Web Appendix

H.A.P.P.Y. Study Organization

Principal investigator - Pier M. Mannucci (Milano, Italy); Study coordinator – Ida Martinelli (Milano, Italy); Coordinating center - A. Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Medicine and Medical Specialties, Fondazione IRCCS Ca’ Granda - Ospedale Maggiore Policlinico, Milano, Italy; Participating centers - Monza (Milano) Anna Locatelli, Sara Ornaghi, Roberta Tironi; Milano Stefania Calabrese, Serena Dalzero, Anna Maria Marconi, Silvia Nozza, Paola Pileri, Sara Saino, Laura Trespidi; Modena Manuela Bellafronte, Francesca Monari; Reggio Emilia Immacolata Blasi, Giuseppina Comitini; Torino Chiara Benedetto, Valentina Donvito, Aldo Maina; Laboratory measurements – Rossella Bader, Eugenia Biguzzi, Emanuela Pappalardo, A. Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Medicine and Medical Specialties, Fondazione IRCCS Ca’ Granda - Ospedale Maggiore Policlinico, Milano, Italy; Study monitoring and investigational medicinal product distribution (Mario Negri Institute) – N. Rubis, G. Gherardi, O. Diadei. W Calini, D Rossoni, A Villa, M Sabatella (Ranica, Bergamo – Italy); Electronic Case Report Form development and data management – B. Ene-Iordache, S. Carminati, G. Gherardi, A. Remuzzi (Ranica, Bergamo Italy); Treatment assignment secretariat – G. A. Giuliano (Ranica, Bergamo, Italy); Data analyses – A. Perna, I. Fojadelli, I. Maffeis, G. Carrara, G. Stanzione (Ranica, Bergamo – Italy); Administrative and Ethical Committee procedures (Mario Negri Institute) – P. Boccardo (Ranica, Bergamo – Italy); Pharmacovigilance – N. Perico, N. Rubis; Data and Safety Monitoring Board – Giovanni Cavalli (Milano, Italy), Valerio De Stefano (Roma, Italy) and Annalisa Perna (Bergamo, Italy); Steering committee – Ida Martinelli, Irene Cetin, Giorgio Pardi, Pier Mannuccio Mannucci (Milano, Italy); Giuseppe Remuzzi (Bergamo, Italy).
INTERIM ANALYSIS

MAIN RESULTS - On April 4, 2010, 50% of planned study participants had been included. Of 135 included participants, 67 had been randomized to receive nadroparin in addition to medical surveillance and 68 to medical surveillance alone. Six of randomized women prematurely withdrew from the study, two had adverse events and 25 were still pregnant, thus 51 women per treatment arm were finally available for primary outcome analyses. Baseline characteristics, including the number of previous uncomplicated pregnancies and the distribution of previous late complications of pregnancy and coagulation abnormalities identified at screening evaluation, were similar between treatment arms. Overall, 9 of 51 women (17.6%) randomized to active treatment compared to 7 of 51 randomized to surveillance alone (13.7%) had a combined endpoint. The percentage of endpoints - absolute (95% CI) risk difference: 3.9. (-10.5 to 18.3), p=0.59 – was similar between treatment arms as well as the distribution of single components of the composite endpoint. Five women on nadroparin compared to two controls had preeclampsia. No pregnancy was complicated by the HELLP syndrome. Apart from skin reaction at the site of injection in 8% of women, no other side effect related to nadroparin was observed. The number of serious and non serious adverse events was similar in the two treatment arms.

CONCLUSIONS – The above interim findings led the Data and Safety Monitoring Board of the Study to conclude that low-molecular-weight heparin prophylaxis was ineffective in the prevention of late pregnancy complications. This conclusion was also based on the following considerations:

a) the absolute risk difference equal to -16% between nadroparin and control arm hypothesized in the sample size assumption was not included within the 95% confidence interval for the primary outcome which ranged from -10.5% to +18.3%;

b) the lack of effect was consistently observed in primary and secondary outcomes.
Moreover, the panel was concerned by the non-significant excess of preeclampsia in women on active treatment compared to controls. Thus, it was considered unethical to include additional women just to complete the recruitment of the originally planned study population and, on December 13, 2010 the Data and Safety Monitoring Board definitely closed the study for futility reasons. No further pregnant women were eventually included and the 25 women (12 in the nadroparin arm), that at that time were still pregnant were maintained in their original treatment arm and were actively followed up to delivery or progression to an endpoint.