trials were industry sponsored is evident, and this should not play any role in its approval by regulatory agencies.

Samy Suissa, PhD
Montreal, QC, Canada
Klaus F. Rabe, MD, PhD
Kiel, Germany

Affiliations: From the Centre for Clinical Epidemiology (Dr Suissa), Jewish General Hospital, Department of Epidemiology and Biostatistics, McGill University; and LungenClinic Grosshansdorf and Department of Medicine (Dr Rabe), University Kiel, member of the German Center for Lung Research (DZL).

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Suissa attended an advisory meeting for a clinical trial involving roflumilast, the drug discussed in this paper, for Nycomed AG and participated in an expert panel meeting for Forest Laboratories, Inc. Dr Rabe has been and is still involved in several clinical trials involving roflumilast, has presented data on behalf of the sponsoring companies Nycomed AG and Takeda Pharmaceutical Company Limited, received financial compensation for talking at scientific meetings and taking part in the expert panels at European Medicines Agency and the US Food and Drug Administration, by Forest Laboratories, Inc, Nycomed AG, and Takeda Pharmaceutical Company Limited. Drs Suissa and Rabe hold no interest or stocks in any of the companies listed above.

Correspondence to: Samy Suissa, PhD, Centre for Clinical Epidemiology, Jewish General Hospital, 3755 Cote Ste-Catherine, H4.61, Montreal, QC, H3T 1E2, Canada; e-mail: samy.suissa@mcgill.ca

© 2014 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.14-0112

REFERENCES

1. Rabe KF, Bateman ED, O'Donnell D, Witte S, Bredenbröker D, Bethke TD. Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*. 2005;366(9485):563-571.
2. Calverley PM, Sanchez-Toril F, McIvor A, Teichmann P, Bredenbroeker D, Fabbri LM. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;176(2):154-161.
3. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374(9691):685-694.
4. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al; M2-127 and M2-128 study groups. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet*. 2009;374(9691):695-703.
5. Calverley PM, Anderson JA, Celli B, et al; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356(8):775-789.
6. Tashkin DP, Celli B, Senn S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554.
7. Aaron SD, Vandemheen KL, Fergusson D, et al; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive

pulmonary disease: a randomized trial. *Ann Intern Med*. 2007;146(8):545-555.

8. Suissa S, Ernst P, Vandemheen KL, Aaron SD. Methodological issues in therapeutic trials of COPD. *Eur Respir J*. 2008;31(5):927-933.
9. Kesten S, Plautz M, Piquette CA, Habib MP, Niewoehner DE. Premature discontinuation of patients: a potential bias in COPD clinical trials. *Eur Respir J*. 2007;30(5):898-906.
10. Suissa S. Lung function decline in COPD trials: bias from regression to the mean. *Eur Respir J*. 2008;32(4):829-831.
11. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2006;173(8):842-846.
12. Wouters EF, Bredenbröker D, Teichmann P, et al. Effect of the phosphodiesterase 4 inhibitor roflumilast on glucose metabolism in patients with treatment-naïve, newly diagnosed type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2012;97(9):E1720-E1725.
13. White WB, Cooke GE, Kowey PR, et al. Cardiovascular safety in patients receiving roflumilast for the treatment of COPD. *Chest*. 2013;144(3):758-765.

Counterpoint: Were Industry-Sponsored Roflumilast Trials Appropriate? No

An appropriate study design is always contextual. Small, uncontrolled studies are useful in ascertaining the toxicity of a novel agent (phase 1) or even whether a drug has clinical activity (phase 2). Randomized trials are needed to confirm the efficacy of therapies, and mega-trials are required to determine mortality effects for blockbuster medications, whose efficacy data only concern subjective end points.¹ When it comes to the clinical care of patients, however, an appropriate study must answer only one question: Does this drug improve quality or quantity of life beyond the best available therapy? Industry-sponsored studies of roflumilast do not meet this mark.

Roflumilast, a novel phosphodiesterase-4 inhibitor, gained US Food and Drug Administration (FDA) approval for severe COPD in 2012.² After just 4 months of promotional activity, roflumilast (Daliresp) had been prescribed approximately 70,000 times, with primary care doctors and other health-care providers writing 78% of scripts (specialists wrote 22%).³ The surge in the popularity of roflumilast, however, cannot be attributed to its evidence base.

Three papers from *The Lancet* (containing five randomized controlled trials) are the best studies to date on roflumilast, but all, unfortunately, fail to answer meaningful clinical questions. The earliest study, by Rabe and colleagues,⁴ published in 2005, assigned 1,411 patients with a diagnosis of COPD for at least 1 year to roflumilast 250 µg, roflumilast 500 µg, or placebo. Besides short-acting β-agonists and short-acting anticholinergics, all other respiratory medicines

were stopped, including long-acting β -agonists (LABAs) and inhaled corticosteroids (ICSs). The trial's authors conclude that the study showed improvements in FEV₁ and the number of patients with exacerbations, but no change in quality-of-life scores. Others, however, have questioned the basic statistical analysis⁵ used by the authors and show that simple (χ^2 test) comparisons of the number of patients with exacerbations do not yield significant results. Additionally, new COPD medications should show benefit over current and maximal therapy,⁶ and the 2005 study did not attempt to do this. Finally, nearly 20% of patients discontinued the study medication, almost double that of the control group, with diarrhea being the most common side effect.⁷ Thus, given real side effects, a questionable benefit, and a starting point that was unfair (withholding existing therapy), the case for roflumilast was not made in 2005. Accordingly, at this time, the FDA failed to approve the drug.⁸

By the time the next two pivotal papers were published on roflumilast, there were significant advances in COPD research. In 2007, the Towards a Revolution in COPD Health (TORCH⁹) study compared salmeterol plus an ICS (fluticasone) against each component alone and placebo in a trial whose primary end point was mortality. In the TORCH trial, patients were allowed to use all other drugs besides the classes of drug being intervened upon (ICSs and LABAs). The TORCH trial found that the combination of salmeterol and fluticasone decreased exacerbations, improved spirometric function, and exhibited a strong trend toward overall mortality benefit (17.5% relative risk reduction) compared with patients taking placebo. In 2008, the Understanding Potential Long-Term Impacts on Function with Tiotropium¹⁰ (UPLIFT) trial tested tiotropium against placebo in patients with COPD who were permitted to use all respiratory medications except inhaled anticholinergics. The majority (60%) of these patients used LABAs at baseline. The UPLIFT trial found improvements in lung function, quality of life, exacerbations, and a trend toward improved survival.

Against this backdrop, the next two roflumilast papers emerge. The Calverley et al¹¹ study contains two trials and is listed as pivotal in the FDA application of the drug.¹² Trial sponsors randomized > 3,000 patients with COPD, bronchitis symptoms, a history of exacerbations, and severe airflow limitation to roflumilast or placebo. Although β -agonists and short-acting anticholinergics were allowed, long-acting muscarinic antagonists (such as tiotropium) and inhaled corticosteroids were not. The trial showed a 17% decrease in the rate of moderate to severe COPD exacerbations (from 1.37 to 1.14 per patient per year), but that was largely driven by a decrease in moderate exacerba-

tions, defined as requiring oral or IV steroids. Severe exacerbations, those leading to admission or death, were not statistically different.

In summary, the pivotal roflumilast studies prevented patients from using one class of drugs that is of benefit (long-acting muscarinic antagonists) and halted another that is standard of care (ICSs). Regardless of the results, the trial does not inform real-world practice. If the authors wanted to enroll patients who could not tolerate tiotropium, that would be a separate hypothesis, but requiring patients to stop this drug and ICSs raises serious doubts about the generalizability of the trial.

The third high-impact paper on roflumilast¹³ again contained two randomized trials, which examined > 1,500 patients with moderate to severe COPD based on spirometry. In one study, roflumilast was added to salmeterol. In the other, it was added to tiotropium. The authors note, "no inhaled corticosteroids, short acting anticholinergic drugs, other long acting bronchodilator drugs, theophylline, or other respiratory drugs were allowed after study enrollment."¹³ Out of the many end points examined, there were some improvements, but with rules like this, do the results even matter? Whose clinical practice does this trial inform?

Thus far, we have ignored the implications of withholding ICSs in the roflumilast trials. Although the data for the use of ICSs have been disputed,¹⁴ it is worth highlighting that regardless of its purported efficacy, analysis of randomized controlled trial data suggests that the abrupt discontinuation of ICSs worsens exacerbation.¹⁵ Thus, in the roflumilast studies that show some marginal improvement in exacerbations, we might ask whether the drug offers benefit or merely temporizes harm.

Altogether, the roflumilast studies enrolled 9,394 adult patients.¹⁶ Together, nearly 10,000 patients gave their time and energy to take part in inconclusive medical research—and not just because the results were ambiguous, but because the trials were flawed from the start. COPD has been called a "neglected epidemic,"¹⁷ but, if the trend we have examined continues, it may be transformed into a manipulated one.

The impact of industry-sponsored studies has been investigated in countless publications. Two systematic reviews^{18,19} find industry-sponsored studies are more likely to reach pro-industry conclusions than those by nonconflicted bodies. Industry-sponsored studies are more likely to use inactive controls.¹⁸ Thus, such analyses use straw man opponents. However, regarding study quality, industry-sponsored studies have not been seriously faulted.¹⁸ At least four analyses have found industry-sponsored studies to be of comparable quality to non-industry-sponsored ones.²⁰⁻²³

The roflumilast trials we have discussed may make sense of previous negative findings. Industry-sponsored studies have typically been compared against nonprofit studies²⁰ using validated rating systems. However, such scales are insensitive tests of study quality. The Jadad scale,²⁴ for instance, consists of three questions: Was the study described as randomized? Was the study described as double-blind? Was there a description of withdrawals and dropouts? All of the roflumilast studies we examined achieve top marks by this metric. The studies are nevertheless of limited usefulness, not because they defy basic rules governing randomized controlled trials but by virtue of asking questions of little value and restricting the use of alternative standards of care.

The FDA's approval letter¹⁶ for roflumilast reminds the manufacturers of their post-marketing commitment to "conduct a controlled clinical trial to evaluate the efficacy of roflumilast as an add-on therapy to a LABA and inhaled corticosteroid...in the population of COPD patients for which Roflumilast is indicated...[and] appropriate to demonstrate a clinically relevant beneficial effect...". In a way, this statement is a commentary on the poor evidence base for roflumilast. Although randomized trials examined > 9,000 patients, a basic request to show efficacy is relegated to a post-marketing commitment. The roflumilast studies can be thought of as seeding trials, studies that "appear as if they answer a scientific question but primarily fulfill marketing objectives."²⁵ We have yet to see a single appropriate trial of this novel agent.

Jason Rho, MD
Chicago, IL

Nancy Ho, MD
Baltimore, MD

Vinay Prasad, MD
Bethesda, MD

Affiliations: From the Department of Medicine (Dr Rho), Northwestern University; the Department of Medicine (Dr Ho), University of Maryland Medical Center; and the Medical Oncology Branch (Dr Prasad), National Cancer Institute, National Institutes of Health.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Correspondence to: Vinay Prasad, MD, Medical Oncology Branch, National Cancer Institute, National Institutes of Health, 10 Center Dr, 10/12N226, Bethesda, MD 20892; e-mail: vinayak.prasad@nih.gov

© 2014 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.
DOI: 10.1378/chest.14-0114

ACKNOWLEDGMENTS

Other contributions: The views and opinions are the authors alone and do not represent any of the organizations or entities with which they are associated.

REFERENCES

- Ioannidis JP. Mega-trials for blockbusters. *JAMA*. 2013;309(3):239-240.
- Nycomed's novel COPD therapy roflumilast receives FDA approval. WorldPharmaNews website. <http://www.worldpharmanews.com/nycomed/1600-nycomeds-novel-copd-therapy-roflumilast-receives-fda-approval>. Accessed March 13, 2012.
- Forest Laboratories management discusses Q3 2012 results-earnings call transcript 2012. Seeking Alpha website. <http://seekingalpha.com/article/320088-forest-laboratories-management-discusses-q3-2012-results-earnings-call-transcript?part=single>. Accessed October 2, 2012.
- Rabe KF, Bateman ED, O'Donnell D, Witte S, Bredenbröker D, Bethke TD. Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*. 2005;366(9485):563-571.
- Bergmann JF. Roflumilast for chronic obstructive pulmonary disease. *Lancet*. 2005;366(9500):1845.
- Vassiliou V. Roflumilast for chronic obstructive pulmonary disease. *Lancet*. 2005;366(9500):1846.
- Gupta S. Side-effects of roflumilast. *Lancet*. 2012;379(9817):710-711.
- US Department of Health and Human Services. Pulmonary-Allergy Drugs Advisory Committee meeting on roflumilast. US Food and Drug Administration website. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM212606.pdf>. Accessed March 4, 2013.
- Calverley PM, Anderson JA, Celli B, et al; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356(8):775-789.
- Tashkin DP, Celli B, Senn S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554.
- Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374(9691):685-694.
- Center for Drug Evaluation and Research. Application number 022522Orig1s000: medical review(s). US Food and Drug Administration website. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000MedR.pdf. Accessed March 14, 2011.
- Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al; M2-127 and M2-128 study groups. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long-acting bronchodilators: two randomised clinical trials. *Lancet*. 2009;374(9691):695-703.
- Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: the case against. *Eur Respir J*. 2009;34(1):13-16.
- Suissa S, Ernst P, Vandemheen KL, Aaron SD. Methodological issues in therapeutic trials of COPD. *Eur Respir J*. 2008;31(5):927-933.
- NDA No. 022522 drug label. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/022522s000ltr.pdf. Accessed March 15, 2012.
- Barnes PJ. Chronic obstructive pulmonary disease: a growing but neglected global epidemic. *PLoS Med*. 2007;4(5):e112.
- Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA*. 2003;289(4):454-465.
- Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ*. 2003;326(7400):1167-1170.

20. Djulbegovic B, Lacey M, Cantor A, et al. The uncertainty principle and industry-sponsored research. *Lancet*. 2000; 356(9230):635-638.
21. Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. *Ann Intern Med*. 1996;124(5): 485-489.
22. Kjaergard LL, Nikolova D, Gluud C. Randomized clinical trials in HEPATOLOGY: predictors of quality. *Hepatology*. 1999;30(5):1134-1138.
23. Knox KS, Adams JR, Djulbegovic B, Stinson TJ, Tomor C, Bennet CL. Reporting and dissemination of industry versus non-profit sponsored economic analyses of six novel drugs used in oncology. *Ann Oncol*. 2000;11(12):1591-1595.
24. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
25. Hill KP, Ross JS, Egilman DS, Krumholz HM. The ADVANTAGE seeding trial: a review of internal documents. *Ann Intern Med*. 2008;149(4):251-258.

Rebuttal From Drs Suissa and Rabe

Dr Rho and colleagues¹ claim that “an appropriate study must answer only one question: Does this drug improve quality or quantity of life beyond the best available therapy?” The authors deem that studies of roflumilast “do not meet this mark.” On the other hand, the Towards a Revolution in COPD Health (TORCH) trial of the fluticasone/salmeterol inhaler is presented as an example of such an appropriate study. We show below that this is not so; had the authorization of this combination inhaler been based on such a mark for the TORCH trial, the drug would simply not have been approved. Indeed, the trial does not satisfy the three criteria set down by Dr Rho and colleagues, namely, quality of life, quantity of life, and best available therapy.

First, quality of life as measured by St. George's Respiratory Questionnaire determined a mean change score of 4 units was needed to establish the treatment to be slightly efficacious, 8 for moderately efficacious, and 12 for very efficacious.² The TORCH trial found a difference of only 3.1 units with the study treatment, which, although statistically significant, does not even reach the clinically significant threshold of 4 determined by patients for a slightly efficacious treatment. Second, quantity of life is not significantly improved with the fluticasone/salmeterol combination inhaler, though the effect was on the border of statistical significance. Further analyses of these data, using the full 2 × 2 factorial design of the trial, confirmed that the effect on mortality was entirely due to the bronchodilator component of the combination and statistically significant, whereas the inhaled corticosteroid

component was associated with no effect on mortality whatsoever.³⁻⁵ Third, whether the improvements are “beyond the best available therapy” is, in fact, the major weakness of the TORCH trial. Indeed, at least 60% of the patients in the comparison group who were on usual maintenance therapy of corticosteroids, inhaled long-acting bronchodilators, or both at the time of randomization discontinued their treatment and replaced it with a placebo for the 3-year follow-up, hardly the best available therapy for COPD.

Additionally, a major adverse side effect of roflumilast is diarrhea, whereas for the fluticasone/salmeterol combination it is pneumonia. The number needed to treat is a useful measure to compare these adverse effects.⁶ The TORCH trial data arrive at 16 patients needed to be treated with fluticasone/salmeterol for 3 years for one to develop pneumonia.⁶ The two identical 1-year trials of roflumilast (trials 3 and 4) involving > 3,000 patients arrived at around 20 patients needing to be treated with roflumilast for 1 year for one to develop with diarrhea.⁷

In all, we agree that trials of new drugs must demonstrate clinically meaningful effects. It is, however, unreasonable to expect that mortality benefits be established initially for a drug to be approved for use by regulatory agencies. No drug would ever be on the market. There are several COPD outcomes other than mortality that can provide valuable information on clinical benefits of drugs and can be used for regulatory approval purposes. Once the drug is on the market, it is then imperative that industry sponsor real-life mega-trials of major outcomes, as advocated by Ioannidis.⁸

Samy Suissa, PhD
Montreal, QC, Canada
Klaus F. Rabe, MD, PhD
Kiel, Germany

Affiliations: From the Centre for Clinical Epidemiology (Dr Suissa), Jewish General Hospital, Department of Epidemiology and Biostatistics, McGill University; and LungenClinic Grosshansdorf and Department of Medicine (Dr Rabe), University Kiel, member of the German Center for Lung Research (DZL).

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Suissa attended an advisory meeting for a clinical trial involving roflumilast, the drug discussed in this paper, for Nycomed AG and participated in an expert panel meeting for Forest Laboratories, Inc. Dr Rabe has been and is still involved in several clinical trials involving roflumilast, has presented data on behalf of the sponsoring companies Nycomed AG and Takeda Pharmaceutical Company Limited, received financial compensation for talking at scientific meetings and taking part in the expert panels at European Medicines Agency and the US Food and Drug Administration, by Forest Laboratories, Inc, Nycomed AG, and Takeda Pharmaceutical Company Limited. Drs Suissa and Rabe hold no interest or stocks in any of the companies listed above.

Correspondence to: Samy Suissa, PhD, Centre for Clinical Epidemiology, Jewish General Hospital, 3755 Cote Ste-Catherine, H4.61, Montreal, QC, H3T 1E2, Canada; e-mail: samy.suissa@mcgill.ca