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:	11799	NCT 00327379
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 Elective Spinal Fusion Surgery.	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	BAY A0128/aprotinin/Trasylol®	
Name of Active Ingredient:	Aprotinin	
Dose and Mode of Administration:	All subjects received a 1 mL intravenous (IV) test dose of aprotinin (1.4 mg) to assess the potential for allergic reactions to the product, at least 10 minutes prior to the start of the loading dose infusion. Subjects received 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)	
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 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 or placebo was administered until the end of surgery.	
Studied period:	Date of first subjects' first visit:	27 FEB 2006
	Date of last subjects' last visit:	01 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 19 DEC 2005) specified the following 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, though it could predispose to local thrombophlebitis. In either case, the IV line was allowed to be used only for the administration of study medication. Administration could be done with the subject in the prone position after ensuring that immediate remedial therapy could be given should an allergic reaction occur. A peripheral venous line was used in another study (11694), with no apparent safety concern. • To clarify an exclusion criterion by identifying methods of contraception considered reliable. • To remove two US trade names of antifibrinolytic agents and anticoagulants from an exclusion criterion. Amendment no. 2 (dated 11 Jan 2006) incorporated the following changes limited to Germany: • To emphasize that subjects with known drug hypersensitivity, allergic diathesis and/or receiving aprotinin more than 6 months earlier were to 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 06 JAN 2006) would have introduced changes limited to France. However, the sponsor withdrew its clinical trial application in France. The protocol was amended for the following reasons: • To add 2 exclusion criteria (history of myocardial infarction and history of CABG), as a special safety precaution. Amendment no. 4 (dated 22 AUG 2006) specified the following changes: • To clarify one inclusion criterion, namely, the meaning of a vertebral level. • To specify the procedure to be performed in the event that a subject prematurely terminates from the study. The same procedures were to be performed at the time of premature termination as would have been performed at hospital discharge. • To clarify one secondary efficacy criterion, stating that total drainage until removal of drains was to be total drainage until removal of drains or until hospital discharge (whichever was earlier); further to correct a health economics and outcomes variable, whether subject had phlebitis was corrected to whether subject had deep vein thrombosis (DVT). • To modify health economics and outcomes variables to match the survey information collected, to clarify the collection of cost data, and to include pre-operative blood donation. • To emphasize that all adverse events occurring after obtaining the informed consent had to be recorded; further to clarify that a DVT assessment was to be performed on the day of discharge or at premature termination. • To specify that a chest X-ray was to be performed within 3 months of screening in order to approximate current clinical practice. • To remove the measurement of forced expiratory volume in 1 second (FEV_1) 24 hours (± 30 min) after the end of surgery (and on Day 2, which is the same FEV_1 measurement time), because

	measurement of FEV_1 on the first post-operative day often was not feasible for a variety of reasons (e.g., post-operative pain, prone position, continuing intubation). • To indicate that cost data were to be obtained directly from the hospitals, so that the sites would not need to obtain cost data. • To specify that blood for all protocol-specified laboratory analyses was to be obtained by venipuncture, and that all protocol-specified electrocardiograms (ECGs) were to be performed using centrally-provided equipment and read at a central ECG center. • To add a blood sample to be shipped for storage for possible future determination of aprotinin antibodies at 6 ± 2 weeks after surgery. • To add a Data Monitoring Committee (DMC) in order to ensure continuous monitoring of safety in the 3 clinical studies (11799, 11800, and 12002) designed to evaluate aprotinin. • To base the exclusion criterion regarding renal function on calculated creatinine clearance (rather than creatinine). Further, to increase the frequency of renal function monitoring. Creatinine and BUN were to be measured daily till Day 7 or discharge.
Study Centre(s):	This study was conducted at 14 centers in 3 countries (3 in Canada, 5 in Germany, and 6 in Spain).
Methodology:	Subjects successfully meeting all screening criteria were randomized to receive an infusion of aprotinin or matching placebo. The maximum total dose of aprotinin that could be administered in this study was 6 million KIU, regardless of the duration of surgery. The relevant study evaluations done on Day 1 (day of start of surgery) were vital signs, adverse events, surgery information, assessing blood loss, drainage measure, and transfusion requirements. On Day 2 (the day after the start of surgery), Day 3 (the second day after the start of surgery), and at discharge (or Day 7) similar study evaluations were done except blood loss assessment. In addition, at a follow-up visit 6 ± 2 weeks post-surgery, questionnaires regarding health and economic outcomes were filled out. The expected duration of the study was approximately 14 months, with enrollment of approximately 12 months. Although planned for 14 months, study duration was increased by 6 months due to slower than expected enrollment.
Indication/ Main Inclusion Criteria:	Indication Elective spinal fusion surgery Main Inclusion criteria Adult subjects, males or non-pregnant females, requiring elective spinal fusion surgery
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 elective spinal fusion surgery involving 3 to 7 vertebral levels with instrumentation. <u>Primary:</u> Not applicable

	Secondary: Not applicable
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was the percentage of subjects requiring a blood transfusion any time in the intra- or post-operative period. Efficacy (Secondary): Not applicable Safety: 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 DVT and major pulmonary events (defined as pneumonia and adult respiratory distress syndrome [ARDS] and pulmonary embolism.
Statistical Methods:	Efficacy (Primary): Only descriptive statistics were used because the study was prematurely terminated. Efficacy (Secondary): Not applicable Safety: Descriptive statistics were used to present safety data.
Number of Subjects:	A total of 540 subjects was planned. However, the study was prematurely terminated by the Sponsor and only 54 subjects were randomized; 49 were valid for safety. Subjects valid for safety analysis were 24 (89%) in the placebo group and 25 (93%) in the aprotinin group, respectively. All subjects valid for safety were included in the intent-to-treat (ITT) analyses.

Study Results
Results Summary — Subject Disposition and Baseline
Of the 56 subjects that were enrolled into the study, total number of subjects randomized were 54 (2 were screening failures), 27 each in the placebo and aprotinin group. Twenty-three subjects in each group completed the study and 4 subjects in each group were prematurely discontinued. All subjects were of White race. The number of females were 19 (79%) in the placebo group, and 19 (76%) in the aprotinin group. Mean age at enrollment was 60.7 years (range: 19.0 to 79.0) and mean BMI was 26.1 kg/m^2 (range: 17.8 to 37.0).
Results Summary — Efficacy
Overall, 67% (16/24) of placebo-treated subjects, and 44% (11/25) of aprotinin-treated subjects required blood transfusion.

Results Summary — Safety
Adverse events through the end of the study were reported by 71% (17/24) of placebo-treated subjects and 76% (19/25) of aprotinin-treated subjects. The incidence of drug-related adverse events through the end of the study among aprotinin-treated subjects was 20% (5/25) and among the placebo-treated subjects was 13% (3/24). Serious adverse events were reported in 21% (5/24) of placebo-treated subjects and 40% (10/25) of aprotinin-treated subjects. One placebo-treated subject died of lung carcinoma and 1 aprotinin-treated subject died of myocardial infarction; both events occurred during the follow-up period. One aprotinin-treated subject had an adverse event (drug hypersensitivity) that resulted in premature discontinuation on the study drug. Adverse events of special interest included: • Myocardial infarction was reported in 2 placebo-treated subjects and 2 aprotinin-treated subjects. The event resulted in the death of 1 aprotinin-treated subject during the follow-up period. • Hemiparesis was reported in 1 placebo-treated subject. • There were no reports of venous thromboembolic events. • Increased blood creatinine was reported in 1 aprotinin-treated subject. • There were no reports of renal failure. 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 elective spinal fusion surgery involving 3 to 7 vertebral levels with instrumentation may reduce the percentage of subjects who require a blood transfusion compared to placebo. The adverse event profile was consistent with the safety profile in CABG 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):

Date Created or Date Last Updated:	30 MAR 2012	Date of Clinical Study Report:	06 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	Hotel Dieu-Grace Hospital	1030 Ouellette Avenue	N9A 1E1	Windsor	CANADA
2	Lakeridge Health-Oshawa	One Hospital Court	L1G 2B9	Oshawa	CANADA
3	Montreal Neurological Hospital	3801 University Street	H3A 2B4	Montreal	CANADA
4	Charité Campus Virchow-Klinikum (CVK)	Klinik für Unfall- und Wiederherstellungschirurgie Augustenburger Platz 1	13353	Berlin	GERMANY
5	Park-Klinik Weißensee	Orthopädie Schönstraße 80	13086	Berlin	GERMANY
6	Schön-Kliniken Klinikum Neustadt GmbH & Co. Betriebs-KG	Am Kiebitzberg 10	23730	Neustadt	GERMANY
7	SRH Klinikum-Karlsbad-Langensteinbach gGmbH	Orthopädie-Traumatologie I Wirbelsäulen-Chirurgie Guttmannstr. 1	76307	Karlsbad	GERMANY

8	Universitätsklinikum Münster	Klinik und Poliklinik für Allgemeine Orthopädie Albert-Schweitzer-Str. 33	48149	Münster	GERMANY
9	Ciutat Sanitària i Universitaria de la Vall d'Hebron	Servicio de Traumatología Passeig de la Vall d'Hebrón, 119-129	08035	Barcelona	SPAIN
10	Clínica Universitaria de Navarra	Servicio de Hematología Avda. Pio XII, 36	31008	Pamplona	SPAIN
11	Hospital Clínic i Provincial de Barcelona	Servicio de Traumatología C/ Villarroel, 170	08036	Barcelona	SPAIN
12	Hospital Clínico Universitario de Valencia	Servicio de Traumatología Avda. Blasco Ibañez, 17 46910 Valencia	46010	Valencia	SPAIN
13	Hospital del Mar	Servicio de Traumatología Paseig Marítim, 25-29	08003	Barcelona	SPAIN
14	Hospital Ramón y Cajal	Servicio Cirugía de Columna 2ª plant-Centro Ctra. de Colmenar, Km. 9,1	28034	Madrid	SPAIN