

## 5.6 CONCLUSION

Study D-10 was initially reviewed at the time of the NDA 20-287 submission on 8-6-1992. Although at that time the study was planned and submitted as an adequate and well controlled clinical trial, it was considered to be marginally acceptable as single pivotal study because of the selection of a suboptimal regimen (sc heparin) as comparator and because the second pivotal study in hip replacement surgery (D-4) was unacceptable. Study D-10 was, however considered adequate to provide supportive evidence for the indication of Fragmin for thromboprophylaxis in hip replacement surgery when combined with the pivotal study 91-137.

Study D-10 indicates that Fragmin was superior to Heparin in prophylaxis of proximal DVT (mostly in the perioperative hip region) and of PE (as detected by lung scans). No statistically significant difference was observed between treatment groups for the incidence of symptomatic DVT and/or PE.

Compared to other studies, the observed incidence of VTE and DVT in study D-10 was high in both treatment groups (F=31.7%/H=43.5% for VTE and F=30.1%/H=41.6% for DVT). This finding was attributed to the increased sensitivity of the methods of detection of thrombosis used: ascending VG which visualized thrombosis in superficial and deep proximal veins of the hip region and mandatory lung scans in asymptomatic patients.

Safety, assessed as hemorrhagic and non-hemorrhagic adverse events, was comparable between two treatment groups.

## 6.0 INTEGRATED SUMMARY OF EFFICACY

A total of 1,244 hip replacement patients were enrolled in 6 studies. All received anticoagulation before surgery according to various dose regimens and schedules of administration. Five regimens of Fragmin, two regimens of Heparin and one of Warfarin were used in the clinical trials. The regimens are summarized below.

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## STUDY DRUG REGIMENS

**Fragmin:**

- 2500 U 2h before surgery followed by 2500 U within 24h, then 5000 U q.d. for 5-9 days. 292 patients treated in study 91-137
- 5000 U in the evening before surgery, then 5000 U q.d. for 10 days. 67 patients treated in study D-10
- 2500 U 2h before surgery, 2500 U 12h after surgery, then 2500 U q.d. for 10 days. A total of 205 patients were treated in studies E-4, E-5, and E-8.
- 2500 U 2h before surgery, 2500 U 12h after surgery, then 2500 U q12h for 9-13 days. 41 patients were treated in study E-8.
- 2500 U 2h before surgery followed by 5000 U q.d. for 9-13 days. 42 patients were treated in study E-8.

**Heparin:**

- 5000 IU 2h before surgery, followed by 5000 IU q12h for the duration of Fragmin therapy. 41 patients were treated in study E-8
- 5000 IU 2h before surgery, followed by 5000 IU t.i.d for the duration of Fragmin therapy. 268 patients were treated in study D-10, E-4, E-5 and E-7.

**Warfarin**

- Warfarin was the control drug in 288 patients in study 91-137. The initial dose was 5 or 7.5 mg before surgery and within 24 hours after surgery; the dose was subsequently adjusted to maintain INR 2.5.

Anticoagulation was well tolerated for up to 14 days after surgery. In one study (E-7), Warfarin maintenance therapy followed successful prophylaxis.

**a. Summary of efficacy of all controlled studies**

Efficacy data from several controlled clinical trials were provided to support the claim that Fragmin is superior or equivalent to low-dose Heparin for thromboprophylaxis in patients undergoing hip surgery.

The data from these studies and from the two pivotal trials are summarized in the following Table.

## CLINICAL STUDIES TO SUPPORT EFFICACY OF FRAGMIN FOR THROMBOPROPHYLAXIS IN HIP SURGERY

STUDY	DESIGN/PATIENTS	DOSE	EFFICACY	SAFETY
<b>PIVOTAL STUDIES</b>				
91-137 U.S. 05/92-03/95 Hip replacement	Multicenter[8], open-label, randomized, two parallel group: fragmin vs. warfarin.  Randomization prior to surgery. Total:580. F:292; W:288	F: 2500 preop. and 2500 within 24 hours, followed by 5000 q.d. W: 5 or 7.5 mg preop and same within 24h, followed by warfarin adjusted to INR 2.5	Endpoint: venography (blinded) after 1-9 days of surgery. ITT and PP. PP-DVT F: 28/192(15%) W:49/190(26%) p=0.006	1. AE⇒disc F:3(1 related) W:3 2. Hemorrhage: F>W majority= minor
D-10 Sweden 11/87-06/89 Hip replacement	Single-center, randomized, double-blind, two parallel group:fragmin vs. heparin sc. Total:136. F:67; H:69	F: 5000. Start evening before surgery H: 5000 t.i.d. Start 2h before surgery	VG and scan day 10 F:20/63(31.7%); H:27/62(43.5%) p=0.199 sPE=H>F p=0.032	blood loss H<F Overall AE H>F
<b>SUPPORTIVE STUDIES. Meta-analysis</b>				
E-4 France 10/85-08/86 Hip replacement	Single center, open-label, randomized, two parallel groups: fragmin vs. heparin Total:80. F:40;H:40	F:2500 2h before surgery, 12h after, and 2500 q.d. for 10 days H:5000 2h before surgery, then q8h	VG, PE-scan DVT after 10 days F:7/40(17.5%) H:4/40(10.0%) p=0.33 PE=5(F=3/H=2)	Blood loss in drainage H>F. Transf: H=F
E-5 Spain 01/88-01/91 Hip replacement	Multicenter (6), open-label, randomized, two parallel group: fragmin vs. heparin Total:229. F:117; H:112	F:2500 2h preop, then q12h for 10-15 days. H: 5000 2h before surgery, then q8h	VG: DVT after 10-15 days F:15/74(20.3%) H:9/68(13.2%) PE=3(H=2/E=1)	Blood loss for 7 days: H=F
E-7 Germany 7/84-4/86 Hip replacement	Single center, open-label, randomized, parallel group: fragmin vs. heparin Total:95. F:48;H:47	F:2500 2h preop, 12h after, and 2500 q.d. for 7 days. H:5000 2h preop, then q8h. FUP: warfarin	Fibrinogen uptake test F:7/48(14.6%) H:7/47(14.9%) Phlebography (only 8) H:3/4; F:0/4	Intraoperative blood loss, required transf. H=F
E-8 France 09/85-04/87 Hip replacement	Single center, open-label, randomized, three parallel group: fragmin 1&2 vs. heparin. Total: 124. F1:42;F2:41;H:41	F1:2500 2h preop., 12h after, then q12h for 9-13 ds. F2: same for 2 days, then 5000 q.d. H:5000 2h preop,q12h.	Fibrinogen uptake test after surgery + end F1:2/38(5.3%) F2:3/39(7.7%) H:4/38(10.5%) No PE	Intraoperative blood loss and transfusion requirements F1=F2=H

F= fragmin; H= heparin; W= warfarin; ITT= intent-to-treat; PP= per-protocol; [8]= number of centers; >= superior to; = = equal to; FUP = follow-up period; AE = adverse event.

Efficacy was assessed as incidence of VTE (DVT, PE, death by thromboembolism, or any combination).

Incidence of DVT was assessed as incidence of symptomatic DVT, or DVT found on venography performed at discharge (Study 91-137, D-10, E-4, E-5, E-7). Fibrinogen uptake test was used in study E-7 (with venography) and E-8.

Incidence of PE was assessed as incidence of symptomatic PE, and of pulmonary microembolism as found on pulmonary scan performed at the end-of-study (Study D-10).

No patient died of thromboembolic complication.

Five fragmin regimens were compared with two heparin and one warfarin regimen for prophylaxis of thromboembolism in hip replacement surgery.

Overall efficacy assessment in those studies was based on rejecting the null hypothesis of equivalence between Fragmin and the control drug regimen for postoperative prophylaxis of DVT and PE. In comparison with low-dose heparin this hypothesis could not be rejected in E-4, E-7 and E-8 suggesting comparable efficacy of Fragmin and low-dose Heparin. The hypothesis was rejected in D-10 and E-5 suggesting different efficacy. In E-5 a low-dose Heparin regimen was more efficacious than fragmin. In the two pivotal studies 91-137 and D-10, Fragmin was superior, although marginally to Warfarin (91-137) and low-dose heparin (D-10). In D-10 Fragmin was also superior to low-dose Heparin for prevention of pulmonary microembolism (scan-detected PE).

In summary, these studies indicate that Fragmin is either comparable or better (with some exceptions) than the low-dose heparin or warfarin for thromboprophylaxis in patients undergoing hip replacement surgery.

**b. Summary of efficacy analyses in two pivotal studies.**

The two pivotal studies assessed different efficacy endpoints. In study 91-137 the primary efficacy variable was the incidence of DVT in the per-protocol patient population whereas in study D-10 efficacy was assessed in the all-treated population. The second primary efficacy endpoint in the D-10 study was the incidence of PE as detected by lung scan at the end of the study. DVT in the popliteal vein was considered proximal in 91-137 and distal in D-10. In study 91-137, superficial vein thromboses were also recorded.

In the two pivotal clinical trials, the overall efficacy of Fragmin was superior to that warfarin and heparin respectively.

The efficacy results of each study are summarized in the following table.

**Study 91-137**PRIMARY EFFICACY ENDPOINT: RATES OF VERIFIED DVT AND SUPERFICIAL VEINS THROMBOSIS IN P-P POPULATION<sup>1</sup>.

DVT Location	Fragmin		Warfarin		P=value
	N=192	%	N=190	%	
Any Deep Vein Thrombosis (total DVT)	28	14.6	49	25.8	0.006*
Any Superficial Vein Thrombosis**	23	11.9	43	22.6	0.005*
Superficial and deep venous thrombosis	51	26.5	92	48.4	<0.001*
Distal DVT (Calf): Total	21	10.9	43	22.6	0.005*
Proximal DVT (Leg): Total	10	5.2	16	8.4	0.185

\* Significant difference.

\*\* Superficial vein category (not in the protocol). Some DVT may have been counted in more than one location.

**Study D-10**

SUMMARY OF TEST RESULTS: PRIMARY ANALYSIS OF EFFICACY. EVALUABLE PATIENT POPULATION

Event	Fragmin		Heparin		Fisher's Exact 2-tailed test
	N = 65	%	N = 62	%	
Total VTE	20	31.7%	27	43.5%	0.199
DVT	19	30.1%	25	41.6%	0.194
sPE	9	13.8%*	19	30.6%*	0.032*
Proximal DVT (femoral)	6	9.5%*	18	30.0%*	0.006*

\* = Significant difference. PE diagnosed by lung scans.

The secondary efficacy analyses show that fragmin was superior to warfarin in all categories except "proximal" veins, and superior to low-dose heparin in some, but not the "any DVT" category.

Superficial vein thromboses were visualized at the hip region where surgically-related trauma may have contributed to their development. This category of VTE was analyzed separately from DVT in study 91-137, but it was included into assessment of DVT in the study D-10. When superficial vein thromboses were excluded from "any DVT" in study D-10, the percentages of DVT incidence in Fragmin and low-dose Heparin treatment groups were similar to those in study 91-137. The revised statistical analysis of study D-10 confirmed the superiority of the Fragmin regimen.

**c. Conclusion on Efficacy**

The data provided by the pivotal studies and by the supportive studies (Fragmin vs. heparin or vs. Warfarin) indicate that Fragmin is effective for prophylaxis of postoperative DVT/PE in hip surgery. Based on these data, it can be concluded that the

administration of Fragmin in hip surgery provides protection for patients against postoperative DVT and PE which is at least as effective well as that of the comparator drugs: low-dose Heparin or Warfarin.

#### 7.0 INTEGRATED SUMMARY OF SAFETY

The sponsor has submitted two documents for assessment of Fragmin safety. This supplement (NDA#20-287/S-008) with a cut-off date 04/17/97, and the Safety Update to cover a period from 07/01/95 to 02/28/97. The updated safety data provided in the two documents were compared to the safety data described in the current Fragmin Package Insert.

Prior Safety Updates were submitted November 5, 1993, November 17, 1994, and January 1, 1996, and in NDA #20-287. The most recent 4-Month Safety Alert Report is reviewed separately.

#### 7.1 Summary of Safety Data in Supplement NDA 20-287/S-008.

This submission contains safety information from 11 clinical trials: 91-137, D-10, D-4, D-16, E-4, E-5, E-6, E-7, E-8, E-9 and E-10. Pertinent information for studies, 91-137, D-10, E-4, E-5, E-7 and E-8, were included with the table on page of this review.

A total of 1893 patients were randomized in the 11 trials and 1916 of them (95.6%) were treated. Fragmin was administered to 908 patients, Heparin to 469 patients, Dihydroergotamine with Heparin to 124 patients, Dextran-70 to 50 patients, Warfarin to 288 patients and placebo to 101 patients.

The majority of patients received Fragmin as single daily injection of 5000 U (9730 patients), while others received the same dose split in two daily sc injections of 2500 U.

The safety information for studies D-4, D-16, E-6, E-9, and E-10 are summarized in the following table.

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## CLINICAL STUDIES SUBMITTED FOR SAFETY EVALUATION ONLY

STUDY	DESIGN/PATIENTS	DOSE
D-4 Denmark, 6/92 HR or hip fracture	Randomized, double-blind, parallel group, placebo-controlled Pts: 202. F:101. PL:101.	F:2,500 pre- and post-op; 5000 for 6 days. Pl: sc for 6 days
D-16 Spain, (1982) Hip fracture	Randomized, double-blind, parallel-group, heparin controlled. Pts:96. F:46. H:44	F:2500 pre-op, 5000 for 9 days. H: 5000 pre-op, 5000 tid for 9 days.
E-6 Germany, HR	Randomized, open-label, parallel group, heparin/DHE Pts:130. F:66.H:64	F:2500 pre- and post-op, 5000 for 8 (7-10) days. H:5000 pre- and post-op 5000 bid for 8 days. DHE:0.5 mg with H.
E-9 Sweden HR	Randomized, open-label, parallel-group dextran-70 control. Pts:101. F:51.Dx:50	F:2500 pre- and post-op 2500 bid for 6 days. Dx (iv): 500 mL pre- and post-op. 500 mL bid.
E-10 Germany Leg surgery+HR	Randomized, open-label, parallel-group, heparin/DHE control Pts:120. F:60.H:60	F:2500 pre- and post-op, 5000 for 10-14 days. H:5000 pre- and post-op, 5000 bid. DHE:0.5mg with H.

HR= hip replacement. F= fragmin. H= heparin. Pl= placebo. DHE= dihydroergotamine.

The adverse events described in the ISS consist mainly of hemorrhagic events, including:

#### Blood Loss:

In five studies (91-137, D-4, E-5, E-6, and E-8), mean perioperative blood loss was larger in fragmin treated patients than in controls. However, the difference was calculated in mL and was not statistically significant. In the remaining six studies the opposite was noted. In conclusion, blood loss was almost equal in both treatment groups.

#### Blood Transfusions:

The majority of patients received transfusion only on the day of surgery. The percent of patients who received transfusion varied among studies from 30%-100% (day of operation), but there was no significant difference between patients in two treatment groups. Mean transfusion requirement was (mean of means) 868.28 ± 473 for Fragmin and 891.96 ± 526 for the control drug treated groups.

#### Wound Hematoma:

The incidence of wound hematoma was slightly higher in fragmin than in control drug groups in 9 studies. The difference was never significant.

**Re-Operation or Evacuation of Hematoma:**

This intervention was required in 4 patients, 2 on Dextran, 1 Fragmin and 1 randomized to Heparin.

**Hematoma at Injection Site:**

In three studies (D-10, E-5, and E-7) once daily Fragmin was compared to BID or tid heparin. In all studies, the incidence of this event was higher in Heparin-treated patients. However, if corrected for frequency of drug administration, Fragmin showed more frequent injection site hematoma. Neither difference reached any statistical significance.

**Deaths and Premature Withdrawal due to Adverse Events:**

A total of 12 deaths occurred in all studies (F=5, H=4, Pl=3). Ten of them occurred in hip fracture studies. Two deaths occurred in the elective hip surgery (F=1/H=1). None of deaths was related to study medication, except one patient (D-6 study) on heparin who had acute GI bleeding from peptic ulcer (autopsy finding).

A total of 27 withdrawals including 12 deaths was recorded in 11 studies. Four premature withdrawals due to hemorrhagic adverse events occurred in the fragmin treated group. No other withdrawal was clearly related to any study medication.

**Laboratory Data:**

There were no unexpected or unexplained changes in laboratory values in any of the studies. A postoperative transient reactive increase in platelet count was seen in many patients.

**Subset Analyses:**

Data regarding blood loss, patients requiring blood transfusions, amount of blood transfused, and patients with adverse hemorrhagic events were examined and compared in elderly vs. young, male vs. female, patients with  $\geq 2$  vs.  $< 2$  risk factors. The results show some trends (patients with  $\geq 2$  risk factors). Patients with revision surgery had more blood loss, more transfusion requirements, and hemorrhagic adverse events. No significant difference between treatment groups was found.

**Thrombocytopenia:**

Thrombocytopenia was reported only in E-5 (8 cases=3/H=5). One heparin patient had HITT. In other studies thrombocytopenia was either non recorded or not reported.

**Conclusions on Safety**

The data support the safety profile of Fragmin as presented in the original NDA. No changes in the Labeling pertaining to safety information are required based on this NDA Supplement.

**7.2 Four-month Safety Update (SE1/008/SU submitted on 8/18/97)**

This is the third Safety Update since the original submission of NDA 20-287. It covers a period between 07/01/95 and 02/28/97.

Integrated safety data from 24 trials of thromboprophylaxis (15 in general surgery and 9 in orthopedic surgery) were included in the Safety Update for the period ending on April 30, 1993 and submitted on November 5, 1993.

New safety data from 19 trials that were ongoing at the time of the previous Safety Update, and data from 5 trials that were initiated after this date, are included in this submission. Updated information on serious adverse event is summarized in the following table.

The submission also contains updated information on serious adverse events reported to a central database, an updated post-marketing safety experience in countries where Fragmin has been marketed, and literature reports relevant to the safety of Fragmin.

The new safety data are consistent with those reported in the Safety Updates submitted November 5, 1993, November 17, 1994 and January 11, 1996. No unexpected adverse event occurred and no increased frequency of expected events have been recorded.

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## Summary of serious Adverse Events from 19 ongoing and 5 new Fragmin trials

INDICATION	STUDY	SAFETY CONCERN
Orthopedic	91-137 (PIVOTAL) 90-065 93-Frag-016	No new concerns
Myocardial infarction	90-044 92-Frag-012	No new concerns
Unstable Coronary Artery Disease	91-115 91-128 95-Frag-025	No new concerns
PTCA	90-014	No new concerns
DVT Treatment	91-030 91-051 91-196	No new concerns
PE Treatment	90-129 91-134	No new concerns
Prolonged Thromboprophylaxis Following Orthopedic Surgery	91-139, 91-064 93-Frag-015 93-Frag-016	No new concerns
Thromboprophylaxis in total knee replacement	91-138	No new concerns
Thromboprophylaxis in pregnancy	92-Frag-008	No new concerns
Other Indications	Tendonitis (90-118, 90-134) Stage II arteriopathy (92-Frag-002) Peripheral bypass for limb ischemia(95-Frag-024) Children undergoing hemodialysis (92-Frag-010). Chronic hemodialysis (92-Frag-013). Medical patients (95-Frag-023)	No new concerns

From: Safety Update (Vol.1, pp.9/1/1-56), and Clinical Trial Synopses (Vol.1, pp.9/1/58-107) . No new concerns = The new information did not add to the already known safety issues covered in the current Labeling.

### 7.3 Post-Marketing Surveillance

A total of 304 spontaneous adverse event reports had been received prior to February 28, 1997. These reports included 374 adverse events.

Forty-seven new reports were of thrombocytopenia. In four cases other Heparins were given before or concomitantly with Fragmin, and in three cases thrombocytopenia occurred prior to Fragmin. In 15 cases antibodies against heparin-PF4 were documented. Twelve of them were without any previous exposure to heparins.

#### 7.4 Review of Literature

This periodical review includes summary of 39 articles published elsewhere. Original clinical data appeared in 21 articles.

The reports were on thromboprophylaxis in surgery, orthopedic surgery, in stroke, in urologic surgery, in pregnancy, treatment of DVT, treatment of massive PE, in venous access devices; prevention of thrombosis after stent implantation, anticoagulation and MI, effects on hemostasis in by-pass surgery, anticoagulation and unstable CAD, and anticoagulation and hemodialysis.

There were three case reports: 1) cross reactivity of fragmin in heparin-induced HIT, 2) a vertebral fracture in long-term treatment of a female with acute leukemia, and 3) skin necrosis after short-treatment with heparin followed by fragmin in a patients with cancer and massive DVT.

#### 8.0 SUMMARY AND CONCLUSIONS

Fragmin® Injection (dalteparin sodium) is a low-molecular-weight Heparin developed in Europe [REDACTED] twelve years ago first approved in Germany in 1985.

Currently, Fragmin is authorized for use in 44 countries for thromboprophylaxis, hemodialysis, and treatment of DVT. In the U.S., Fragmin is approved for thromboprophylaxis in patients undergoing high risk abdominal surgery.

Since the first approval (Germany, 1995) approximately 22 million patients have been treated with Fragmin.

The current sponsor, Pharmacia & Upjohn, has submitted an NDA efficacy supplement for Fragmin for the new indication of thromboprophylaxis in hip replacement surgery.

Two adequate and well controlled clinical trials (91-137 and D-10) provide substantial evidence that Fragmin is an effective agent for prophylaxis of postoperative DVT and PE in patients undergoing hip replacement surgery. In both trials, Fragmin was found to be superior (although marginally) to warfarin (study 91-137) and low-dose subcutaneous Heparin (study D-10).

According to data presented in this supplement, patients receiving Fragmin may experience more hemorrhagic episodes, and more severe events than patients on Warfarin, but not more than patients on Heparin. The most frequent hemorrhagic adverse event of Fragmin was injection site hematoma.

HIT (heparin induced thrombocytopenia) occurred rarely, one case in the two trials. There was no other adverse event that can be attributed to Fragmin specifically.

All other reported adverse events were those commonly seen postoperatively, and were comparably distributed among the three treatment groups.

The overall safety of Fragmin in both trials was comparable to that of the control drug.

Several (11) studies were added to this supplement to support efficacy and safety of the proposed fragmin prophylaxis in hip surgery. Although Fragmin was given in different regimens, to relatively small number of patients, and in open-label fashion, these studies, together with the pivotal two, support the sponsor's claim.

Notably, no increased frequency of expected adverse events and no new serious and unexpected adverse event emerged from the studies involving more than 900 patients treated with Fragmin in the clinical trials nor from the Safety Update report submitted on 8-18-1997. Major hemorrhage was a rare event, as well as heparin-induced thrombocytopenia.

The efficacy of Fragmin was superior to that of control regimens (low dose Heparin or Warfarin) in two pivotal studies. The claim of Fragmin safety is supported by its tolerability in approximately 1000 patients who received Fragmin for prophylaxis of VTE in orthopedic surgery.

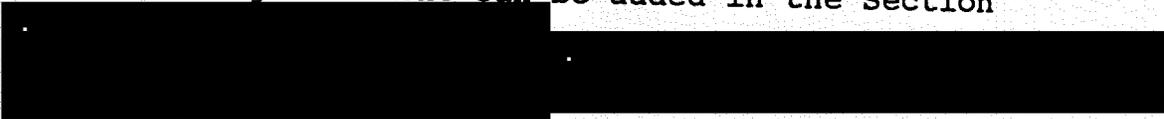
In conclusion, the efficacy and safety data obtained from two pivotal trials 91-137 and D-10 support the conclusion that the risk/benefit for Fragmin for the proposed indication of prophylaxis of DVT and PE in patients undergoing hip surgery is favorable.

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9.0 RECOMMENDATION

Based on the evidence presented in this supplement I would recommend Fragmin to be approvable for the new proposed indication of thromboprophylaxis in hip replacement surgery.

The Labeling for Fragmin® Injection is APPROVABLE with the following changes:

- a. The efficacy results of the two pivotal trials of Fragmin in hip replacement must be included in the "Clinical Trial" section.
- b. The following statement can be added in the Section  

- c. The sponsor's dosing recommendations should be added in the Section "ADMINISTRATION AND DOSING".

/s/ 

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NDA 20-287  
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HFD-10/LTalarico  
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