

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM  
UNDER 35 U.S.C. § 156

PATENT NO. : 4,303,651  
ISSUED : December 1, 1981  
INVENTOR(S) : Ulf P. F. Lindahl et al.  
PATENT OWNER : Pharmacia Aktiebolag

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

FIVE YEARS

from the original expiration date of the patent, January 4, 2000, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).



I have caused the seal of the Patent and Trademark Office to be affixed this 31st day of May 1996.

A handwritten signature in cursive script, reading "Bruce A. Lehman".

Bruce A. Lehman  
Assistant Secretary of Commerce and  
Commissioner of Patents and Trademarks

**DEBARMENT CERTIFICATION**

Fragmin for Unstable Angina and non-Q-wave Myocardial Infarction

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

*Edward L. Patt*

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Ed L. Patt  
Manager  
Regulatory Compliance

*5/26/98*

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Date

**MEMORANDUM OF MEETING MINUTES**

**Meeting Date:** December 17, 1997  
**Time:** 1:30-3:30pm  
**Location:** 6B-45 Parklawn Building

**Application:** NDA 20-287

**Type of Meeting:** Pre-Supplement

**Meeting Chair:** Lilia Talarico, M.D., Division Director, HFD-180

**Meeting Recorder:** Karen Oliver, Project Manager, HFD-180

**FDA Attendees, titles, and Office/Division:**

Lilia Talarico, M.D., Division Director, HFD-180  
Nenad Markovic, M.D., Ph.D., Medical Reviewer, HFD-180  
Kurt Sizer, M.D., Medical Reviewer, HFD-180  
Karen Oliver, MSN, Regulatory Health Project Manager, HFD-180  
A.J. Sankoh, Ph.D., Biometrics Acting Team Leader, HFD-720  
M.Rashid, Ph.D. Biometrics Reviewer, HFD-720

**External Constituent Attendees and titles:****Pharmacia & Upjohn**

Susan Mondabaugh, Ph.D., Director, US Regulatory Affairs  
Ilze Antons, MS, Senior Manager, US Regulatory Affairs  
James Vanderlugt, M.D., Director, Clinical Development  
John Schoenfelder, Ph.D, Director, Biostatistics and Data Management, Sweden  
Thomas Pollare, M.D., Vice President Clinical Development, Sweden  
Kathe Brystrom, Senior Regulatory Adviser, Sweden  
Joseph Aquilina, M.D., Clinical Development

**Background:**

On November 6, 1997, Phamacia & Upjohn submitted background material and a request for a pre-supplement meeting to discuss their plans to extend the duration of treatment in unstable coronary artery disease (UCAD) on the basis of the ongoing FRISC II study. Further, the firm notified the Agency that they are currently preparing a supplemental application to NDA 20-287, with an anticipated submission in the 1-2 quarter, 1998, which will provide for a proposed new indication, the treatment of the acute phase of unstable coronary artery disease.

**Meeting Objectives:**

To obtain Agency feedback on the following issues related to the FRISC II Study:

1. The statistical analysis implications associated with both treatment groups receiving the same treatment during the open-label acute phase of the study and the ramifications of the "one-step" randomization procedure.
2. The most "usable" definition of Day 1 for all computations.
3. The procedure for imputing missing values in the intent-to-treat (ITT) analysis.
4. The acceptability of NOT making any adjustments for multiple comparisons, either for multiple objectives or for multiple endpoints within the same objective.

**Discussion Points:**

1. The firm presented background information on the 2 major completed clinical trials, designated FRISC and FRIC, conducted to support Fragmin, given in conjunction with ASA (96% patients received ASA 75 mg daily), for the acute treatment of coronary artery disease (CAD).
  - a. FRISC Study (TRN 91-115) [see overheads 1-4]
    - A multicenter study conducted in Sweden; 1506 patients enrolled (Fragmin 746/Placebo 760).
    - Phase I (days 1-6): The primary objective was to compare Fragmin (120 IU/kg/12h s.c.) with placebo (kg/12h/s.c.) for effects on the incidence of death and/or MI. The secondary objectives were evaluation of cardiac events and rates of revascularization by day 6 (Phase I), by day 34 (Phase I and II) and by 6 months.
    - Phase II (days 6-45): Ischemia exercise tests on day 6 (5-8) and day 45 (40-50); Fragmin 7500 IU/24h s.c vs Placebo/24h/s.c.; and evaluation of cardiac events and rates of revascularization on day 45.
    - Phase III (6 month follow-up): ECG completed.

- The firm concluded that Fragmin was significantly more effective than aspirin alone in the early reduction (up to day 6) of death or MI, with a sustained effect up to day 40.
- b. FRIC Study (TRN 91-128) [see overheads 5-8]
- Large international study (Europe, US and Canada) in unstable CAD patients; primary objectives to evaluate the incidence of cardiac events including death, MI and/or recurrence of angina; secondary objectives to evaluate cardiac events and revascularization in Phase I, Phase II and until 3 months follow-up.
  - Acute Phase I: Open label study of 1482 patients; Fragmin 120 IU/kg/12hr/s.c. vs heparin regimen of 5000 IU by iv bolus followed in less than 2 hours with 1000 IU/hr continuous iv infusion for at least 48 hrs followed by 12500 IU heparin/12hr/s.c. as determined by the physician with reference to APTT. In the acute phase, the firm reported that Fragmin had a comparable effect with heparin on the composite outcome of death, MI and recurrent angina but with an increased number of deaths.
  - Prolonged Phase II (days 6-45): Double-blind study. Fragmin and heparin groups subdivided with half the patients in each group receiving Fragmin 7500 IU s.c. daily and half received a placebo. In the prolonged therapy, the firm reported that Fragmin did not reduce the incidence of cardiac events (death, MI and/or recurrent angina) compared to placebo.
3. The firm presented information on the ongoing FRISC II study (see overheads 9-25).
- A prospective, randomized, multicenter (50-60) study using a parallel group and factorial design comparing Fragmin and placebo in a prolonged phase of 3 months treatment and a comparison of two revascularization policies. All patients will receive Fragmin in the acute phase of treatment (7-10 days).

- Sample size 3100 patients with non-Q-wave MI or unstable angina; study objectives: to compare continued treatment with Fragmin 5000 alternatively 7500 IU or placebo s.c. twice daily for 3 months and 2 policies of coronary interventions during a 6 month period.
- Primary endpoint: reduction in the risk of death or acute non-fatal MI at month 3.
- Secondary endpoint: comparison of a direct invasive approach with early coronary angiography and revascularization (invasive policy) vs a stepwise selective approach with coronary angiography and revascularization only at recurring or incapacitating symptoms or severe ischemia (non-invasive policy) at exercise concerning incidence of death or acute MI at 6 month visit.

**Agency Comments the identified issues and meeting objectives related to the FRISC II Study:**

1. In the proposed one-step randomization procedure: (1) the patients receive Fragmin 120 IU/kg/12h or heparin for <72 hours upon admission; (2) prior to the acute phase of treatment (days 5-7 in which all patients receive Fragmin 120 IU/kg/12h), all patients are stratified into one of two groups: contraindications to direct invasive procedure or no contraindications to an early invasive procedure; (3) after stratification patients are randomized to an invasive/Fragmin/placebo vs non-invasive/Fragmin/placebo regimen in the chronic phase of treatment.
  - The long-term, prolonged (chronic) treatment efficacy benefit of Fragmin vs placebo is dependent on the short-term, acute study, i.e., failure in the acute phase cannot lead to success in the chronic phase.
  - Since survival time is time dependent, the proportional hazards of events are unequal in the acute and prolonged (chronic) study. Consider the Cochran Mantel-Haenszel Statistic.
  - Begin the analysis of the primary comparison of the prolonged benefit of the Fragmin vs placebo after the study population has completed the acute phase of therapy.
  - Analyze the study in its entirety (acute and chronic phase) as the results in the chronic phase will be dependent on the acute phase. Analysis of the various subgroups will be necessary.

- Consider how to differentiate survival due to Fragmin only vs that due to procedure/Fragmin.
2. The most "usable" definition of Day 1 for all computations is "hospital admission" day.
  3. Regarding imputation of missing values:
    - Define the "intent-to-treat" population. Provide information on how missing data and/or protocol violators including "study drop outs" will be handled.
    - Perform "worse case scenario" analysis of all of the missing data for the comparison of Fragmin vs placebo.
    - Define the "evaluable" population. Consider such factors as % of doses received, medication compliance with regimen, withdrawal due to adverse events, acceptability of treatment by the study population.
  4. Because the multiplicity of endpoints is a result of multiple indication, and since to obtain approval all indication, significant benefit must be demonstrated in each case, there is no need for multiple endpoint adjustments. Consider providing efficacy and safety data at 1,2, 4, and 5 month time points.
  5. Additional Agency comments and recommendations:
    - Since the ongoing study is still blinded, consider changing the primary endpoint of the study to a composite endpoint of death and MI, with a composite secondary endpoint of death, MI, or revascularization (angioplasty or CABG). Any changes in the study endpoint(s) should be submitted to the application as a protocol amendment.
    - The acceptance of a single study submission, FRISC II, for the extended duration of treatment in unstable coronary artery disease, is result dependent. The Agency recommends review of the draft guidance for a single study supportive of a new indication.

- Consider providing an analysis of subgroups, invasive vs selective policy.
- Since study conducted in Europe, consider providing an evaluation and comparison of the practice of medicine (especially in terms of invasive vs noninvasive practices) in the US vs Europe and the applicability of European study results to the US patient population.
- Consider providing a center evaluation by treatment interaction effect.
- Consider providing additional patient population data including demographics, associated medications, and concomitant diseases/medical conditions.
- Please provide CRF and CRTs electronically and statistical data on SAS (6.11) data sets on 3 ½ floppy diskettes. Other information to be submitted in electronic format should be negotiated with the division prior to submission of the application.

Minutes Preparer: ISI [REDACTED] 22/11/98  
Karen Oliver  
Regulatory Health Project Manager

Chair Concurrence: ISI [REDACTED] 2-11-98  
Lilia Talarico, M.D.  
Division Director, HFD-180

Attachments/Handouts: Overheads APPEARS THIS WAY ON ORIGINAL [REDACTED]

cc: Original NDA 20-287  
HFD-180/Div. Files  
HFD-180/Meeting Minutes files  
HFD-180/K.Oliver

HFD-180 and HFD-720/reviewers & attendees. Please include the overheads with the minutes to ALL reviewers and attendees.

Drafted by: KO/February 2, 1998

Initialed by: A.J. Sankoh 02/09/98

Initialed by: L.Talarico 02/10/98

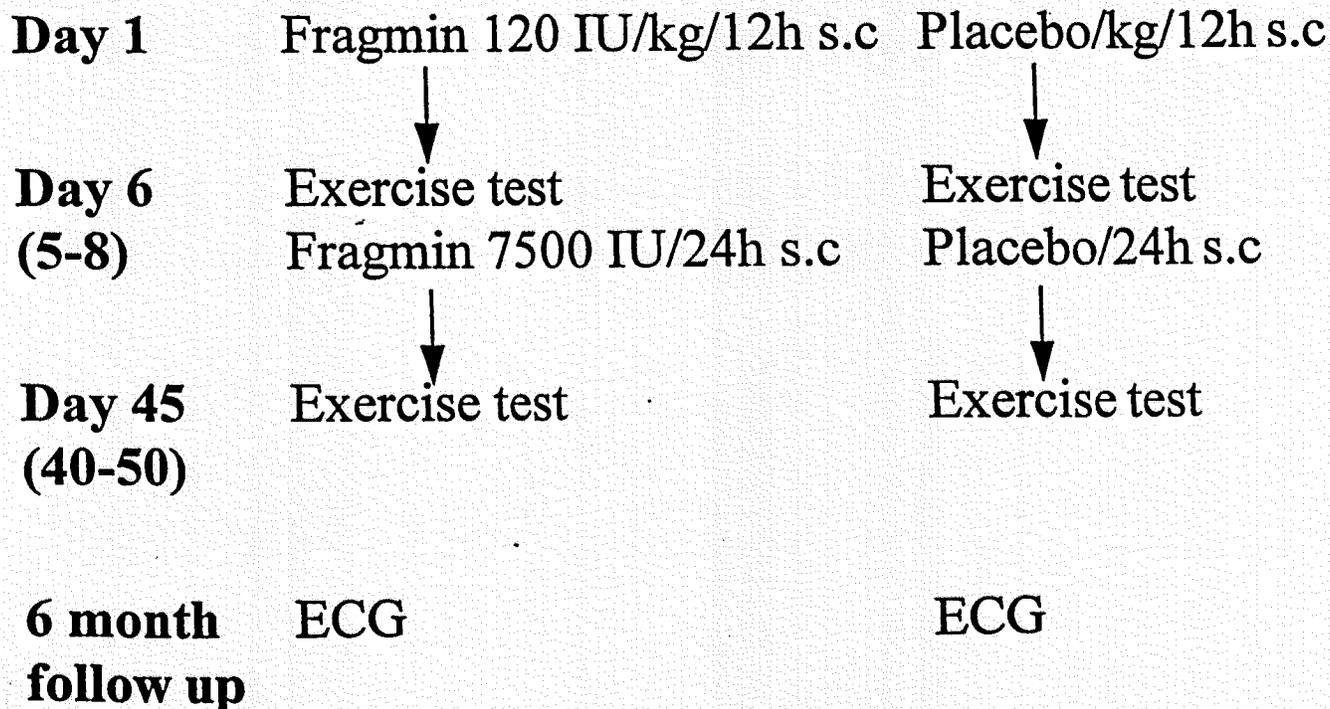
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MEETING MINUTES

APPEARS THIS WAY ON ORIGINAL

**FRISC study**

Patient log, all admitted to CCU

↓  
Unstable CAD < 72 hours according to inclusion criteria↓  
Non existence of exclusion criteria↓  
Informed consent↓  
Randomization  
Basic treatment

# FRISC

## Primary endpoint; incidence of death or MI during day 1-6 (Intent-to-treat analysis)

	Placebo		Fragmin		p-value
	n	N %	n	N %	
Death, MI	36	754 4.8	13	741 1.8	0.001

# FRISC

## Conclusion

•Fragmin 120 IU/kg s.c BID is significantly more effective than aspirin alone in the early reduction (up to day 6) of death or MI.

The effect was sustained up to day 40.

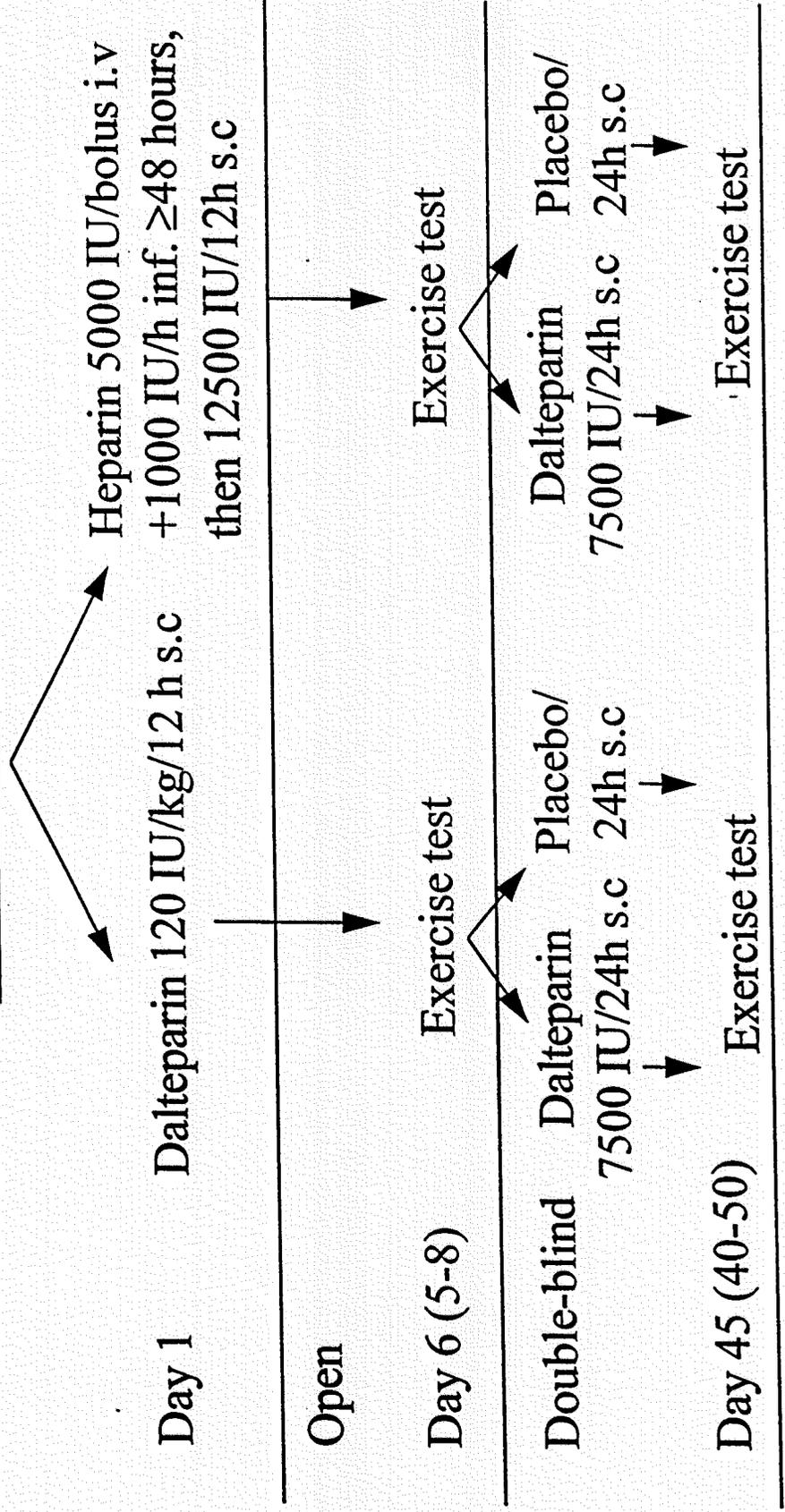
The study:

- predefined primary endpoint; 63 % risk reduction,  $p=0.001$
- clinical important endpoints
- internally consistent multicenter trial

115 slide  
has to change

# FRIC

Randomization Basic treatment Aspirin, $\beta$ -blocker
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ECG

ECG

3 month follow-up

# FRIC

## Events during phase I (days 1 to 6) Intent-to-treat analysis

	Fragmin		Heparin		p***
	n/N	%	n/N	%	
Death / MI / Recurrence*	(69/743)	9.3	(55/722)	7.6	0.323
Revascularization**	(36/746)	4.8	(39/729)	5.3	0.549
Death / MI / Recurrence / Revascularization	(94/740)	12.7	(87/721)	12.1	0.876

\* i.v. nitroglycerine

\*\* PTCA and CABG

\*\*\* Cochren-Mantel-Haenszel test

# FRIC

## Primary endpoint; (phase II, prolonged treatment)

Intent-to-treat analysis

	Placebo			Fragmin			p-value
	n	N	%	n	N	%	
Death, MI and recurrent angina	69	561	12.3	69	562	12.3	0.956
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Death, MI	26	558	4.7	24	562	4.3	0.766

## **FRIC**

### **Conclusion**

#### **Prolonged phase**

In the FRIC home treatment phase, no significant differences were seen between patients treated with Fragmin and those treated with placebo.

#### **Acute phase**

Fragmin had comparable effect with Heparin on the composite outcome of death, MI and recurrent angina but with an increased number of deaths.

# FRISC II

## Primary Objective

### **Prolonged treatment of Fragmin vs. placebo**

In patients treated according to a selective policy or because of contraindications to a direct invasive policy:

Compare the continued treatment of Fragmin 5,000 IU alternatively 7,500 IU vs. placebo s.c. twice daily, concerning the incidence of death or acute myocardial infarction from admission until three months visit (90 days after start of Fragmin 120 IU/kg 12 h treatment).