Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare Pharmaceuticals Inc.	
Study Number:	11800	NCT00306137
Study Phase:	IIIa	
Official Study Title:	A multi-center, randomized, double-blind, placebo-controlled, parallel design, 2-arm study to investigate the effect of aprotinin on transfusion requirements in patients undergoing surgical procedures for lung cancer or esophageal cancer.	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	Aprotinin (Trasylol, BAY A0128)	
Name of Active Ingredient:	Aprotinin	
Dose and Mode of Administration:	A 1 mL intravenous (IV) test dose of aprotinin (1.4 mg) to assess the potential for allergic reactions to the product and a loading dose of 2 million KIU (200 mL) administered IV followed by 0.5 million KIU (50 mL) per hour constant infusion until the end of surgery.	
Reference Therapy/Placebo		
Reference Therapy:	Placebo (normal saline; 200 mL vials identical to those used for aprotinin)	
Dose and Mode of Administration:	Administration of placebo was identical to administration of aprotinin (i.e., 200 mL loading dose followed by 50 mL per hour constant infusion until the end of surgery). All subjects received a 1 mL test dose of study drug (placebo) to assess the potential for allergic reactions to the product.	
Duration of Treatment:	Following the loading dose, a continuous infusion of aprotinin/placebo was administered until the end of surgery.	
Studied period:	Date of first subjects' first visit:	20 DEC 2005
	Date of last subjects' last visit:	16 MAR 2007
Premature Study Suspension /Termination:	The study was prematurely terminated on 25 JAN 2007. At that time, revised labeling (approved by the US FDA on 15 Dec 2006 and under evaluation by other Regulatory Authorities) included a recommendation that, in order to manage possible anaphylactic reactions, Trasylol should be administered only in surgical settings where CPB can be rapidly initiated. Since the use of CPB is not practical in non-cardiac surgical settings, on 25 Jan 2007, the Sponsor made the decision to terminate the trial. The Sponsor's decision to discontinue this trial (and other non-CABG trials) was not made based on any safety findings in these studies.	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 18 JAN 2006) specified the following substantial changes: • To permit another route of administration, besides infusion, through a central venous line. When possible, aprotinin was to be administered via a central line and in the supine position. Administration via a peripheral vein could be used, even though expected to predispose to local thrombophlebitis. In	

	either case, the IV line was allowed to be used only for the administration of study medication. A peripheral venous line was used in another study (11694), with no apparent safety concern. • To specify an exclusion criterion through identifying methods of contraception considered reliable. • To remove two US trade names of antifibrinolytic agents and anticoagulants from an exclusion criterion. • To define more clearly the subject population to be enrolled in Stratum I. Amendment no. 2 (dated 18 JAN 2006) introduced changes limited to Germany prior to approval being granted by the German regulatory authority to conduct this study. The protocol was amended for the following reason: • To emphasize that subjects with known drug hypersensitivity, allergic diathesis and/or receiving aprotinin more than 6 months ago should be treated only under careful observation; further to require administration of histamine 1 and 2 (H1 and H2) antagonists in those subjects. Amendment no. 3 (dated 09 JUN 2006) introduced changes limited to France prior to approval being granted by the French regulatory authority to conduct this study. The protocol was amended for the following clarifications: • To clarify that the follow-up (i.e., telephone follow-up or review of subject records at 3 months post-surgery and at 3 months intervals until 2 years post-surgery) was to be performed by the investigator or his/her designee, and that no other information besides survival was to be sought or recorded. • To clarify that the duration of time between the administration of the loading dose and the first incision was to be according to each surgeon's practice. • To clarify the manner in which the surgeon's evaluation of intra-operative blood loss and the assessment of the degree of bleeding was to be performed. • To clarify that the pre-donation information refers to pre-operative blood donation. • To clarify what was to be evaluated at the brief physical examination that was to be performed at the 6-week follow-up visit. Amendment no. 4 (dated 11 JUL 2006) introduced additional changes limited to Germany prior to approval being granted by the German regulatory authority to conduct this study. The protocol was amended for the following reason: • To modify an exclusion criterion ensuring highly effective contraception. Amendment no. 5 (dated 15 AUG 2006) was approved for all countries. The protocol was amended for the following main reasons: • To perform all protocol-specified electrocardiograms (ECGs) using centrally-provided equipment and read at a central ECG center, to ensure maximum consistency of results. • To add a data monitoring committee (DMC) that ensures continuous monitoring of safety in the 3 clinical studies (11799,

	11800, and 12002) designed to evaluate aprotinin. • To cancel all forced expiratory volume in one second (FEV_1) assessments in this study due to difficulty of performing this procedure in subjects with lung cancer and esophageal cancer. • To change health economics and outcomes variables, including the collection of data regarding pre-operative blood donation. • To clarify the analysis of health-related quality of life (HRQoL) based on the functional assessment of cancer therapy - lung cancer (FACT-L) and functional assessment of cancer therapy - esophageal cancer (FACT-E).
Study Centre(s):	This study was conducted at 31 centers in 8 countries (1 in Austria, 1 in Australia, 3 in Belgium, 5 in Canada, 2 in Denmark, 4 in Germany, 3 in Spain, and 12 in the US). No subjects were enrolled in France and the UK prior to early termination of the study.
Methodology:	Subjects meeting all screening criteria were randomized to receive an infusion of aprotinin or matching placebo. The subjects were to be stratified at entry by type of surgery (complete primary pneumonectomy, completion pneumonectomy for lung cancer, or undergoing esophagectomy (by transthoracic or transhiatal approach) for esophageal cancer) and the intent was to have approximately equal numbers of lung and esophageal cancer subjects. The maximum total dose of aprotinin that could be administered in this study was 7 million KIU, regardless of the duration of surgery. Visits on Day 1 (day of surgery), on Day 2 (the day after the start of surgery), on Day 3, and at discharge or Day 7 were done to collect relevant study observations and laboratory data. At a follow-up visit 6 ± 2 weeks post-surgery, relevant study observations and laboratory data were collected, and questionnaires regarding health and economic outcomes were filled out. A phone call every 3 months during the 2-year follow-up of subjects was made to evaluate overall survival. The expected duration of the study was approximately 36 months from the first subject being screened, including an additional 2-year long-term follow-up. Duration of study enrollment was increased by 8 months due to slower than expected enrollment.
Indication/ Main Inclusion Criteria:	Indication: Surgical procedures for lung cancer or esophageal cancer Main Inclusion Criteria: Adult subjects, males or non-pregnant females, requiring surgical procedures for lung cancer or esophageal cancer.
Study Objectives:	<u>Overall:</u> The objective of this study was to evaluate the safety and efficacy of aprotinin as compared to placebo, in reducing the need for blood transfusion in adult subjects undergoing surgical procedures for lung cancer or esophageal cancer. <u>Primary:</u> Not applicable <u>Secondary:</u> Not applicable

Evaluation Criteria:	<u>Efficacy (Primary):</u> The primary efficacy variable was the percentage of subjects requiring a blood transfusion any time in the intra- or post-operative period (up to the 6 ± 2 week follow-up visit). <u>Efficacy (Secondary):</u> Secondary efficacy variables included: • The number of units of blood or packed red cells transfused. • The number of units of blood or packed red cells transfused per subject requiring transfusion. • The intra-operative blood loss determined as follows: a) By surgeon's qualitative estimate (categorized as minimal blood loss, average blood loss, substantial blood loss). b) By surgeon's quantitative estimate (summing weight of the blood in gauze, swabs and other materials, and the suction drainage). Both evaluations were performed based on the surgeon's expertise and experience with similar procedures (per Amendment 3). • The drainage volume (in mL) from the operative site in the first 8 hours post-operatively, and total drainage until removal of drains. • Transfusion of platelets, colloids, plasma and number of subjects requiring these products. • The change from pre-operative hemoglobin (Hb) concentration to post-operative Hb concentration (obtained in the morning of Day 3 or, if transfused earlier, prior to transfusion). • Surgeon's qualitative assessment of the degree to which bleeding obscured his/her view of the surgical field, based on the surgeon's expertise and relative to past, similar procedures (categorized as substantially less bleeding, slightly less bleeding, the usual amount of bleeding, slightly more bleeding, substantially more bleeding) per Amendment 3. • Changes in blood markers related to inflammation and blood coagulation. • Time of discontinuing mechanical ventilation. • Changes in FEV_1. • Changes in the subject's health-related quality of life (HRQoL) measured using the FACT-E or FACT-L questionnaire. <u>Safety:</u> Safety assessment was based on reported adverse events, physical examination findings, clinical laboratory test results, vital sign measurements, ECG findings, and on incidence of clinical deep vein thrombosis (DVT) and major pulmonary events (defined as pneumonia, adult respiratory distress syndrome [ARDS], and pulmonary embolism).
Statistical Methods:	<u>Efficacy (Primary):</u> Only descriptive statistics were used because the study was prematurely terminated. <u>Efficacy (Secondary):</u> Only descriptive statistics were used because the study was prematurely terminated.

	Safety: Descriptive statistics were used to present safety data.
Number of Subjects:	A total of 592 subjects were planned. However, the study was prematurely terminated by the Sponsor and only 104 subjects were randomized; 101 were valid for safety analysis; 100 were valid for intent-to-treat (ITT) analysis.

Study Results

Results Summary — Subject Disposition and Baseline

In subjects valid for safety analysis, 70% of the subjects were male and 30% were female. Ninety-six percent of the subjects valid for safety were White. Mean age was 63.7 years (range: 42 - 83 years). The subjects were, on average, slightly overweight, as assessed by their body mass index (BMI). Mean BMI was 25.9 kg/m^2 (range: 17.8 - 37.7 kg/m^2). Overall, the treatment groups were balanced with respect to these demographic variables.
Out of 115 subjects enrolled into the study, 104 were randomized: 51 subjects were randomized to receive placebo and 53 to receive aprotinin. Out of 104 randomized subjects, 43 (84%) subjects in the placebo group and 46 (86%) subjects in the aprotinin group completed the study. In the placebo group, 8 (16%) subjects and in the aprotinin group, 7 (13%) subjects were prematurely discontinued.

Results Summary — Efficacy

Overall, 45% (22/49) of placebo-treated subjects and 37% (19/51) of aprotinin-treated subjects required a blood transfusion up to the 6 ± 2 week follow-up visit.

Results Summary — Safety

Adverse events through the end of the study were reported by 94% (47 of 50) of placebo treated subjects and 100% (51 of 51) of aprotinin-treated subjects. The incidence of drug-related adverse events was the same for both placebo and aprotinin treatment groups (8%; 4 of 50, and 4 of 51, respectively). Serious adverse events were reported in 48% (24 of 50) of placebo-treated subjects and 35% (18 of 51) of aprotinin-treated subjects. Five subjects in the placebo group died (of end-stage metastatic esophageal cancer; pneumonia and multi organ failure; septic shock; respiratory failure; and ARDS). Five subjects in the aprotinin group died (sepsis, small bowel perforation, and cardiogenic shock; fulminating abscessing pneumonitis with secondary vasculitis; a surgical tear in the left atrium; congestive heart failure; and right cardiac dysfunction).

One aprotinin subject had an adverse event of atrial rupture that resulted in discontinuation of study participation; this event resulted in death. Adverse events of special interest included the following:

- Drug hypersensitivity was not reported in aprotinin-treated subjects.
- Myocardial ischemia and an increase in troponin (during episodes of hypertension) were reported in 1 aprotinin-treated subject. Blood creatine phosphokinase increased and blood creatine phosphokinase MB increased, both assessed by the investigator as non-serious, were reported in 1 placebo-treated subject.
- Hemiparesis was reported in 1 placebo-treated subject. No cerebrovascular accidents were reported in any subject.
- There were no reports of venous thromboembolic events.
- Renal failure was reported in 1 aprotinin-treated subject assessed by the investigator as non-serious; this subject died. Renal failure acute was reported in 2 placebo-treated subjects; both assessed by the investigators as non-serious. One placebo-treated subject died of ARDS. Renal impairment was reported in 2 placebo-treated subjects, both assessed by the investigators as non-serious. Blood creatinine increased, assessed by the investigator as non-serious, was reported in 1 aprotinin-treated subject. Oliguria, assessed by the investigator as non-serious, was reported in 1 placebo-treated subject.

There were no clinically important differences between the aprotinin and placebo treatment groups based on the evaluation of laboratory or vital signs parameters and ECG findings.

Conclusion(s)
In this study, treatment with aprotinin in adult subjects undergoing surgical procedures for lung cancer or esophageal cancer may reduce the percentage of subjects who require a blood transfusion compared to placebo. The adverse event profile was similar to the safety profile in coronary artery bypass grafting surgery studies as presented in the package insert/product monograph. The small number of subjects evaluated in this prematurely terminated study was not sufficient to conclusively demonstrate the efficacy and safety of aprotinin in this subject population.

Publication(s):	None		
Date Created or Date Last Updated:	04 MAR 2012	Date of Clinical Study Report:	09 AUG 2007

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D-51368 Leverkusen, Germany
Sponsor in Germany (if applicable)	
Legal Entity Name	Bayer Healthcare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Mount Hospital	140 Mounts Bay Road	6000	Perth	AUSTRALIA
2	Universitätsklinikum Innsbruck	Univ. Klinik f. Chirurgie Klin. Abtielung f. Allg. Chirurgie Anichstraße 35 Chirurgie Hauptgeb.	6020	Innsbruck	AUSTRIA
3	UZ Antwerpen	Wilrijkstraat 10	2650	EDEGEM	BELGIUM
4	UZ Gent	De Pintelaan 185	9000	GENT	BELGIUM
5	UZ Leuven Gasthuisberg	Dienst Heelkunde	3000	LEUVEN	BELGIUM
6	Hotel Dieu-Grace Hospital	1030 Ouellette Avenue	N9A 1E1	Windsor	CANADA
7	Lakeridge Health-Oshawa	One Hospital Court	L1G 2B9	Oshawa	CANADA
8	London Health Sciences Centre	800 Commissioners Rd. E Suite E2-122	N6A 5W9	London	CANADA
9	Surrey Memorial Hospital	13750 96th Avenue	V3V 1Z2	Surrey	CANADA

10	Toronto General Hospital-University Health Network	200 Elizabeth Street	M5G 2C4	Toronto	CANADA
11	H:S Rigshospitalet	Thoraxkirurgisk Klinik Afsnit 2.15.2 Blegdamsvej 9	DK-2100	Copen hagen	DENMARK
12	Odense Universitetshospital	Odense University Hospital Thoraxkirurgisk - Karkirurgisk Afd Sdr. Boulevard 29	DK-5000	Odense C	DENMARK
13	Asklepios Klinik Harburg	Thoraxchirurgie Eißendorfer Pferdeweg 52	21075	Hamburg	GERMANY
14	Kliniken der Medizinischen Hochschule Hannover	Allgemein-, Viszeral- und Transplantationschirurgie Carl-Neuberg-Str. 1	30625	Hannover	GERMANY
15	Universitätsklinikum Hamburg Eppendorf (UKE)	Klinik und Poliklinik für Allgemein-, Viszeral- und Thoraxchirurgie Martinistr. 52	20251	Hamburg	GERMANY
16	Universitätsklinikum Heidelberg	Chirurgische Universitätsklinik Allgemeine, Viszerale, Unfallchirurgie und Poliklinik Im Neuenheimer Feld 110	69120	Heidelberg	GERMANY
17	Hospital Clínic i Provincial de Barcelona	C/ Villarroel, 170	08036	Barcelona	SPAIN

18	Hospital Clínico de Salamanca	Servicio De Cirugía Torácica Paseo de San Vicente 58-182	37007	Salamanca	SPAIN
19	Hospital Joan XXIII	Servicio de Cirugía Torácica C. del Dr. Mallafré i Guasch, 4	43007	Tarragona	SPAIN
20	Barnes-Jewish Hospital	One Barnes-Jewish Hospital Plaza	63110-1094	St. Louis	UNITED STATES
21	Brigham & Women's Hospital	Thoracic Clinic 75 Francis Street	02115	Boston	UNITED STATES
22	CorVasc, MDs, PC	8433 Harcourt Road Suite 100	46260	Indianapolis	UNITED STATES
23	Duke University Medical Center	Erwin Road	27710	Durham	UNITED STATES
24	Emory University School of Medicine	1364 Clifton Road, NE	30322	Atlanta	UNITED STATES
25	Georgia Health Sciences University	Medical College of Georgia Hospital and Clinics 1120 15th Street	30912-4005	Augusta	UNITED STATES
26	Indiana University Hospital	Cancer Center 535 Barnhill Drive	46202	Indianapolis	UNITED STATES
27	M. D. Anderson Cancer Center - University of Texas	Thoracic & Orthopedic Center 1515 Holcombe Boulevard	77030-4009	Houston	UNITED STATES
28	University Hospitals Case Medical Center	11100 Euclid Avenue	44106-2602	Cleveland	UNITED STATES

29	University of Pittsburgh Medical Center Health System	Shadyside Hospital M-140 5230 Centre Avenue	15213-2592	Pittsburgh	UNITED STATES
30	University of Utah	Division of Cardiothoracic Surgery School of Medicine 3C-127 30 North 1900 East	84132	Salt Lake City	UNITED STATES
31	University of Virginia Health System	Department of Surgery Lee Street	22908	Charlottesville	UNITED STATES