Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
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:	12002	NCT00306150
Study Phase:	IIIa	
Official Study Title:	A multi-center, randomized, double-blind, placebo controlled study to investigate the efficacy and safety of aprotinin on transfusion requirements in subjects with bladder cancer undergoing radical or total cystectomy.	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	Aprotinin (Trasylol, BAYA0128)	
Name of Active Ingredient:	Aprotinin	
Dose and Mode of Administration:	All subjects received 1 mL intravenous (IV) test dose of aprotinin (1.4 mg) to assess the potential for allergic reactions to the product. Subjects randomized to the aprotinin treatment group 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:	All subjects received 1 mL IV test dose of placebo to assess the potential for allergic reactions to the product. 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).	
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:	21 DEC 2005
	Date of last subjects' last visit:	14 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 OCT 2005) was approved prior to subject enrollment. The protocol was amended for the following reasons: • To clarify an exclusion criterion and measurements on Day 7 and day of discharge • To specify the breaking of the code in case of serious adverse events • To extend the list of major pulmonary events, also including pulmonary embolism • To extend the US locations eligible to participate in the study (specific cost data collection no longer required) Amendment no. 2 (dated 19 DEC 2005) was approved prior to subject enrollment. The protocol was amended for the following reasons: • To clarify exclusion criteria with respect to contraception methods and anticoagulant treatment (to substitute warfarin with vitamin K antagonists) • To allow the use of either a central or peripheral venous line for study drug administration, since not all subjects undergoing the protocol-specified surgeries would receive a central line. A peripheral venous line was used in another study, in subjects undergoing hip replacement surgery, with no apparent safety concern Amendment no. 3 (dated 22 FEB 2006) introduced changes limited to France. The protocol was amended for the following reason: • To specify the criteria to stop the subject's treatment in case aprotinin caused allergic reactions, adding warnings/precautions Amendment no. 4 (dated 23 MAR 2006) introduced changes limited to France. The protocol was amended for the following reason: • To add an additional exclusion criterion, namely subjects with known disseminated intravascular coagulation • To specify the transfusion threshold, an efficacy variable, and observations and measurements • To exclude autologous transfusion Amendment no. 5 (dated 18 SEP 2006) was approved after 57 subjects (i.e., all but one) had been enrolled in the study. The protocol was amended for the following reasons: • To add a Data Monitoring Committee (DMC) to ensure continuous monitoring of safety in 3 clinical studies (11799, 11800, and 12002) • To base the exclusion criterion regarding renal function on calculated creatinine clearance rather than creatinine. Serum creatinine and BUN were to be measured daily till Day 7 or till discharge

	• To clarify and specify the health economic and outcomes variables, including collection of cost data for the secondary efficacy variables • To delete forced expiratory volume in 1 second (FEV_1) measurement at 24 hours post-operation, considering the difficulty of the subject to perform it • To clarify the cystectomy definitions and to correct other inconsistencies • To perform all protocol-specified ECGs using centrally-provided equipment and read at a central ECG center, to ensure maximum consistency of results
Study Centre(s):	This study was conducted at 14 centers (2 in Belgium, 5 in Germany, 1 in the Netherlands, 3 in Sweden, and 3 in the United States). No subjects were enrolled in France prior to early termination of the study.
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 7 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 requirement. 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 as was done on Day 1. At a follow-up visit 6 ± 2 weeks post-surgery, questionnaires regarding health and economic outcomes were filled out. In addition, a phone call was made every 3 months during the 2-year follow-up of subjects to evaluate overall survival. The duration of the study was approximately 36 months from the first subject being screened, including a 2-year long-term follow-up. Duration of study enrollment was increased by 6 months due to slower than expected enrollment.
Indication/ Main Inclusion Criteria:	Indication: Radical or total cystectomy for bladder cancer Main Inclusion Criteria: Adult subjects (18 years of age and older), males or non-pregnant females, requiring elective radical or total cystectomy for bladder 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 subsequent blood transfusion in subjects with bladder cancer undergoing radical or total cystectomy. <u>Primary:</u> Not applicable <u>Secondary:</u> 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 (up to the earlier of Day 7 or discharge). 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 deep vein thrombosis (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 284 subjects were planned. However, the study was prematurely terminated by the Sponsor and only 57 subjects were randomized; 56 subjects were valid for safety and efficacy.

Study Results
Results Summary — Subject Disposition and Baseline
There was no difference in the subjects valid for safety and the subjects in the intent-to-treat (ITT) efficacy analyses, thus all demographic data summaries apply to both populations. No subjects made pre-operative autologous blood donation. All subjects valid for safety were White. The subjects were, on average, overweight, as assessed by body mass index (BMI). Their mean age was 55.4 years (range: 42 to 85) and BMI was 27.1 kg/m^2 (range: 18.3 to 26.8). Of the 56 subjects, 17 subjects (30%) were females.
Results Summary — Efficacy
Overall, 43% (13/30) of placebo-treated subjects and 46% (12/26) of aprotinin-treated subjects required blood transfusions during the intra-operative or post-operative period up to the earlier of Day 7 or discharge.

Results Summary — Safety

Adverse events through the end of the study were reported by 93% of placebo subjects and 96% of aprotinin subjects. The incidence of drug-related adverse events through the end of the study was the same for both treatments (23%).

Serious adverse events were reported in 43% of placebo subjects and 23% of aprotinin subjects. Serious adverse events resulting in prolonged hospitalization occurred in 33% of placebo subjects and 23% of aprotinin subjects.

Two subjects receiving placebo died (of multiple organ insufficiency and cardiac arrest) and 3 subjects receiving aprotinin died (of heart circulation failure, cancer progression, and pulmonary embolism 22 days after surgery). All 5 deaths occurred during the follow-up phase, and all events resulting in death were considered non drug-related.

No subject experienced an adverse event that resulted in premature discontinuation of the study drug.

Adverse events of special interest for placebo and aprotinin included:

- No cases of drug hypersensitivity were reported
- One aprotinin-treated subject had myocardial ischemia, which occurred 7 days after surgery
- Cerebrovascular accidents were not reported in any subject
- One aprotinin-treated subject had a DVT and a pulmonary embolism within 7 days after surgery, i.e., 4 days after surgery
- A further 2 aprotinin-treated subjects had an increase in creatinine > 0.5 mg/dL over baseline to a value >2 mg/dL within 7 days after surgery
- Treatment-emergent adverse events related to renal dysfunction and occurring within 7 days of surgery were reported in 2 aprotinin-treated subjects; one subject had "oliguria" (reported as non-serious by the investigator) and another subject had renal failure (increase in creatinine of >0.5 mg/dL over baseline to a value of >2 mg/dL)

There were no clinically important differences between treatment groups for the change from baseline in mean values for vital signs, ECG findings, laboratory parameters at any time-point, other than creatinine.

Conclusion(s)

In this study, it was concluded that treatment with aprotinin in adult subjects undergoing elective radical or total cystectomy for bladder cancer may not 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): None

Date Created or Date Last Updated:	30 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	UZ Gent	Dienst blaas- en nierziekten De Pintelaan 185	9000	GENT	BELGIUM
2	UZ Leuven Gasthuisberg	Dienst Urologie Herestraat 49	3000	LEUVEN	BELGIUM
3	Johannes-Gutenberg-Universität Mainz	Urologische Klinik und Poliklinik Langenbeckstr. 1	55131	Mainz	GERMANY
4	LMU Klinikum der Universität München - Großhadern	Urologische Klinik und Poliklinik Marchioninistr. 15	81377	München	GERMANY
5	Medizinische Fakultät Carl Gustav Carus	Technische Universität Dresden Klinik und Poliklinik für Urologie Fetscherstraße 74	01307	Dresden	GERMANY

Appendix to Clinical Study Synopsis for study 12002

6	Universitätskliniken des Saarlandes	Klinik für Urologie und Kinderurologie Kirrberger Str.	66242	Homburg	GERMANY
7	Universitätsklinikum Regensburg	Klinik und Poliklinik für Urologie Caritas-Krankenhaus St. Josef Landshuter Str. 65	93053	Regensburg	GERMANY
8	Academisch Ziekenhuis Maastricht	Afd. Urologie - P. Debyelaan 25	6229 HX	MAASTRICHT	NETHERLANDS
9	Akademiska Sjukhuset	Urologmottagningen	751 85	Uppsala	SWEDEN
10	Karolinska Universitetssjukhuset i Solna	Urologiska kliniken	171 76	Stockholm	SWEDEN
11	Universitetssjukhuset i Linköping	Urologiska kliniken i Östergötland	581 85	Linköping	SWEDEN
12	Columbus Urology Research, LLC	500 Thomas Lane Suite 3-C	43214-1419	Columbus	UNITED STATES
13	University of Chicago	Urology 5841 South Maryland Avenue	60637	Chicago	UNITED STATES
14	University of Pittsburgh Medical Center Health System	Shadyside Hospital Posner Pain Center Suite M-104 5230 Centre Avenue	15232	Pittsburgh	UNITED STATES