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Implications of product withdrawal on a post-approval pragmatic trial: The VOLUME study experience

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ABSTRACT

Introduction: Many clinical trials terminate early due to safety and efficacy concerns, and less often due to unexpected "positive" findings. However, early termination of post-approval (Phase IV) pragmatic randomized trials for commercial reasons is less frequent, may be more complex, and may require added flexibility in closure methods, including short term follow-up. VOLUME was a randomized, open-label, post-approval pragmatic clinical trial (PCT) or large simple trial that terminated early due to product withdrawal. The aim of this paper is to describe circumstances unique to post-approval PCTs that may require a closure amendment rather than immediate study termination, and our recommendations for operational study closure in these circumstances. We use the VOLUME case study throughout to provide a practical example.

Methods: Study closeout considerations at the study level include: notifying external governance bodies, e.g., data monitoring committees (DMC), and scientific steering committees (SSC); executing a study closure amendment; notifying and training of study physicians; and institutional review board (IRB)/ethics committee (EC) approvals. Study closure considerations at the patient level focus on patient safety and include: patient notification, efficient transition to alternative treatments, the need for re-consenting; and drug supply shortages.

Conclusions: Early study closeout logistics require careful analysis, detailed planning, and close coordination, and are ideally considered at the study planning phase. Lessons learned from the VOLUME closeout should help other researchers devise contingencies when terminating post approval pragmatic trials that utilize a marketed product.

ClinicalTrials.gov: **NCT00359801**.

1. Introduction

Many clinical trials are terminated early due to safety and/or efficacy concerns, and less often due to unexpected "positive" findings [1–3]. However, early termination of post-approval (Phase IV) pragmatic randomized trial, for commercial reasons [4–10] is less frequent, may be more complex, and may require added flexibility in closure methods, including short term follow-up [8,11].

VOLUME was a randomized, open-label, post-approval pragmatic clinical trial (PCT) or large simple trial that aimed to evaluate long-term Exubera use as the first inhaled insulin approved in the US and Europe for treatment of diabetes mellitus (DM). Recruitment was halted when 37% of 5,300 planned patients were randomized, after Pfizer announced it would cease marketing Exubera due to inadequate sales [12]. A study closure amendment provided the greatest patient protection and care, minimized burden to patients/physicians, and maintained data integrity. Here we describe circumstances unique to post-approval PCTs that may require a closure amendment (rather than immediate study termination) and our recommendations for addressing these circumstances. We use the VOLUME case study throughout to provide a practical example; Fig. 1 provides a timeline of the key VOLUME milestones.

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[1] At the time of study conduct.

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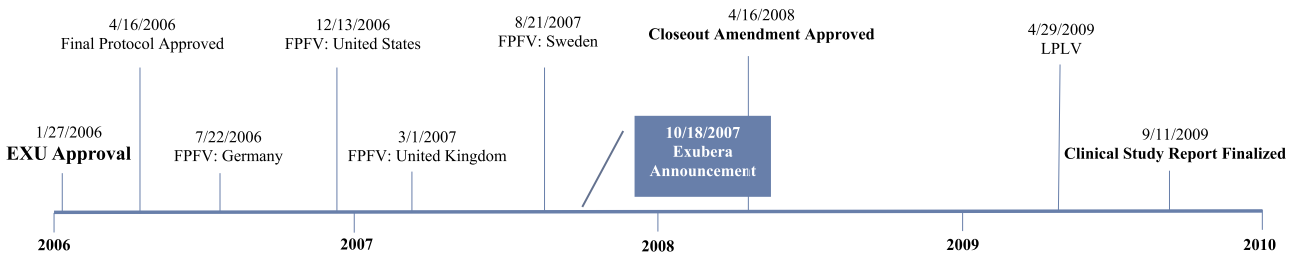

Fig. 1. Timeline of key study milestones in participating countries, VOLUME 2006–2009.

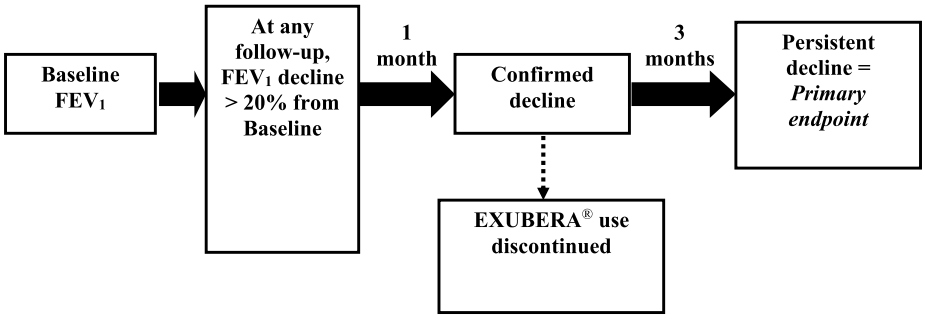

Fig. 2. Definition of the primary endpoint, VOLUME study.

2. Methods

2.1. VOLUME study design

Following 1:1 random assignment to Exubera plus usual diabetes care or usual diabetes care alone, patients received unblinded medication with minimal interventions. Patients with clinically diagnosed DM were recruited from geographically varied treatment centers to ensure broad physician/patient representation. Patients were eligible if their physician considered Exubera or other diabetes care to be suitable treatments.

Patients underwent spirometric tests according to the approved local label: at baseline, 6 months and yearly thereafter. A physician-administered questionnaire collected data on forced expiratory volume (FEV_1), pulmonary, allergic and/or cardiovascular serious adverse events (SAEs), diabetes medication, and hemoglobin A_{1c}.

The primary outcome was persistent decline in FEV_1 exceeding 20% from baseline (Fig. 2). A persistent decline was defined as an observed decline in FEV_1 exceeding 20% from baseline, confirmed after one month, and persisting 3 months after confirmation. All patients reaching the primary endpoint were referred to a pulmonologist.

The study was reviewed by the Central Institutional Review Board (IRB), 3 local IRBs, and national health authorities/IRBs.

2.2. Product withdrawal

VOLUME enrollment began July 2006 and ended in October 2007, when Exubera marketing discontinued; 1,976 were randomized in the US, Germany, the United Kingdom (UK) and Sweden. It was imperative to safely transition patients from Exubera within a short timeframe as product manufacture was terminated and in-date product would become unavailable within one year, or sooner depending on pharmacy stock. In the following sections, general considerations for early study closure are provided in italics, followed by the VOLUME study example. The results

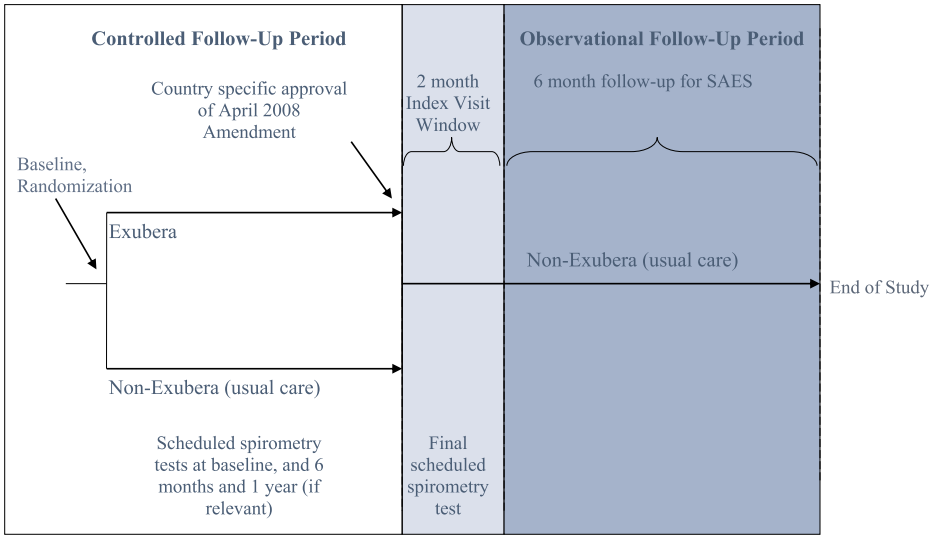

Fig. 3. Amended study design flowchart, VOLUME study.

from this study have been described elsewhere [13].

2.3. Study closure considerations (study level)

2.3.1. External oversight committee and regulatory body notification

External governance bodies, such as data monitoring committees (DMC), and scientific steering committees (SSC) are charged with providing unbiased study oversight, evaluating blinded safety data, and assisting in rapid decision-making for randomized studies. These committees are integral to study termination proceedings.

At the time of Exubera withdrawal, urgent SSC and DMC meetings were convened and the committees endorsed a closure amendment which transitioned Exubera patients to usual care and followed patients for 6 additional months to obtain safety data. This allowed comparison of SAEs according to the original randomized groups. Notification letters were sent to the US Food and Drug Administration and European Medicines Agency.

2.3.2. Study closure amendment to transition and monitor patients

In rare circumstances, the decision to terminate a post approval PCT may be driven by circumstances unrelated to product safety. In these cases, a study closeout amendment can help ensure safe transition of patients to another product when marketed product is discontinued, monitor patient safety during/after transition, and help preserve the study's objectives.

To illustrate, VOLUME was divided into Controlled and Observational Follow-up Periods via a closeout amendment. Fig. 3 presents a schematic of the amended protocol procedures. Follow-up periods were distinguished by the Index Visit Date or date of final spirometry. The controlled follow-up period included data collected according to the original protocol, i.e., from randomization to the Index Visit. All patients underwent spirometric tests in adherence with the approved local label and at the Index Visit to preserve the primary endpoint definition. Exubera-randomized patients who did not experience a >20% FEV_1 decline from baseline at the Index visit transitioned to other diabetes care. Any Exubera patient who experienced a >20% FEV_1 decline at the Index visit remained on Exubera until a confirmatory spirometry test was performed 3–4 weeks later. All remaining Exubera patients transitioned to usual diabetes care on the day of the confirmatory test. If the decline was confirmed, the patient underwent a further spirometry test in 3 months, consistent with how the primary endpoint was evaluated in the original study design. Patients were followed thereafter by their usual care physician.

The observational follow-up period was the 6 month period following the Index Visit and information was collected consistent with the original physician-administered questionnaires.

2.3.3. Study physician notification/training

Existing resources, operational framework (i.e., staff in international studies), and technical expertise of external vendors can facilitate physician notification and training (e.g., web-based, in-person) for closeout.

In VOLUME, immediately following the corporate announcement, tailored letters were sent to notify all study centers that enrollment was halted. Once the amendment was finalized, the US operations vendor and Pfizer European regional offices, facilitated planning, training, and closure of international centers.

2.3.4. IRB/ethics committee (EC) approvals

Finalizing a protocol amendment to close a study is a multi-faceted, staged process. The turnaround time for review/approval by internal collaborators, the SSC/DMC, IRB/ECs, and national health authorities in Europe can significantly delay study closure. It is necessary to ensure closure timelines include sufficient time for external review cycles.

For VOLUME, amendment approvals by IRB/EC and national health authorities were typically expedited; however, some approvals took from 2 to 3 months. By July 2008 (or 10 months after the announcement),[2] all appropriate approvals were obtained, the amendment implemented, and by October 2008, all index visits were complete, representing a one-year turnaround from marketing discontinuation to final completed index visit.

Table 1
Issues identified from the VOLUME closeout experience and recommended closure strategies for large simple trials.

	Issue	Recommended strategy
At the study level	Notification and involvement of many external oversight committees in rapid decision making.	Immediately schedule meetings with members of study oversight committees to proactively establish a formal closeout strategy.
	Notification of very large number of sites of early closure and (ideally) exact termination plan.	Send tailored letters to study centers that communicate an enrollment cessation plan and assure further information to be will be forthcoming.
	Where relevant, submission of protocol amendments to regulatory agencies, and others, for approval	Turnaround times for review and approval of amendment by the sponsor, oversight committees, IRB/ECs, and national health authorities may pose a significant barrier to prompt study closure. Make use of existing resources, operational framework, and technical expertise of external vendors to devise a study physician training strategy comprised of web-based and in-person training describing closure procedures.
At the patient level	Impact on patient medication supplies when manufacturing stops. Notification of very large numbers of patients of early closure and anticipated impact on management of their illness.	Discuss potential options (with sponsor) for medication mail order distribution. Devise drug supply contingency plans to enabled dissemination of remaining marketed product. For example, a mail-order system can be devised with a pharmacy card reimbursement vendor or local medication supplier
	Identification of risks associated with unexpectedly transitioning patients to new treatment under routine care.	Ensure study physicians are adequately monitoring patient treatment and any adverse reactions.

2.4. Study closure considerations (patient level)

2.4.1. Patient notification and informed consent

All patients must be notified of any condition that may impact their study participation. Ideally, this notification is standardized ensuring that all patients receive the same information. If it is determined that continued monitoring of patient safety is warranted, patients must be re-consented to ensure their agreement to the revised study procedures.

In VOLUME, notification letter templates were sent about Exubera marketing discontinuation, to all sites for further distribution to study patients. Patients were re-consented according to the amended protocol, which included their transition to usual care.

2.4.2. Drug supply shortages during transition period

In post approval PCTs that utilize marketed drug (e.g., prescription filled at pharmacy), patients should transition to usual care swiftly. If

[2] Instituting a study closure amendment is complex and took 10 months due to i) meetings with external governance bodies, ii) authoring study closure amendment and discussions with collaborators, iii) site notifications of Exubera withdrawal, iv) coordination of drug supply contingencies, and v) IRB/EC review/approvals.

patients obtain medication through usual means, it is unethical to continue a study where long-term medication availability and study objectives are compromised.

VOLUME study conduct during amendment review and index visit window periods were most compromised in the US (with the majority of enrolled patients), and in Sweden. Patients randomized in the US filled prescriptions at pharmacies using a study pharmacy card. After several patients could not locate Exubera at their local pharmacy, an informal survey of local pharmacies confirmed that Exubera supply reorders were not possible. In the US, a mail-order system was devised with the pharmacy card reimbursement vendor that delivered Exubera to the patient's address. In the EU, a reliable local Exubera supply was secured until the amendment was approved. These contingency measures ensured Exubera supply was available until index visits were complete, ensuring continuity of patients' diabetes management.

3. Contingency planning

It was decided that continued patient monitoring was warranted to provide the greatest protection and care, to minimize burden to both patients and investigators, and to maintain data integrity. Ideally, at the study planning stage of a post-approval pragmatic trial, early closure scenarios should be considered and contingencies planned. In addition to the usual reasons for early study closure (safety and futility), plans should be implemented for early closure due to corporate events (e.g., discontinued marketing, manufacturing/supply issues). Planning may include high-level close-out procedures (e.g. transition to alternative care with some period of continued monitoring), and alternate study-drug distribution plans (e.g., mail-order).

4. Discussion

As illustrated, several important study and patient level considerations exist when terminating a post approval phase IV study for reasons other than safety or lack of efficacy. Table 1 summarizes study and patient level issues from the VOLUME closeout experience and our recommendations. Monitoring patient safety during and immediately after transition to usual care is likely warranted. Early study closeout logistics require careful analysis, detailed planning, and close coordination at a time when rapid action is needed. Consideration of these circumstances at the study planning phase should ensure smooth medication transitions for patients with minimal inconvenience, and may significantly reduce resources and time needed.

Contributors

Mrs. Kolitsopoulos served as epidemiology project manager overseeing all participating countries, acquisitioned/interpreted the data, and drafted/finalized the manuscript. Mr. Sweetland served as study manager overseeing operational decisions, provided management of study vendors, and acquisitioned the data. Drs. Gatto, Jackson and Bracken participated in the design of the study, were involved with scientific/logistical/operational decisions, assisted with drafting of the study statistical analysis plan, interpreted the data, and helped draft the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

This study was sponsored by Pfizer. Dr. Bracken has served as a paid consultant to Pfizer, Forest Labs, GlaxoSmithKline, Lilly, Procter and Gamble, and Sanofi-Aventis. Dr. Gatto, Mrs. Kolitsopoulos, and Mr. Sweetland are full time employees and stock shareholders of Pfizer. At the time of study conduct, Dr. Jackson was a full-time employee and stock shareholder of Pfizer.

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