Dalteparin Sodium for the Prevention of Clotting of the Extracorporeal Circuit in Hemodialysis: A Phase IIIB Open-Label Study to Optimize a Single-Bolus Dose – the PARROT Study

S. Soroka,[1] M. Agharazii,[2] S. Donnelly,[3] L. Roy,[4] N. Muirhead,[5] S. Cournoyer,[6] M. MacKinnon,[7] N. Pannu,[8] B. Barrett,[9] F. Madore,[10] J. Wilson,[1] F. Hilton,[11,12] N. Sherman,[12] K. Wolter,[12] J. Orazem,[12] G. Feugère[13]

[1]Division of Nephrology, Dalhousie University, Halifax, NS, Canada; [2]Endocrinology and Nephrology, CHU de Québec Research Center, Université Laval, Québec City, QC, Canada; [3]Division of Nephrology, William Osler Health System, Brampton, ON, Canada; [4]Department of Medicine, Université de Montréal, Montreal, QC, Canada; [5]Department of Medicine, London Health Sciences Centre, London, ON, Canada; [6]Nephrology, Hôpital Charles-LeMoyne, Greenfield Park, QC, Canada; [7]Division of Nephrology, Horizon Health, Saint John, NB, Canada; [8]Nephrology, University of Alberta, Edmonton, AB, Canada; [9]Division of Nephrology, Memorial University of Newfoundland, St. John's, NL, Canada; [10]Faculté de Médecine, Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada; [11]Pfizer Essential Health, Pfizer Inc, New London, CT, USA; [12]Pfizer Essential Health, Pfizer Inc, New York, NY, USA; [13]Pfizer Essential Health, Pfizer Canada Inc., Kirkland, QC, Canada

INTRODUCTION

- Dalteparin sodium, a low-molecular weight heparin (LMWH), has been approved for the prevention of clotting in the extracorporeal system during hemodialysis (HD) in Canada since 1994.
- Current product labeling recommends a fixed, single bolus dose of 5000 international units (IU) for HD sessions lasting ≤4 hours.
- However, the anticoagulant effect may be impacted by body weight, preexisting conditions such as thrombophilias, and clotting stimuli produced by different dialysis circuits and membranes.
- A flexible dose regimen for dalteparin sodium, above or below 5000 IU, may be beneficial to optimally dose patients and better meet the needs of clinical practice.

AIM

- To assess the safety and efficacy of a flexible dosing regimen of dalteparin sodium to prevent clotting in the extracorporeal system during HD lasting ≤4 hours in patients with chronic renal failure.

METHODS

Study Population

- Inclusion Criteria
  - Adults (aged 18–85 years; >45 kg) with end-stage renal disease, requiring 3 or 4 HD sessions (≤4 hours each) per week, with no major intercurrent illness
  - Received HD for ≥30 days with only unfractionated heparin (UFH) or LMWH for anticoagulation and had well-functioning vascular access
  - Receiving ≤10,000 IU UFH or LMWH on dialysis at enrollment.
- Participants were excluded if they had bleeding or blood disorders; were taking contraindicated medications; had active cancer, liver disease, or uncontrolled hypertension; anticipated kidney transplant, hemofiltration, or predicted survival <1 year; positive platelet aggregation test with dalteparin sodium and other conditions for which the use of dalteparin sodium is contraindicated, including diabetic or hemorrhagic retinopathy; or were pregnant or lactating.

Study Design and Treatment

- An open-label multicenter study with a single-treatment arm, conducted at 10 sites in Canada between October 2013 and March 2016.
- All participants received 5000 IU dalteparin sodium administered as a single bolus into the arterial side of the dialyzer at the beginning of the first HD session.
- Participants received 3 to 4 HD sessions per week, each lasting up to 4 hours, for up to 20 HD sessions.
- The same dose was continued unless there was indication for adjustment (**Table 1**).

Table 1. Criteria leading to dose adjustment

Time of clinical event	Criteria leading to a dose adjustment
During or immediately following HD session	Grade 3 or 4 clotting in bubble trap and/or dialyzer
	Access compression time >10 min (AVF or AVG)
	Minor bleeding
	Use of saline flushes to prevent loss of ECC
	Other clinical events
Between the end of the last and the next planned HD session	Minor bleeding Other clinical events

AVF, arteriovenous fistula; AVG, arteriovenous graft; ECC, extracorporeal circuit.

- Dose could be adjusted by 500 IU or 1000 IU (increment/decrement), dependent on the outcome of the previous HD session and any intervening clinical events.
- Maximal or minimal doses were not restricted.

Assessments

- At each HD session, the following were assessed:
  - Clotting in the HD circuit (visual inspection following a 4-point scale [**Table 2**])
  - Bleeding events
  - Access compression time (for participants with arteriovenous fistula [AVF] or graft [AVG])
  - Access thrombosis.
- Safety assessments were conducted throughout the duration of the study.
- Anti-Xa levels were assessed at HD sessions 1, 10, and 20 using a validated chromogenic assay in a central laboratory.

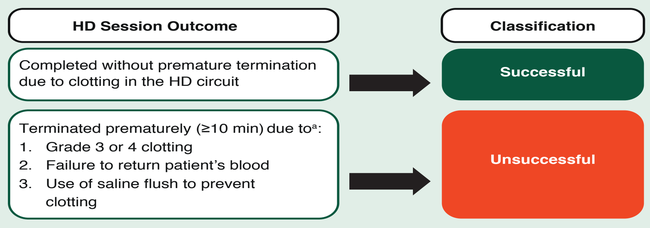
Table 2. Clot grading following visual inspection of the extracorporeal circuit at the end of each HD session

Clot grade	Arterial or venous chambers (bubble trap)	Dialyzer filter	
		Appearance	Description
Grade 1	No clotting	None	Clean filter, residual uniform pinkish tinge only
Grade 2	Fibrinous ring	Small	Few blood stripes, <5% of the fibers
Grade 3	Clot formation	Moderate	Many blood stripes, >5% but <80% of the fibers
Grade 4	Coagulated system	Large	>80% of the fibers

Efficacy measures

- The outcome of each HD session was classified as successful or unsuccessful (**Figure 1**).
- The primary efficacy endpoint was the mean proportion of successful HD sessions.

Figure 1. Criteria for classification of HD session outcomes



HD, hemodialysis.
[a] If a HD session was terminated prematurely for any other reason, it was omitted from analyses but not considered unsuccessful.

Statistical analysis of primary and secondary endpoints

Primary analysis

- The mean percent of successful HD sessions was calculated and analyzed using a generalized estimating equation model for clustered binomial data, with participant as the clustering variable. If the lower bound of the corresponding 95% confidence interval (CI) was greater than the prespecified value of 86%, the study was considered positive.

Secondary analysis

- Comparative analyses between the fixed- and adjustable-dose regimens were performed using a split-sample approach:
  - Two drug-administration periods were defined for each participant: period 1 (fixed dose), followed by period 2 (from when dose first changed). Fixed dosing was represented by period 1 only, and flexible dosing was represented by periods 1 and 2.
  - Participants were randomly split into groups A and B. To compare fixed versus flexible dosing, only period 1 data were used for group A subjects, and periods 1 and 2 data were used for group B, to provide estimates of success rates.
  - Using a permutation resampling approach, which repeatedly and randomly split the sample into groups A and B and analyzed the outcomes, percentile-based 95% CI were provided for differences in success rates between fixed- versus adjustable-dosing regimens.
- The success rates for period 1 and period 2 were compared for participants with dose adjustments.

RESULTS

- 152 participants were enrolled in the study (**Table 3**).
- 21 participants discontinued the study: 4 due to study drug–related adverse events (AEs), 1 due to an AE not related to study drug, and 16 whose relation to study drug was not defined.

Table 3. Baseline characteristics for study participants

	Total (n=152)
Male, n (%)	106 (69.7)
Mean age, y (%)	57.1 (14.7)
Weight[a], kg	82.2 ± 19.7
BMI[b], kg/m² (range)	29.1 ± 6.8 (18.0–54.0)
Male	28.2 ± 5.6 (18.0–42.5)
Female	31.0 ± 8.8 (19.3–54.0)
Race, n (%)	
White	117 (77.0)
Black	14 (9.2)
Asian	7 (4.6)
Other	14 (9.2)
Systolic blood pressure[a], mm Hg (range)	139.9 ± 19.9 (86–186)
Diastolic blood pressure[a], mm Hg (range)	75.9 ± 14.8 (32–120)
Cause of ESRD, n (%)	
Diabetes mellitus	19 (12.5)
Hypertension	23 (15.1)
Glomerulonephritis	53 (34.9)
Polycystic kidney disease	15 (9.9)
Other	42 (27.6)
Years since diagnosis of ESRD[c], median (range)	2.2 (0.2–25.7)
Vascular access type[d], n (%)	
AVF	91 (59.9)
Central venous catheter	61 (40.1)
AVG	11 (7.2)
Medical history, n (%)	
Diabetes	46 (30.3)
Hypertension	143 (94.1)
Cardiovascular disease	84 (55.3)
Prior and concomitant drug treatments, n (%)	
≥1 prior UFH treatment	135 (88.8)
≥1 prior LMWH treatment	18 (11.8)
Aspirin	32 (21.1)
Tissue plasminogen activator (Alteplase)	10 (6.6)

Data are mean + SD (range) unless otherwise stated.
AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; ESRD, end-stage renal disease; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.
[a] Screening visit pre-HD value. [b] Defined as weight/(height*.01)**2 at screening, n=151. [c] n=101.
[d] Participants could have more than 1 type of access over the course of the study.

Primary efficacy endpoint

- 2826 HD sessions were performed for the 152 participants
  - 2776 (98.2%) sessions from 151 participants were evaluable for the primary efficacy endpoint
  - Fifty HD sessions were omitted from the primary analysis: all 20 sessions from one participant were omitted due to the use of prohibited medication at the first HD session; 5 were not evaluable due to premature interruption of HD for reasons other than grade 3 or 4 clotting; and the remaining 25 were excluded due to incomplete clotting data, or participants not receiving dalteparin sodium.
- 99.9% (95% CI, 99.7, 100.0) of evaluable HD sessions were completed without premature clotting in the HD circuit and were considered successful.
- Two (0.07%) HD sessions terminated early due to grade 3 or 4 clotting at a dose of 5000 IU and were considered unsuccessful.
- No HD sessions terminated prematurely due to bleeding.
- 75.5% (114) of the participants received all 20 HD sessions successfully.
- Sensitivity analyses of the primary endpoint were performed, where successful HD sessions were reclassified as unsuccessful if there was any grade 4 clotting or any grade 3 or 4 clotting. Among HD sessions which did not terminate prematurely:
  - Grade 4 clotting was reported for 32 (21.2%) participants in 76 (2.8%) HD sessions
  - Grade 3 or 4 clotting was reported for 93 (61.6%) participants in 477 (17.3%) HD sessions.

Secondary endpoints

HD session outcomes and dose adjustment

- Over half (79 [52.3%]) of the 152 participants who completed ≥1 HD session received a dose adjustment, with the remainder (72 [47.7%]) maintaining the standard dose of 5000 IU.
- Among participants whose dose was adjusted, the median number of dose adjustments was 3 for those who completed ≥1 HD session (range, 1–12) and also for those who completed all 20 HD sessions (range, 1–10).
- Dose was adjusted for 10% (279) of HD sessions, with grade 3 or 4 clotting at the previous HD session the most common reason for dose adjustment (72.8%; **Table 4**). Generally:
  - Grade 3 or 4 clotting or use of saline flushes resulted in a dose increase
  - Extended access compression times and minor bleeding resulted in a dose decrease.

Table 4. Reasons for dose adjustment

	HD sessions with dose adjustment[a], n (%) N=279
Reason for dose increase	
Use of saline flushes	2 (0.7)
Grade 3 or 4 clotting at previous HD session	203 (72.8)
Minor bleeding during previous HD session	1 (0.4)
Other clinical event	6 (2.2)
Reason for dose decrease	
Access compression time >10 minutes at previous HD session	47 (16.9)
Minor bleeding during previous HD session	9 (3.2)
Minor bleeding since previous HD session	16 (5.7)
Other clinical event	9 (3.2)

HD, hemodialysis.
[a]Participants could have more than 1 reason for a dose change.

- For the 128 (84.8%) participants who completed all 20 HD sessions, more received a dose adjustment (70 [54.7%]) than remained on the standard 5000 IU dose (58 [45.3%]).
- More than half of the HD sessions (1658 [58.9%]) were performed with a fixed dose of 5000 IU
  - Median dose per session was 5000 IU (mean [SD] 5488 [1191] IU)
  - Maximum and minimum doses were 13,000 IU and 500 IU, respectively.

Acceptable dose

- The dose administered was considered acceptable, ie, no reason for adjustment at the next HD session, in 89.8% (2363/2630 [95% CI, 87.4, 91.9]) of HD sessions
  - Each participant received an average (mean) of 16.1 (SD 3.79) HD sessions with an acceptable dose.
- The proportion of HD sessions with an acceptable dose increased by 8.3% (95% CI, 2.6, 16.5) after dose adjustment compared with the period of fixed dosing, for the 79 participants whose dose was changed.

Safety

- 95 (62.5%) participants reported 218 treatment-emergent adverse events (TEAEs).
- Treatment-emergent serious AEs were reported by 3 participants (atrial fibrillation, pneumonia, influenza), none of which were considered treatment-related.
- 30 (19.7%) participants received dose changes or temporarily discontinued the study due to TEAEs.
- 5 participants discontinued the study prematurely due to a TEAE (catheter site bleeding, stoma site bleeding, blood present in urine, maculopapular rash, ocular hyperemia).

Bleeding

- Bleeding events and treatment-emergent bleeding-related AEs are displayed in **Table 5**.
- 66 (2.3% [95% CI, 1.6, 3.4]) HD sessions were associated with a bleeding event.
- There were no major bleeds.

Table 5. Bleeding events and treatment-emergent bleeding-related adverse events

	No. of participants, n (%) N=152
Bleeding events by category	
Major bleed	0 (0.0)
Clinically relevant non-major bleed	1 (0.7)
Minor bleed	38 (25.0)
Bleeding-related AEs by type	
Non-access-related bleeding	13 (8.6)
Prolonged compression time (>15 min) with bleeding from AVF (N=91)	8 (8.8)[a]
Bleeding from access site	
Central venous catheter (N=61)	6 (9.8)[b]
AVF (N=91)	15 (16.5)[c]
AVG (N=11)	0 (0.0)

AVF, arteriovenous fistula; AVG, arteriovenous graft; n, number of participants with adverse event. Includes data up to 30 days after last dose of study drug; participants are counted only once per treatment in each row.
[a]16 episodes in total. [b]7 episodes in total. [c]38 episodes in total.

Anti-Xa levels

- There was no evidence of dalteparin sodium accumulation in the intradialytic period over 20 HD sessions (serum levels below the prespecified bioaccumulation threshold of <0.4 IU/mL).

CONCLUSIONS

- A flexible dalteparin sodium dosing regimen was generally well tolerated and effective.
- 99% of all HD sessions were successful (ie, completed as planned without the need for premature termination due to clotting).
- No HD session was prematurely terminated due to bleeding.
- The PARROT study demonstrates that a flexible dalteparin sodium dosing regimen has clinical benefits over the fixed-dose regimen for preventing clotting in the extracorporeal circuit during HD.

REFERENCE

1. Fragmin product monograph (Canada). Pfizer Canada Inc, Kirkland, Quebec, Canada; 2016. http://www.pfizer.ca/sites/g/files/g10028126/f/201605/FRAGMIN_PM_193875_27April2016_E.pdf. Accessed March 15, 2017.

Acknowledgments: Co-author Irina Kaplan died in January 2017.
This study was sponsored by Pfizer. Medical writing support for the production of this poster was provided by Alexandra Bound, PhD, of Engage Scientific Solutions and was funded by Pfizer.

Copyright © 2017

Presented at the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA 2017); June 3–6, 2017; Madrid, Spain.
Previously presented at the Canadian Society of Nephrology (CSN 2017); May 4–6, 2017; Montreal, Canada.