Prematurely ended phase III trials in Sweden during the years 2002-2008

Karin Hedenmalm, Annika Johansson, Kristoffer Bäckman, Patrik Öhagen

Prematurely ended phase III trials in Sweden during the years 2002-2008

by

Karin Hedenmalm, MD, PhD, Clinical Trial Unit, Medical Products Agency, Uppsala, Sweden and Department of Medical Sciences, Clinical Pharmacology, Uppsala University, Uppsala, Sweden

Annika Johansson, MSc, Clinical Trial Unit, Medical Products Agency, Uppsala, Sweden and Division of Pharmacokinetics and Drug Therapy, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Kristoffer Bäckman, MSc, Clinical Trial Unit, Medical Products Agency, Uppsala, Sweden and Division of Pharmacokinetics and Drug Therapy, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Patrik Öhagen, statistician, Clinical Trial Unit, Medical Products Agency, Uppsala, Sweden

Address of corresponding author:

Karin Hedenmalm

Clinical Trial Unit

Medical Products Agency

Box 26

751 03 Uppsala, Sweden

Tel: +46 18 17 42 70

Fax +46 18 54 85 66

E-mail: karin.hedenmalm@mpa.se

Short running head: Prematurely ended phase III trials

Abstract

Purpose The present investigation is aimed at identifying prematurely ended phase III clinical trials (CTs) and their proportion of all phase III CTs, reviews reasons for the premature ending, examines if a data monitoring committee (DMC) was involved in the decision, identifies the data source on which the decision was based and reviews consequences of the premature ending for product development. A further aim is to identify risk factors for a premature ending.

Methods Prematurely ended phase III CTs in Sweden during the years 2002-2008 were identified by database searches. Identified trials were reviewed with regard to tested treatment, study design, reasons for the premature ending, data source, on which the decision was based, and existence of and recommendation from a DMC. Three randomly selected not prematurely ended control trials were identified matched on application year starting 1 May 2004.

Results A total of 84 phase III CT applications (8%), were prematurely ended. Most trials were ended due to safety and/or efficacy concerns. A DMC was more common among trials investigating mortality as primary endpoint and oncology trials. A recommendation from the DMC to terminate the trial was most likely in case of combined safety and efficacy related issues arising from within the trial. Possible risk factors for a premature ending included mortality as an endpoint, obesity as indication and a longer planned study duration. Around 30% of trials with active substances without a marketing authorisation at the time of the clinical trial application were discontinued from further development.

Conclusions DMCs in phase III CTs are used in accordance with guidelines. Use of DMCs was associated with possible risk factors for a premature ending. Use of DMCs was numerically, but not significantly associated with a premature ending.

Key words: clinical trials phase III, data monitoring committee, safety, efficacy, premature ending

Background

Phase III is the last phase of the drug development process [1] before a new marketing authorization application can be submitted. Phase III clinical trials are intended to verify the clinical efficacy and characterize the safety profile of a drug in a therapeutic indication. Whilst it is important that such trials are not ended prematurely before efficacy has been unequivocally demonstrated it is equally necessary to avoid continued exposure to a harmful drug. In order to accommodate these needs without risking the scientific integrity of the trial, the review of data from ongoing clinical trials is usually delegated to an independent external committee or advisory board which makes recommendations to the sponsor of the trial [2]. Recently, both the EU and the FDA have published guidelines on the use of such committees in clinical trials [3, 4]. For consistency, the term data monitoring committee (DMC) will be used throughout this document.

The aim of this investigation was to identify phase III clinical trials which were ended prematurely in Sweden in the years 2002-2008, to review the reasons for the premature discontinuation of the trial, to find out whether or not a DMC had been involved in the decision and if the data on which the decision to stop the trial came from the trial itself or from outside of the trial. Further aims were to identify the proportion of phase III clinical trials that were prematurely ended and to review the consequences of the premature ending for the tested product and its indication.

Methods

In Sweden, approval from the Medical Products Agency (MPA) has been obligatory for all clinical trials involving human subjects since 1988. Limited administrative information related to the clinical trials is stored in the databases LVIS-C (for clinical trials before 1 May 2004) and Documentum (for clinical trials from 1 May 2004). The European Clinical Trial Directive (EU-CTD) was introduced for all clinical trial applications since 1 May 2004. The European database EudraCT also contains administrative information. Information that can be found in the databases include e.g. application date, title of the trial, trial phase (only LVIS-C and EudraCT), name/s of the investigational medicinal product/s, date/s of request/s for supplementary information, name of sponsor, name/s of investigators, date/s when the trial was approved or rejected, and status of the trial (approved, interrupted, completed).

Phase III clinical trials that were prematurely ended between 1 January 2002 and 31 December 2008 were identified in LVIS-C, Documentum and EudraCT. Since trial phase is not included in Documentum, all applications for phase III clinical trials in Sweden since 1 May 2004 were identified in EudraCT and records were matched with the same records from Documentum. In the databases LVIS-C and Documentum, the current status of the trial, i.e. “approved”, “interrupted” or “completed” is indicated. All trials with the status “interrupted” were reviewed and trials that were permanently ended were included in the study. In addition, since the status of a trial changes to “completed” after the final study report has been submitted, the EudraCT database was searched for the term “premature end” and for

reasons for a “premature end” (these reasons are “safety”, “lack of efficacy”, “the trial has not commenced” and “other”), and the LVIS-C database was searched for spontaneous notifications using loose-ending text strings (indicated by *) that may indicate a premature ending (“stop*”, “avbr*”, “prematu*”, “förtid*” and “säkerhet*). All trials retrieved by the searches were reviewed in order to identify trials that were permanently and prematurely ended.

The review was restricted to trials that were both approved and had started patient inclusion in Sweden. A prematurely ended trial was defined as a trial that was ended prior to the last treatment of the last patient according to the last version of the protocol. The reasons for a premature ending were classified as due to safety alone, efficacy alone, both safety and efficacy, and other reasons including e.g. slow patient recruitment, a lower than expected endpoint rate, changes to regulatory guidelines in such a way that the trial hypothesis was no longer of interest etc. A safety issue was considered in case of an overrepresentation of serious adverse events or reactions, even if not formally statistically significant, provided that the pharmacological mechanism of action made a causal relationship likely, and provided that the safety issue was not outweighed by other advantages. A safety issue was also considered if the tested treatment had the opposite to the expected effect on the primary endpoint in the absence of any benefit. A smaller than expected effect or the opposite effect on the primary endpoint was considered a lack of efficacy issue. A greater than expected effect on the primary endpoint was considered an unexpected positive efficacy finding. The categorization was based on an assessment of the overall profile of the tested treatment.

All prematurely ended trials were further reviewed with regard to the tested treatment, the type of control group used in the trial (placebo, active treatment, another dose or regime of the study treatment, background, standard or no treatment or no control group), and the existence of a DMC. It was noted if the primary endpoints concerned mortality.

For clinical trial applications during the years 2002 to 2006 the proportion of all phase III trials that were prematurely ended until 31 December 2008 was calculated. This was not done for clinical trial applications during the years 2007-2008 due to an insufficient period of follow-up that was considered likely to result in a significant number of prematurely ended trials in the years to come.

In order to evaluate the impact of the premature ending on the study duration and to identify possible risk factors for a premature ending, a total of three randomly selected phase III control trials that were not prematurely ended until 31 December 2008 were identified for each prematurely ended trial. The control trials were matched on application year. The comparison was restricted to clinical trial applications between 1 May 2004 and 31 December 2008 due to difficulties in obtaining information from control trials before the introduction of the EU-CTD.

Fisher's exact tests and the Mann Whitney U-test were performed to compare groups of interest. A two-sided p value of <0.05 was considered statistically significant.

Results

A total of 84 prematurely ended phase III clinical trials were identified during the years 2002-2008, see Figure 1. The trials had started up to 7 years before the premature ending, see Table 1. Almost all premature endings had taken place within the first three years after start of the trial (77/84; 92%) with the highest observed frequency during the second year (38/84; 45%). The reasons for the premature ending were safety alone in 28 cases (33%), safety and lack of efficacy in 25 cases (30%), lack of efficacy alone in 12 cases (14%) and other reasons in 19 cases (23 %).

The percentage of prematurely ended phase III trials in relation to the total number of phase III clinical trial applications during the years 2002-2006 is shown in Table 2.

Oncology was the largest treatment indication among prematurely ended phase III trials (24%; 20/84). Mortality was included as a primary endpoint in 29 trials (35%).

A total of 57 prematurely ended phase III clinical trials had a DMC. The distribution of the existence of a DMC in relation to different factors is shown in Table 3. In a total of 30 trials the DMC recommended its termination. This decision was based on safety

alone, lack of efficacy alone or on both safety and lack of efficacy in all except one trial. For the distribution of reasons for termination (excluding reasons for termination other than safety and/or efficacy) in relation to the existence of a DMC, and in relation to the data source upon which the decision was based, see Table 4. No trial was ended prematurely due to unexpected positive benefit.

Compared with control trials, factors that appeared to be associated with a premature ending included treatment indication, mortality as an endpoint and planned study duration. Obesity as an indication was more common (10/48 vs 2/144; p<0.0001) whereas unusual indications (with fewer than five trials in our material) were less common (27/144 vs 2/48; p=0.02) among prematurely ended clinical trials. Mortality as an endpoint was twice as common (33%; 16/48 vs 17%; 24/144; p=0.02) and the planned study duration was slightly longer among prematurely ended clinical trials (median 30 months; 25^{th} to 75^{th} percentile 24-42 months vs 24 months; 25^{th} to 75^{th} percentile 14-46 months; p=0.03). For other factors no significant differences could be observed including design of the study, existence of a DMC or active substance with or without a marketing authorisation at the start of the study, although the existence of a DMC was numerically higher among prematurely ended trials (71%; 34/48 vs 56%; 80/144; p=0.06). Situations when a DMC was used were similar among prematurely ended trials and control trials with no significant differences observed. Despite the longer planned study duration, the real study duration was shorter among prematurely ended clinical trials, see Figure 3. Control trials that were still ongoing at the end of ourstudy were censored.

A total of 36 trials (42%) concerned substances that were approved as medicinal products at the time of the clinical trial application, and 49 trials (58%) concerned substances that had not yet been approved at the time of the clinical trial application. A total of 6 trials with already approved substances (17%; 6/36) were prematurely terminated following the withdrawal of the product from the market due to safety issues (n=3 for rimonabant, n=2 for rofecoxib, and n=1 for melagatran/ximelagatran). In five trials with already approved substances (14%; 5/36) within unapproved treatment indications, a decision to discontinue pursuing the indication appeared to have been taken as a result of the trial; prevention of sporadic colorectal polyps in patients without a history of familial adenomatous polyposis (n=1 for celecoxib), prevention of major coronary events in postmenopausal women (n=1 for raloxifen), prevention of diabetic retinopathy (n=1 for sandostatin), treatment of climacteric symptoms in patients with a history of breast cancer (n=1 for tibolone), and treatment of non-haemophiliac patients with bleeding refractory to standard treatment following major trauma (n=1 for recombinant factor VIIa). Out of 49 trials with substances that had not yet been approved at the time of the clinical trial application there were two trials (4%; 2/49) with substances that later became approved and were withdrawn from the market due to safety issues (n=1 rimonabant, n=1 rofecoxib). The phase III trials were prematurely ended after the market withdrawals. A further 16 trials (33%; 16/49) concerned 10 substances that were discontinued prior to the application for a marketing authorisation.

Discussion

During a 7-year-period a total of 85 prematurely ended phase III clinical trials were identified with a surprisingly large number in 2008 (n=35; 41% vs 14% expected). The peak for premature endings took place about two years after start of the trial and the largest proportion of prematurely ended phase III trials concerned trials that started in 2006 (14% vs 5-10% in the years 2002-2005). In order to study if an increased number of premature endings may have been related to an increased use of DMCs recommended by the guidelines on the use of DMCs in clinical trials by EMEA and the FDA that came into effect in 2006, the use of DMCs among prematurely ended and control trials before (1 May 2004 until 31 December 2005) and since 1 January 2006 was compared. No increased use of DMCs was observed. The withdrawal of rimonabant and other cannabinoid antagonists for obesity importantly contributed to the number of premature endings in 2008, accounting for a total of 10 prematurely ended trials that year.

The use of a DMC seemed to adhere with recommendations in the DMC guidelines as all trials investigating mortality as a primary endpoint had a DMC (29 prematurely ended trials and 24 control trials) as did all trials investigating cannabinoid antagonists due to the psychiatric adverse event profile of these agents (10 prematurely ended trials and two control trials), and all except one oncology trial (all 20 prematurely ended trials and 24/25 control trials). Overall, the use of a DMC was quite high, encompassing as much as 71% of prematurely ended phase III trials and

56% of control trials with an application date from 1 May 2004 and onward. As expected, a DMC was less common in trials that had no control group.

In trials that had a DMC, the DMC was more likely to recommend termination of the trial for combined safety and lack of efficacy issues compared with safety-alone or lack of efficacy-alone related issues. Among trials that had a DMC that were stopped due to lack of efficacy-only issues the recommendation to stop the trial was more likely to be made by the DMC if data arose from the trial itself than if data arose from outside of the trial. The same tendency was also noted for safety issues. A possible explanation for this finding may be that DMCs are not always completely informed of results from other ongoing or recently completed trials with the tested product. Another possible explanation is that DMCs may be more focused on information from within the trial compared with information from outside the trial. Preferably, DMCs should be continuously informed of all results of relevance for their ongoing assessment. The one trial that was stopped for combined safety and efficacy issues without the recommendation of a DMC deserves some attention. The sponsor had analysed the data and made their decision before the DMC was informed; a procedure which puts the role of the DMC somewhat in doubt. In all instances, the sponsor adhered to the recommendations of the DMC.

Out of 29 trials that were recommended to be stopped by the DMC, 15 were stopped as a consequence of having fulfilled pre-specified criteria for futility at interim analysis and 14 trials were stopped without having fulfilled such criteria. No interim analysis was planned in 7 of those 14 trials. In the remaining 7 trials an interim analysis was planned. However, in two of the 7 cases the evaluation was triggered by results from other trials, and hence did not take place at the planned time of the interim analysis.

In all 7 cases the DMC recommended to stop the trial even though formal statistical criteria were not met.

It was difficult to find out what impact, if any, the prematurely terminated trial had on the development of the tested substance. However, at least 30% of trials with active substances that did not have a marketing authorisation at the start of the trial were discontinued from further development. Even 19% of trials with marketed substances were prematurely ended due to withdrawal of the substance from the market for safety reasons. Among trials with approved substances, ten (31%) were stopped for safety reasons without a subsequent withdrawal of the marketed product. Marketing authorisation status did not appear to be associated with the risk of a premature ending as the proportion of trials with active substances with and without a marketing authorisation was similar among prematurely ended and control trials.

Surprisingly, we did not identify any trials that were ended prematurely due to favourable results, which may be in contrast with findings from previous publications [5, 6]. However, it is our genuine experience that stopping a trial for benefit is extremely rare. In the publication by Montori et al, only 143 out of 58357 published trials (0.2% or 2 per 1000) were stopped for benefit. The limited number of phase III trials investigated in this study may therefore explain why no such trial was identified, taking also into account biases associated with the publication of clinical trials. It is also possible that agreed protocol changes are made in case of trials with unexpected benefit in such a way that a premature ending according to our definition can be avoided. This possibility is supported by another publication of early reporting of positive trial results by Korn et al., where follow-up results were later published for 22/27 trials (81%) [7]. We did identify two of the 25 trials reported to have been

stopped early for benefit by Trotta et al. In both cases beneficial interim results had been published. The trials, which were both open-label, were continued in accordance with the protocol. They did, therefore, not fulfil our definition of a premature ending. None of the trials reported by Korn et al. had been carried out in Sweden. It may be noted that according to the new EU guidance document related to the application of clinical trials with medicinal products for human use that was published in the spring of 2010, only premature endings related to safety concerns have to be reported.

Our study has a number of limitations. Firstly, the study was carried out only in Sweden during a limited time period, and results may not be representative for other countries or other periods of time. Secondly, the study has an exploratory character and no corrections for multiple comparisons have been made in the analyses. Some of the findings in the study may hence have arisen purely by chance. Finally, we were only able to compare prematurely ended trials with control trials for trials that had an application date of 1 May 2004 or later. For this reason our study had limited power to study factors that might be related to the risk of a premature ending. The size of the control group in our study (three controls per case) was selected bearing in mind that the incremental increase in statistical power decreases for each added control per case. Almost no further gain in power is achieved with ≥ 4 controls per case. In relation to the achieved increase in power three control trials for each prematurely ended trial seemed to adequately balance the workload.

Conclusion

Five to 14% of phase III clinical trials that had been submitted to the Medical Products Agency during each of the years 2002 to 2006 were prematurely ended. Most trials were ended due to safety and/or efficacy concerns. No trial was ended due to unexpected favourable results. A DMC was used in two-thirds of prematurely ended trials and over half of control trials that were not prematurely ended with no statistically significant difference between the groups. The use of a DMC was more common among trials investigating mortality as primary endpoint and oncology trials. The DMC was more likely to recommend terminating the trial for combined safety and efficacy related issues compared with safety-alone or efficacy-alone related issues. Combined safety and efficacy related issues, in contrast to safety-alone or efficacy-alone related issues, were mainly based on information from the trial itself. Compared with phase III trials that were not prematurely ended, factors that were overrepresented among prematurely ended trials included mortality as endpoint, obesity as indication and planned longer study duration. Unusual indications (with fewer than five trials in our material) were in contrast underrepresented among prematurely ended trials. Despite anticipated longer study durations for prematurely ended trials, actual study durations were shorter. Around 30% of prematurely ended trials with active substances that did not have a marketing authorisation at the time of the clinical trial application resulted in the discontinuation of further development of the substance.

Funding acknowledgement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

References

1 ICH E8 Note for guidance on general considerations for clinical trials (1998). In: ed. EMEA/CPMP/ICH/291/95, pp1-14.

2 ICH E6 (R1) Note for guidance on good clinical practice (2002). In: ed. EMEA/CPMP/ICH/135/95, pp1-58.

3 Guideline on data monitoring committees (2005). In: ed. EMEA/CHMP/EWP/5872/03, pp1-8.

4 Guidance for clinical trial sponsors. Establishment and operation of clinical trial data monitoring committees (2006). In: ed. Center for Biologics Evaluation and Research, FDA, pp1-31.

5 Trotta F, Apolone G, Garattini S, Tafuri G (2008). Stopping a trial early in oncology: for patients or for industry? Ann Oncol 19 (7): 1347-1353.

6 Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, Briel M, Lacchetti C, Leung TW, Darling E, Bryant DM, Bucher HC, Schunemann HJ, Meade MO, Cook DJ, Erwin PJ, Sood A, Sood R, Lo B, Thompson CA, Zhou Q, Mills E, Guyatt GH (2005). Randomized trials stopped early for benefit: a systematic review. JAMA 294 (17): 2203-2209.

7 Korn EL, Freidlin B, Mooney M (2009). Stopping or reporting early for positive results in randomized clinical trials: the National Cancer Institute Cooperative Group experience from 1990 to 2005. J Clin Oncol 27 (10): 1712-1721.

Table 1. Trial duration until the premature ending in relation to the year of the premature ending

Year of the premature ending	Duration of trial (years)					
	0-1	1-2	3-4	4-5	5-6	6-7
2002	3	2	0	0	0	0
2003	3	5	0	0	0	0
2004	4	5	1	0	1	1
2005	3	2	3	0	0	1
2006	2	2	2	0	0	0
2007	1	5	2	0	1	1
2008	5	17	10	2	0	0
Total	21	38	18	2	2	3

Table 2. Percentage of prematurely ended phase III trials in relation to the total number of phase III trial applications

	Total no. of applications for phase III trials	No. of prematurely ended phase III trials	Percentage of prematurely ended phase III trials
2002	157	15	10
2003	138	7	5
2004	170	8	5
2005	152	11	7
2006	155	23	14
Total	772	64	8

Table 3. The existence of a Data Monitoring Committee (DMC) in prematurely ended phase III clinical trials in relation to different factors

		Total no of trials	No. of trials with DMC	Percent of trials with DMC	P value[1]
Total	All	84	57	68	
Endpoints	Primary endpoint includes mortality	29	29	100	**0.0001**
Marketing authorisation	Active substance has marketing authorisation at start of trial	32	21	66	0.83
Design of study	Blinded study treatment	56	41	73	0.57
	Placebo-controlled study	47	37	79	0.23
	Study with active control	16	9	56	0.40
	Study with control group with another dose or regime of the study treatment	6	2	33	0.18
	Study with control group with background, standard or no treatment	12	9	75	0.75
	Study has no control group	7	1	14	**0.008**
Treatment indication	Oncology	20	20	100	**0.0015**
	Obesity	10	10	100	0.06
	Autoimmune disorders	7	3	43	0.22
	Cardiovascular disorders	7	6	86	0.43
	Psychiatric disorders	5	1	20	**0.05**
	Central Nervous System disorders	5	2	40	0.33
	Diabetes mellitus	5	2	40	0.33
	Hormonal disorders	5	2	40	0.33
	Others (hypercholesterolemia, respiratory disorders, thrombotic disorders, organ transplantation, sepsis, liver cirrhosis, chronic renal insufficiency, osteoarthritic pain)	20	11	55	0.30

[1] Compared with all other trials

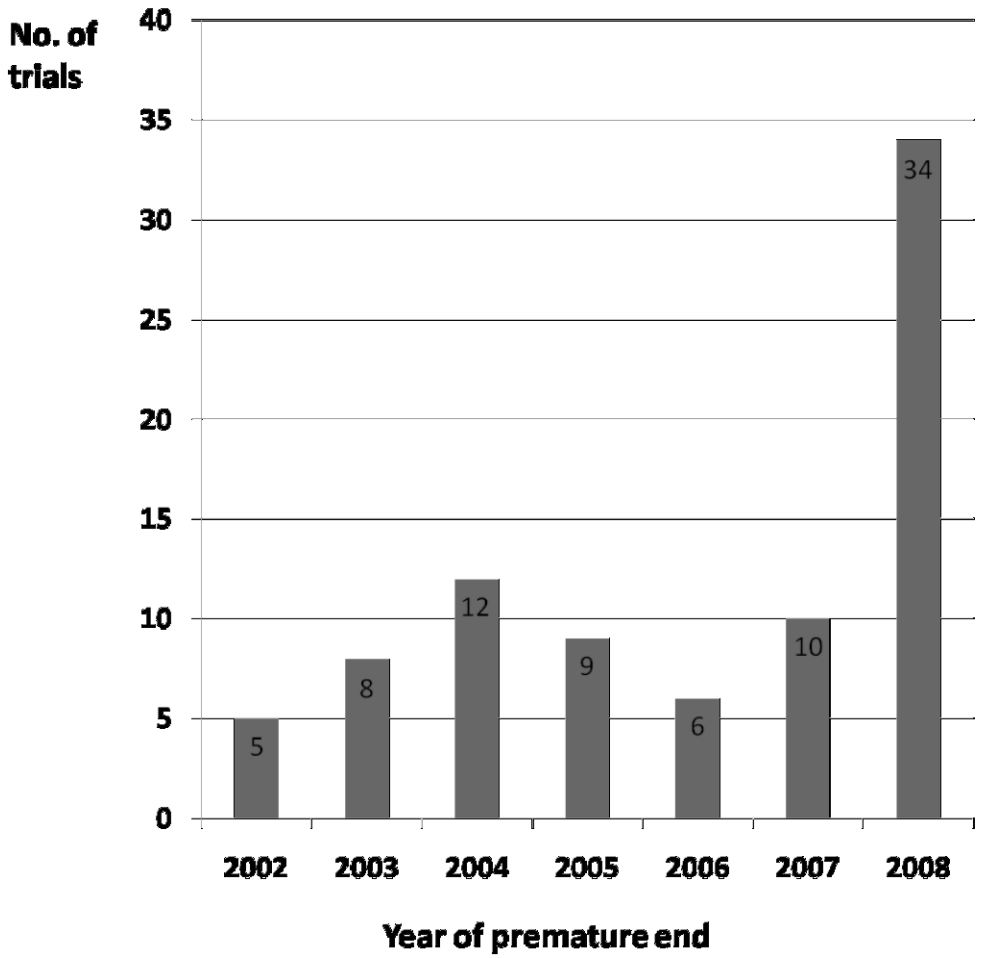
Table 4. Reasons for the premature termination in relation to the existence of a Data Monitoring Committee (DMC), the data source upon which the decision was based, and the DMC recommendation

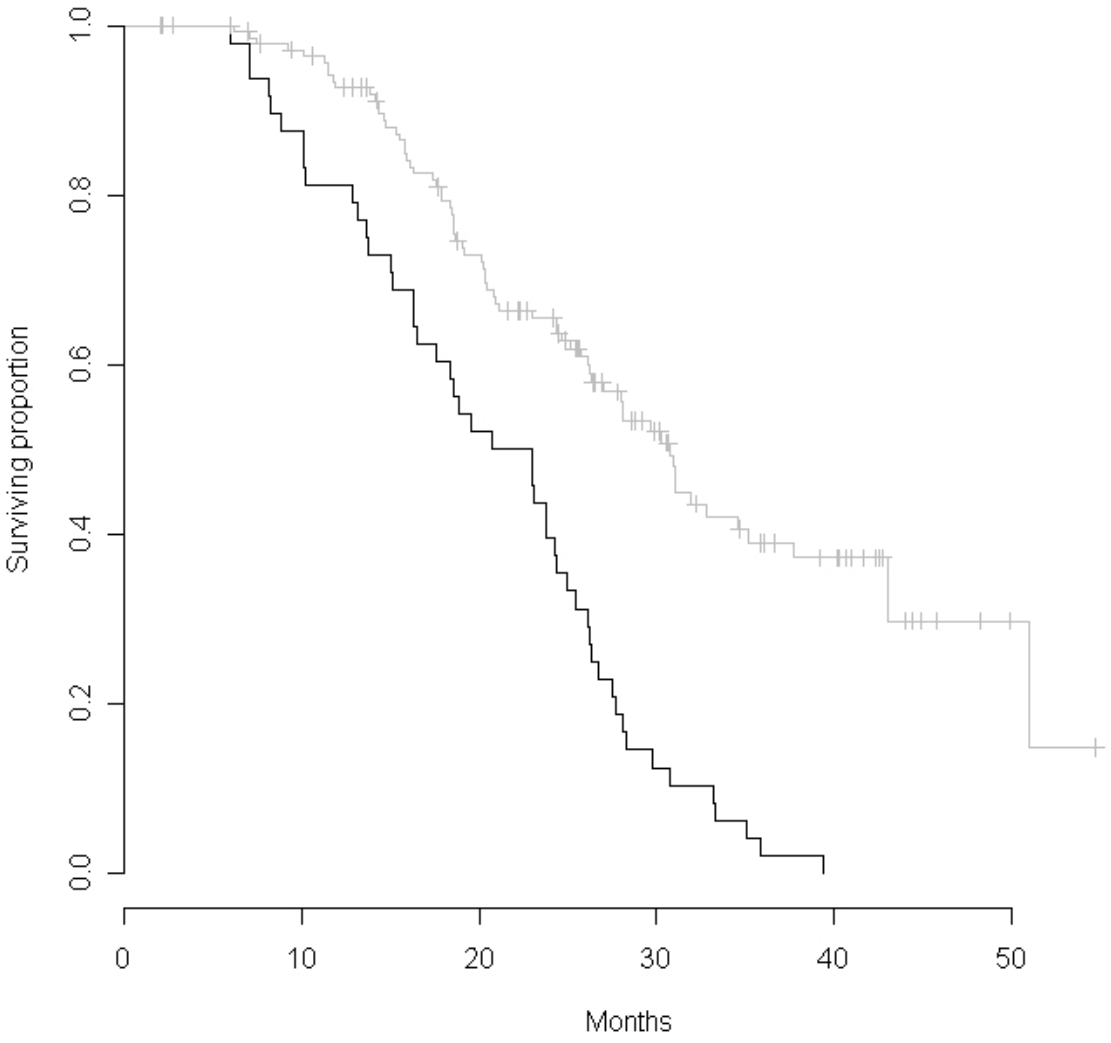
Reasons for stopping the trial	Data on which the decision was made	Total no. of trials with DMC (n=49)	DMC recommended to stop the trial (n=29)	Percent of trials recommended to be stopped by DMC
Safety	**All sources**	**20**	**5**	**25**
	Only from trial itself	3 (15%)	2	67
	Only from outside the trial	8 (40%)	1	12
	From both sources	9 (45%)	2	22
Efficacy	**All sources**	**7**	**3**	**43**
	Only from trial itself	3 (43%)	3	100
	Only from outside the trial	4 (57%)	0	0
	From both sources	0 (0%)	NA	NA
Safety and efficacy	**All sources**	**22**	**21**	**95**
	Only from trial itself	16 (73%)	16	100
	Only from outside the trial	1 (5%)	1	100
	From both sources	5 (23%)	4	80

Figure legends:

Figure 1: Distribution of prematurely ended phase III clinical trials by year of premature end

Figure 2: Kaplan-Meyer survival curves for prematurely ended and control phase III clinical trials matched by application year. Control trials were censored if they were still ongoing after 31 December 2008. Each censored control trial is indicated with a short vertical line.


No. of trials
40
35
30
25
20
15
10
5
0
5
8
12
9
6
10
34
2002
2003
2004
2005
2006
2007
2008
Year of premature end


Surviving proportion
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
Months