Considerations in Reporting Results of Clinical Trials

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National Library of Medicine

Results Reporting to ClinicalTrials.gov

- Defined “minimum reporting set”
  - Focuses on objective results of study
  - Prevents “cherry picking” or creative selection of which results to report
  - Based on accepted scientific standards
- Tabular data instead of narrative text
  - Avoids/minimizes opportunities for “spin”
  - Avoids interpretations (as opposed to facts)
- Resource for scientific community
  - Not specifically designed for lay public

Full Text View | Tabular View | Study Results | Related Studies

Brief Descriptive Title of Clinical Trial

Study Recruitment Status

Information provided by Organization

Study Type:	Interventional
Study Design:	Randomized, Double Masked, Placebo Control, Parallel Assignment
Interventions:	Drug: Drug A; Drug: Drug B

Participant Flow

Recruitment Details – Key information relevant to the recruitment process for the overall study, such as dates of the recruitment.

Pre-Assignment Detail – Significant events and approaches for the overall study following participant enrollment, but prior to assignment.

Overall Study

	Drug A	Drug B	Placebo
STARTED			
COMPLETED			
Not Completed			
Lost to Follow-up			
Adverse Event			

Baseline Characteristics

	Drug A	Drug B	Placebo	Total
Number of Participants				
Age				
Gender				
Female				
Male				

Outcome Measures

Primary Outcome Measure

Measure Name	
Measure Description	
Time Frame	

Population Description – Explanation of how the number of participants for analysis was determined.

Measured Values

	Drug A	Drug B	Placebo
Number of Subjects			
Primary Outcome Measure			

Statistical Analysis for Primary Outcome Measure

Groups	
Method	
P-Value	
Mean Difference	
95% Confidence Interval	

Additional Details About the Analysis – e.g., null hypothesis, power calculation, and whether the p-value is adjusted for multiple comparisons

More Information

Certain Agreements – Information about restrictions on the ability of the principal investigator to disseminate trial data after trial completion

Limitations and Caveats – Limitations of the study, such as early termination leading to small numbers of subjects analyzed

Results Point of Contact – Phone and/or email for additional information about the results

4 Scientific Modules

- Participant Flow
- Baseline Characteristics
- Outcome Measures
- Adverse Events
- Other, including "Certain Agreements"

Concerns about posting narrative summaries of individual study results

- One study is rarely, if ever, a meaningful “unit of analysis”
  - Each study is a link in a chain
  - Not all chains are “straight lines”
- Subjective summaries: Whose perspective is the “right” perspective?
  - The sponsor’s?
  - The investigator’s?
  - This is why “peer review” was invented
- Problem of highly technical, or earlier phase trials
  - Not all research findings can be put into a meaningful narrative

Case Study: Status of Solanezumab for Alzheimer's Disease in 2015

22 Jul 2015

The Telegraph

First drug to slow Alzheimer's Disease unveiled in landmark breakthrough

Solanezumab is the first drug shown to target the disease process itself, clearing sticky plaques in the brain which stop the neurons firing

By Sarah Knapton, Science Editor
12:00PM BST 22 Jul 2015

The first drug which slows down Alzheimer's disease **could be available within three years after trials showed that it prevented mental decline by a third**.

In a landmark announcement, pharmaceutical giant Eli Lilly said that solanezumab has been shown to put the brakes on the disease for people with mild symptoms.

ClinicalTrials.gov

Case Study: Status of Solanezumab for Alzheimer's Disease in 2016

23 Nov 2016

The Telegraph

Science

Bitter disappointment as Alzheimer's wonder drug fails to help patients in final trials

By **Sarah Knapton**, SCIENCE EDITOR

23 NOVEMBER 2016 • 4:45PM

A widely anticipated drug for Alzheimer's disease has failed in final trials in a setback which charities said was hugely disappointing for sufferers and their families.

…on Wednesday pharmaceutical giant Eli Lilly said the **drug had failed to bring benefits in an 18 month trial of more than 2,100 people**. The company said it would not be submitting the drug for regulatory approval.

ClinicalTrials.gov

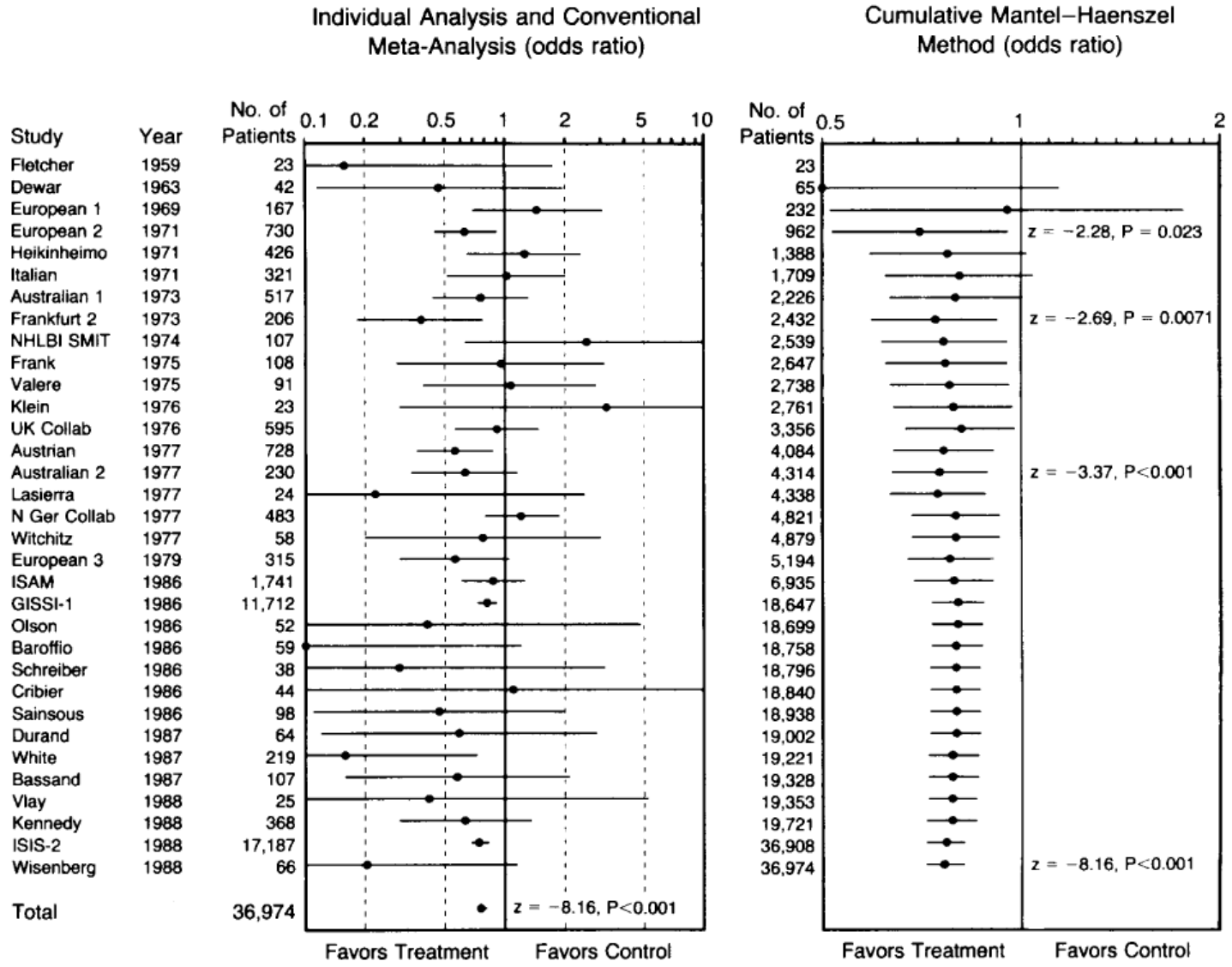

Figure 1. Conventional and Cumulative Meta-Analyses of 33 Trials of Intravenous Streptokinase for Acute Myocardial Infarction. The odds ratios and 95 percent confidence intervals for an effect of treatment on mortality are shown on a logarithmic scale. bibliography of the published trial reports is available from the authors.

Source: Lau J et al. *N Engl J Med*. 1992; 327:248-254.

The Value of Peer Review:

"…the conclusions and interpretations of many research articles change substantially between the initially submitted manuscript and the published article as a direct result of careful peer review, editorial assessment, author revision, and post-acceptance editing.

For most articles, public consumption of research findings prior to peer review will have little influence on health, **but for some articles, the effect could be devastating for some patients if the results made public prior to peer review are wrong or incorrectly interpreted**."

Source: Bauchner H. *JAMA*. 2017 Sep 26;318(12):1109-1110.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

UNITED STATES *ex rel.* GREG THORPE, ET AL. [Consolidated]
Plaintiffs,
v.
GLAXOSMITHKLINE PLC, and GLAXOSMITHKLINE LLC,
Defendants

C.A. No. 11-10398-RWZ

FILED UNDER SEAL

UNITED STATES' COMPLAINT

1. The United States brings this action to recover treble damages and civil penalties under the False Claims Act, damages and other monetary relief under common law and equity against the defendants GlaxoSmithKline plc and GlaxoSmithKline LLC (together "GSK") for causing the submission of false or fraudulent claims to federal health care programs.

2. Fr
to deceive and de
prescribing and p
and promoting fa
physicians to use
safety risks, and f
Administration ("
promoted these pr
or "unapproved"
federal health car
of remuneration t
Jamaica, spa treat

"1. In Publishing Study 329, GSK Falsely Claimed that IT Demonstrated Paxil's Efficacy in Treating Depression in Patients Under 18.

27. The abstract sent to JAMA stated that Paxil was a "safe and effective treatment for major depression in adolescents." The article, however, did not expressly identify the two protocol-specified primary efficacy measures—or that Paxil failed to show superiority to placebo on those two measures. Instead, the article claimed that there were eight efficacy measures and Paxil was statistically significant to placebo on four of them."

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmj.h4320)

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doi: 10.1136/bmj.h4320

Accepted: 03 August 2015

ABSTRACT

OBJECTIVES

To reanalyse SmithKline Beecham's Study 329 (published by Keller and colleagues in 2001), the primary objective of which was to compare the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with unipolar major depression. The reanalysis under the restoring invisible and abandoned trials (RIAT) initiative was done to see whether access to and reanalysis of a full dataset from a randomised controlled trial would have clinically relevant implications for evidence based medicine.

DESIGN

Double blind randomised placebo controlled trial.

SETTING

12 North American academic psychiatry centres, from 20 April 1994 to 15 February 1998.

PARTICIPANTS

275 adolescents with major depression of at least eight weeks in duration. Exclusion criteria included a range of comorbid psychiatric and medical disorders and suicidality.

INTERVENTIONS

Participants were randomised to eight weeks double blind treatment with paroxetine (20-40 mg), imipramine (200-300 mg), or placebo.

MAIN OUTCOME MEASURES

The primary outcome measure was response (HAM-D score ≤8 or ≥50% reduction in baseline HAM-D) at acute endpoint. Prespecified secondary outcomes were changes from baseline to endpoint in depression items in K-SADS-L, clinical global impression, autonomous functioning checklist, self-perception profile, and sickness impact scale; predictors of response; and number of patients who relapse during the maintenance phase. Adverse experiences were to be compared primarily by using descriptive statistics. No coding dictionary was prespecified.

RESULTS

The efficacy of paroxetine and imipramine was not statistically or clinically significantly different from placebo for any prespecified primary or secondary efficacy outcome. HAM-D scores decreased by 10.7 (least squares mean) (95% confidence interval 9.1 to 12.3), 9.0 (7.4 to 10.5), and 9.1 (7.5 to 10.7) points, respectively, for the paroxetine, imipramine and placebo groups (P=0.20). There were clinically significant increases in harms, including suicidal ideation and behaviour and other serious adverse events in the paroxetine group and cardiovascular problems in the imipramine group.

CONCLUSIONS

Neither paroxetine nor high dose imipramine showed efficacy for major depression in adolescents, and there was an increase in harms with both drugs. Access to

FLAME Trial (NCT01782326): Prespecified 1 Primary and 27 Secondary Outcome Measures

1. **Rate of COPD Exacerbations [Time Frame: 52 weeks]**
2. Time to First COPD Exacerbation. [Time Frame: 52 weeks]
3. Rate of Moderate to Severe COPD Exacerbations. [Time Frame: 52 weeks]
4. Time to First Moderate to Severe COPD Exacerbation. [Time Frame: 52 weeks.]
5. Rate of Moderate to Severe COPD Exacerbations Requiring Treatment With Systemic Corticosteroids [Time Frame: 52 weeks]
6. Rate of Moderate to Severe COPD Exacerbations Requiring Treatment With Antibiotics [Time Frame: 52 weeks]
7. Rate of Moderate to Severe COPD Exacerbations Requiring Hospitalization. COPD Exacerbations Starting Between First Dose and One Day After Last Treatment Are Included. [Time Frame: 52 weeks]
8. Rate of Moderate to Severe COPD Exacerbations Requiring Re-hospitalization Within 30 Days [Time Frame: 52 weeks]
9. Time to First Moderate to Severe COPD Exacerbations Requiring Treatment With Systemic Corticosteroids [Time Frame: 52 weeks]
10. Time to First Moderate to Severe COPD Exacerbations Requiring Treatment With Antibiotics [Time Frame: 52 weeks]
11. Time to First Moderate to Severe COPD Exacerbations Requiring Hospitalization [Time Frame: 52 weeks]
12. Time to First Moderate to Severe COPD Exacerbations Requiring Re-hospitalization Within 30 Days [Time Frame: 52 weeks]
13. Time to First Moderate to Severe COPD Exacerbations Requiring Re-hospitalization Within 30 Days [Time Frame: 52 weeks]
14. Forced Expiratory Volume in 1 Second [Time Frame: Baseline, day 1 (30 min and one hour post dose)]
14. Forced Expiratory Volume in 1 Second [Time Frame: Baseline, 4 weeks]
15. Forced Expiratory Volume in 1 Second [Time Frame: Baseline, 12 weeks]
16. Forced Expiratory Volume in 1 Second [Time Frame: Baseline, 26 weeks]
17. Forced Expiratory Volume in 1 Second [Time Frame: Baseline, 38 weeks]
18. Forced Expiratory Volume in 1 Second [Time Frame: Baseline, 52 weeks]
19. Change From Baseline in Forced Expiratory Volume in 1 Second AUC (0-12h) [Time Frame: Baseline, 52 weeks]
20. Change From Baseline in Total St. George's Respiratory Questionnaire Score [Time Frame: Baseline, 4 weeks]
21. Change From Baseline in Total St. George's Respiratory Questionnaire Score [Time Frame: Baseline, 12 weeks]
22. Change From Baseline in Total St. George's Respiratory Questionnaire Score [Time Frame: Baseline, 26 weeks]
23. Change From Baseline in Total St. George's Respiratory Questionnaire Score [Time Frame: Baseline, 38 weeks]
24. Change From Baseline in Total St. George's Respiratory Questionnaire Score [Time Frame: Baseline, 52 weeks]
25. Change From Baseline in the Number of Puffs of Rescue Medication [Time Frame: Baseline, 52 weeks]
26. Change From Baseline in the Safety of QVA149 ((110/50 µg o.d.) vs Fluticasone/Salmeterol (500/50µg Bid) in Terms of HPA Axis Function, as Determined by Collection of 24-hour Urine Cortisol. [Time Frame: Baseline, 52 Weeks]
27. Change From Baseline in Forced Vital Capacity [Time Frame: 4 Weeks, 12 Weeks, 26 Weeks, 38 Weeks, 52 Weeks]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*

ABSTRACT

BACKGROUND

Most guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with chronic obstructive pulmonary disease (COPD) who have a high risk of exacerbations. The role of treatment with a LABA–LAMA regimen in these patients is unclear.

METHODS

We conducted a 52-week, randomized, double-blind, double-dummy, noninferiority trial. Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive, by inhalation, either the LABA indacaterol (110 μg) plus the LAMA glycopyrronium (50 μg) once daily or the LABA salmeterol (50 μg) plus the inhaled glucocorticoid fluticasone (500 μg) twice daily. The primary outcome was the annual rate of all COPD exacerbations.

RESULTS

A total of 1680 patients were assigned to the indacaterol–glycopyrronium group, and 1682 to the salmeterol–fluticasone group. Indacaterol–glycopyrronium showed not only noninferiority but also superiority to salmeterol–fluticasone in reducing the annual rate of all COPD exacerbations; the rate was 11% lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (3.59 vs. 4.03; rate ratio, 0.89; 95% confidence interval [CI], 0.83 to 0.96; P=0.003). The indacaterol–glycopyrronium group had a longer time to the first exacerbation than did the salmeterol–fluticasone group (71 days [95% CI, 60 to 82] vs. 51 days [95% CI, 46 to 57]; hazard ratio, 0.84 [95% CI, 0.78 to 0.91], representing a 16% lower risk; P<0.001). The annual rate of moderate or severe exacerbations was lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (0.98 vs. 1.19; rate ratio, 0.83; 95% CI, 0.75 to 0.91; P<0.001), and the time to the first moderate or severe exacerbation was longer in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (hazard ratio, 0.78; 95% CI, 0.70 to 0.86; P<0.001), as was the time to the first severe exacerbation (hazard ratio, 0.81; 95% CI, 0.66 to 1.00; P=0.046). The effect of indacaterol–glycopyrronium versus salmeterol–fluticasone on the rate of COPD exacerbations was independent of the baseline blood eosinophil count. The incidence of adverse events and deaths was similar in the two groups. The incidence of pneumonia was 3.2% in the indacaterol–glycopyrronium group and 4.8% in the salmeterol–fluticasone group (P=0.02).

CONCLUSIONS

Indacaterol–glycopyrronium was more effective than salmeterol–fluticasone in preventing COPD exacerbations in patients with a history of exacerbation during the previous year. (Funded by Novartis; FLAME ClinicalTrials.gov number, NCT01782326.)

Conclusions

Indacaterol–glycopyrronium was more effective than salmeterol–fluticasone in preventing COPD exacerbations in patients with a history of exacerbation during the previous year. (Funded by Novartis; FLAME ClinicalTrials.gov number, NCT01782326.)

FLAME Trial: Linking Published Article & ClinicalTrials.gov Results Database Entry

"The protocol includes a list of 27 secondary outcome measures; we report data for 19 of these outcomes here and in Sections 4 and 5 in the Supplementary Appendix. The outcomes for which data are not reported herein can be found at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01782326)."

ClinicalTrials.gov

Wedzicha JA et al. *N Engl J Med*. 2016 Jun 9;374(23):2222-34.

The NE
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ORIGINAL ARTICLE

Indacaterol–Glycopyr
COPD

Jadwiga A. Wedzicha, M.D., Donald Ban
Roche, M.D., R. Timothy Ayers, M.Sc., C
Vogelmeier, M.D., for the FLAME Investig
N Engl J Med 2016; 374:2222-2234 | Jun

Abstract | Article | References

glycopyrronium would be superio
exacerbations.

The protocol includes a list of 27
outcomes here and in Sections 4
data are not reported herein can
/results/NCT01782326). Seconda
severity, the first moderate o
exacerbation and the annual rate
exacerbations. We also assessed
from 0 to 12 hours (in a subgroup
George's Respiratory Questionna
with higher scores indicating wors
4 points, as compared with the score with placebo[24]), and the use of rescue medication.

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Text Size

QVA vs. Salmeterol/Fluticasone, 52-week Exacerbation Study, FLAME (EFfect of Indacaterol Glycopyronium Vs Fluticasone Salmeterol on COPD Exacerbations)

This study has been completed.

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01782326

First received: January 30, 2013
Last updated: May 5, 2016
Last verified: May 2016
History of Changes

Full Text View | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Results First Received: May 4, 2016

Measured Values

	QVA149	Long Acting B2 Agonist (LABA) and Inhaled Corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1528	1556
Rate of COPD Exacerbations [units: COPD Exacerbations/year] Least Squares Mean (95% Confidence Interval)	3.59 (3.28 to 3.94)	4.03 (3.68 to 4.41)

Statistical Analysis 1 for Rate of COPD Exacerbations

Groups [1]	All groups
Non-Inferiority/Equivalence Test [2]	Yes
Method [3]	Generalized linear model
Rate Ratio [4]	0.89
95% Confidence Interval	0.83 to 0.96

Final Comments

- Trial participants have different needs than the general public
- General public benefits when
  - Broad access to complete, authoritative information so that various “experts” can access the data
  - Those who conduct systematic reviews and other such products, outside of the regulatory setting, have access to complete data, e.g.
    - Payors
    - Professional associations
    - Patient groups
- Lay language summaries are valuable when there is something to summarize
  - Not all ”clinical trials” are of interest to non-experts