidence that Xenical has any cancer-causing effects. There is currently no definite reason(s) to explain the greater number of breast cancer cases in the women treated with Xenical.

/S/ [redacted] 8/28/98

Eric Colman, MD

Cc: IND Arch /S/ [redacted]

APPEARS THIS WAY ON ORIGINAL

+1255

MAR 10 1998

M E M O R A N D U M

DATE: 10 March 1998

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology

/s/ [redacted]

TO: Solomon Sobel, MD
Director, Division of Metabolism
& Endocrine Drug Products

SUBJECT: Orlistat and Breast Cancer
NDA 20-766, Xenical (orlistat),
Hoffman-La Roche, Inc.

Attached are:

(1) a complete overview of information about orlistat and breast cancer from the phase 3 clinical trials and the follow-up telephone surveys of participants in the trials who were female and ≥45 years of age at randomization. This document is 30 pages long and supersedes the nearly complete overview conveyed with my Memo of 17 February.

(2) a set of paper copies of the slides for my presentation on "Orlistat and Breast Cancer" at the 13 March meeting of the Metabolic-Endocrine Drug Products Advisory Committee. This document is 13 pages long.

Based on the breast cancer findings from the phase 3 clinical trials and the follow-up telephone surveys, and on the evidence pertaining to the hypothesis that these findings might be due to detection bias, I continue to think there is a substantial preponderance of evidence that orlistat accelerates the development of breast cancer in women about 45 years of age or older when given orally at a dose of 120 milligrams three times per day.

Archive: NDA 20-776
HFD 510: BStadel
GTroendle
EColman
Llutwak
Bschneider
MHess
HFD 715: ENevius
Lpian

ORLISTAT
and
BREAST CANCER

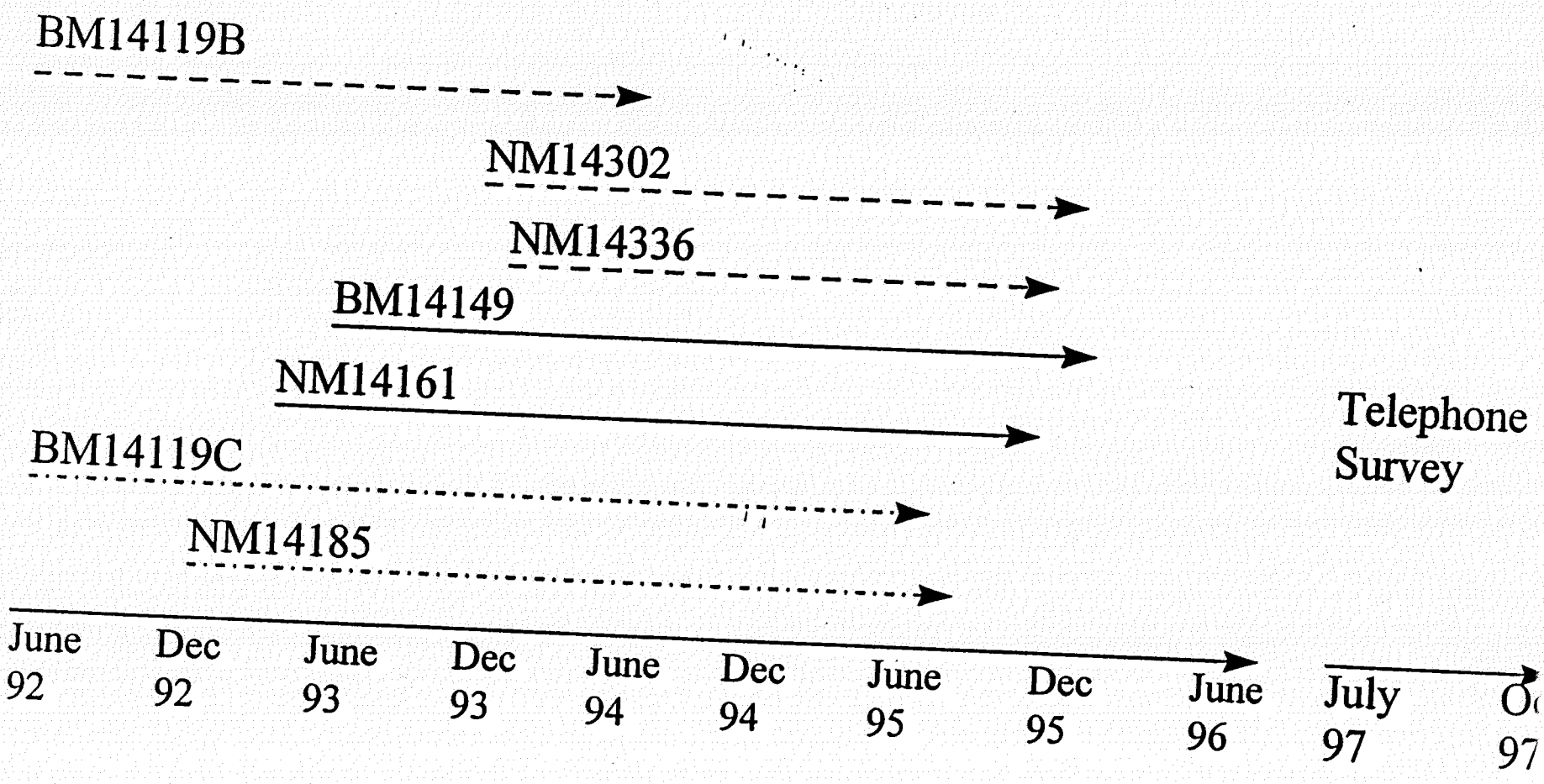
Food and Drug Administration
Bruce V. Stadel, MD, MPH

Breast Cancer in Orlistat Trials
Women ≥ 45 Years Old

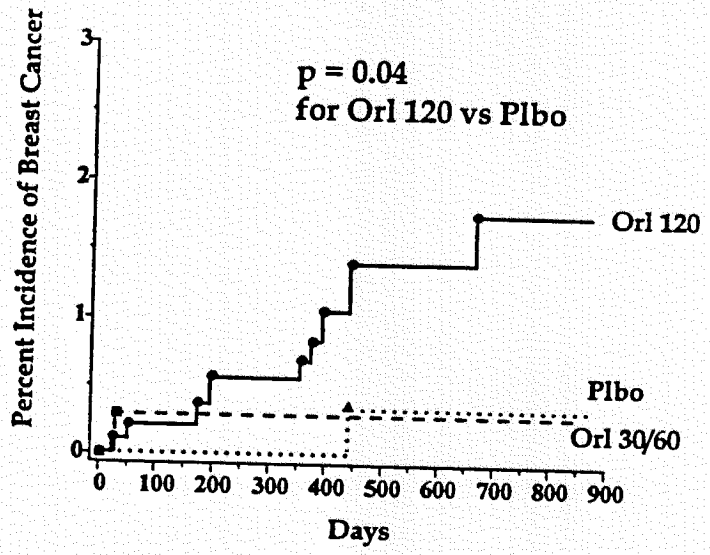
- 11 cases occurred in 4 out of 7 trials
- 9 cases/747 randomized to Orl 120mg tid
- 1 case/225 randomized to Orl 60mg tid
- 0 cases/91 randomized to Orl 30mg tid
- 1 case/579 randomized to Plbo tid

2

Dates of Clinical Trials and Follow-up Survey



Time to Breast Cancer Diagnosis Over Treatment Period

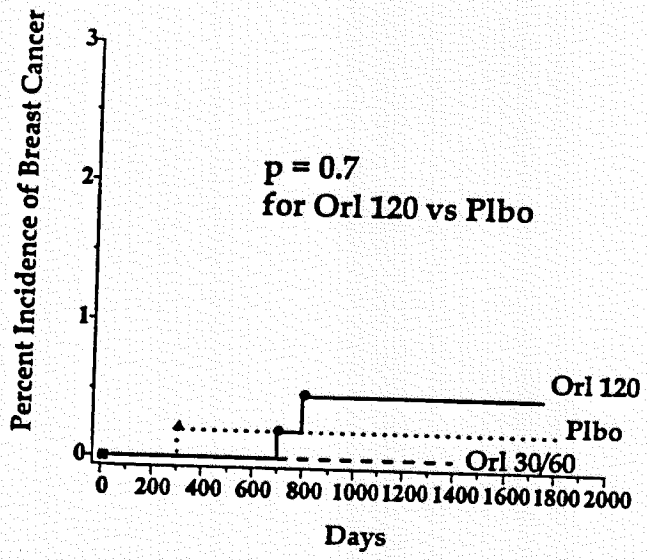


Breast Cancer Diagnosis Over Treatment Period
Dose-Response Analysis

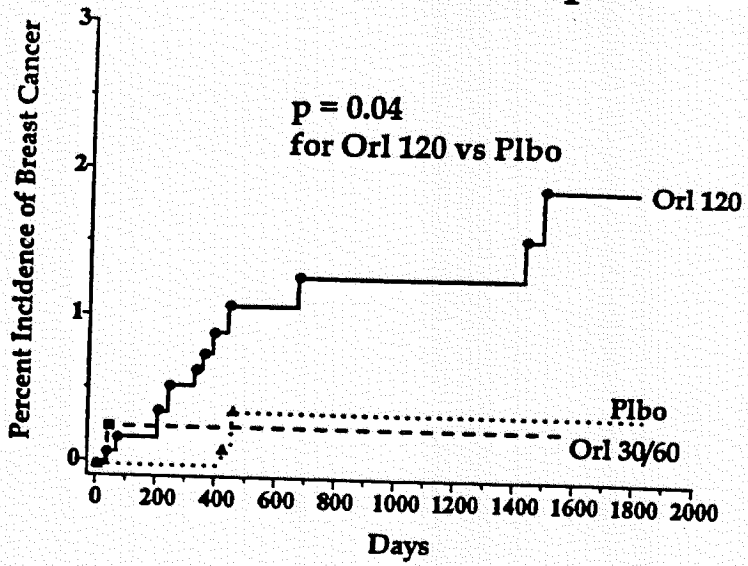
Treatment Group	Person-Years	Incidence x 1000yr (# of cases)
120 mg	944	8.5 (8)
60 mg_{120mg}	49	20.4 (1)
60 mg	314	3.2 (1)
30 mg	81	- (0)
$Plbo_{120mg}$	104	- (0)
Plbo	713	1.4 (1)

Test of Trend p=0.05

Time to Breast CancerDiagnosis Over Follow-up Period



Time to Breast Cancer Diagnosis Treatment + Follow-up Period



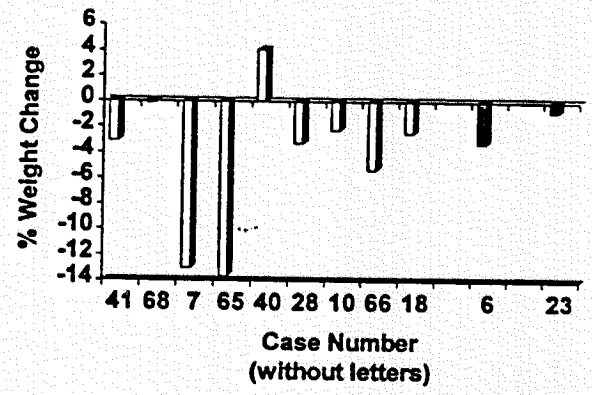
Possible Explanations For Breast Cancer Data

- Detection Bias
  - Weight Loss
  - Mammography/Other Breast Examinations
- Chance
- Causal

Summary of Breast Cancer Cases

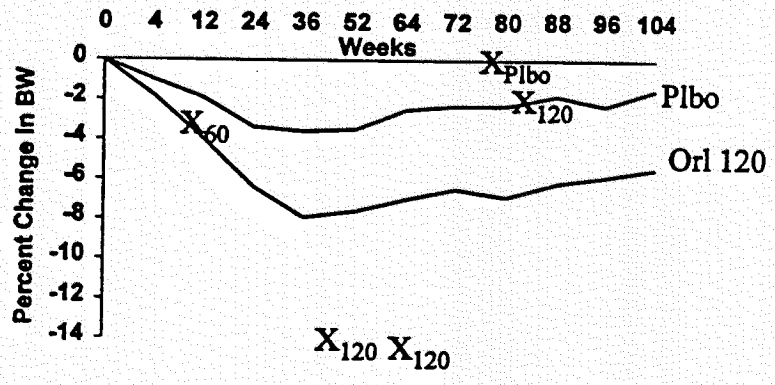
Case	Time (days)	Weight Change From Baseline	
		Kgs	%
GBB41	41	-3.5	-3.1
JDL68	85	-0.1	-0.1
I007	190	-10.7	-13.0
KTM40	197	+2.9	+4.1
AO65	309	-12.6	-13.6
DO10	370	-2.6	-2.2
SW28	435	-3.8	-3.3
CP66	693	-5.0	-5.3
AL18	717	-2.5	-2.5
F006	37	-3.0	-3.3
H023	443	-0.8	-0.8

Percent Weight Change for Breast Cancer Cases



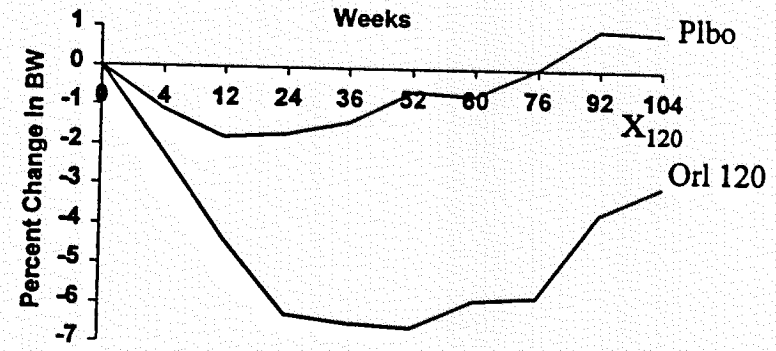
Weight Change Between Randomization and Diagnosis of Breast Cancer

BM14149



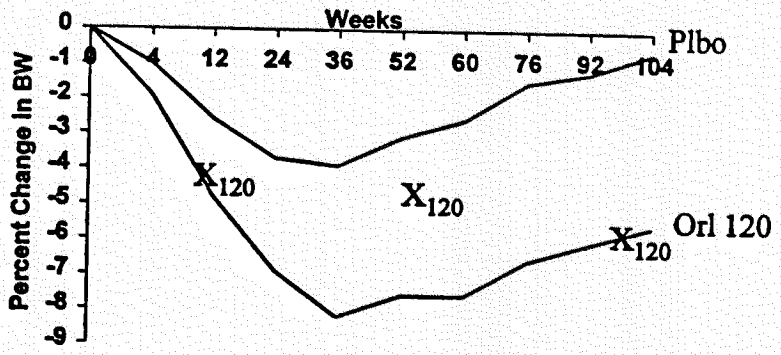
Weight Change Between Randomization and Diagnosis of Breast Cancer

NM14161



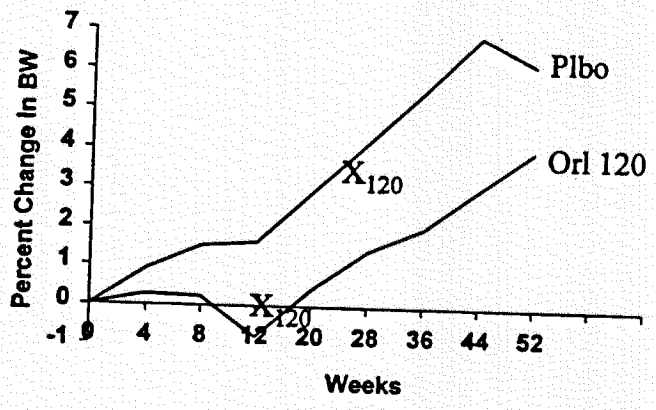
Weight Change Between Randomization and Diagnosis of Breast Cancer

NM14185



Weight Change Between Randomization and Diagnosis of Breast Cancer

NM14302 (Weight Regain Study)



Frequency of Mammography in 5 Years Since Interview

Initial Tx	q1yr	q2yrs	> 2years	None in past 5yrs
Placebo	37%	26%	23%	14%
Orl 30	64%	26%	6%	4%
Orl 60	37%	26%	20%	17%
Orl 120	46%	21%	21%	13%

Frequency of Mammography
Since End of Trials

Initial Tx	N	Frequency
Placebo	399	78%
Orl 30	76	91%
Orl 60	146	75%
Orl 120	536	81%

Frequency of Breast Cancer Risk Factors

Risk Factor	Orl120	Orl30/60	Plbo
Family Hx			
Mother	7%	8%	5%
Sister	5%	5%	7%
Nulliparity	9%	8%	9%
Hx of Breast Bx	18%	16%	16%
Hx of HRT	56%	61%	52%

Breast Cancer
Over Treatment + Follow-up Period
Intent-to-Treat Analysis

Orl 120	Orl 30/60	Plbo
11/747 (1.5%)	1/316 (0.3%)	2/579 (0.3%)

			p-value
Test of Trend	120 vs 30/60 vs Plbo		0.02
Odds Ratio	120 vs Plbo	4.3 (1.1, 28.7)	0.05

Anti-Obesity Drug Use
USA - 1997

About 18 Million Prescriptions

Distribution of Use by Sex and Age was:

Unspecified	7%
Men, all ages	15%
Women, 20-44 yrs	53%
Women, ≥ 45 yrs	25%

Data from IMS America

Breast Cancer Statistics
USA - 1997

Age Group	Incidence
20-44 years	25,500/37,544,000 = 1/1472
≥ 45 years	154,700/49,020,000 = 1/319

Data from American Cancer Society and U.S. Census Bureau

Conclusions

In the phase 3 clinical trials of orlistat and the follow-up study combined, the rates of breast cancer diagnosis in women ≥ 45 years of age at randomization to treatment were:

Orlistat 120 mg tid:	11/747, = 1/68
Orlistat 30-60 mg tid:	1/316, = 1/316
Placebo tid:	2/579, = 1/234

Possible Explanations.....

ORLISTAT AND BREAST CANCER
CONCLUSIONS

IN THE PHASE 3 CLINICAL TRIALS OF ORLISTAT AND THE FOLLOW-UP STUDY COMBINED, THE RATES OF BREAST CANCER DIAGNOSIS IN WOMEN ≥45 YEARS OF AGE AT RANDOMIZATION TO TREATMENT WERE:

ORLISTAT 120 MG TID:	11/747, =	1/68
ORLISTAT 30-60 MG TID:	1/316, =	1/316
PLACEBO:	2/579, =	1/234

DETECTION BIAS DOES NOT SEEM TO EXPLAIN THE INCREASE IN BREAST CANCER FOR ORLISTAT 120 MG TID, BASED ON

- THE AMOUNTS OF WEIGHT LOST BY THE WOMEN WHO RECEIVED BREAST CANCER DIAGNOSES
- THE FREQUENCY OF MAMMOGRAPHY DURING AND AFTER THE TRIALS, FOR WOMEN IN THE 120 MG, 30-60 MG, PLACEBO GROUPS
- THE FINDING OF NO "CATCH-UP" IN THE RATE OF BREAST CANCER DIAGNOSIS FOR THE PLACEBO GROUP, IN THE FOLLOW-UP STUDY

CHANCE SEEMS TO BE ONLY A REMOTE POSSIBILITY FOR EXPLAINING THE INCREASE IN BREAST CANCER FOR ORLISTAT 120 MG TID, BECAUSE

- THE INCREASE IN BREAST CANCER WAS SPREAD ACROSS FOUR OF THE SEVEN TRIALS
- THERE WERE NO MEANINGFUL DIFFERENCES IN THE FREQUENCY OF KNOWN BREAST CANCER RISK FACTORS, FOR WOMEN IN THE 120 MG, 30-60 MG, AND PLACEBO GROUPS
- THE P-VALUES ARE SMALL

CAUSALITY IS A POSSIBLE EXPLANATION, BECAUSE

- THE STUDIES OF ABSORPTION AND DISTRIBUTION WERE DONE BEFORE THE INCREASE IN BREAST CANCER WAS FOUND, AND WERE NOT FOCUSED ON TRYING TO EXPLAIN THIS FINDING
- THERE HAVE BEEN STUDIES TO INVESTIGATE THE POSSIBILITY THAT ORLISTAT MIGHT ALTER ENDOGENOUS ESTROGEN METABOLISM BY AN INDIRECT MECHANISM INVOLVING THE GASTROINTESTINAL FLORA
- THINKING ABOUT BIOLOGICAL MECHANISMS SHOULD BE RESPONSIVE TO FINDINGS FROM RANDOMIZED TRIALS, RATHER THAN SERVING AS A BASIS FOR TRYING TO DISCOUNT THEM

Conclusions

- Detection Bias
- Chance
- Causal
  - Biological Mechanism?

Benefit/Risk

? ? ?