Latest Results from the PUP-GCP Clinical Trial: A Low Inhibitor Rate in Previously Untreated Patients with Severe Haemophilia A Treated with octanate®

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Introduction

octanate® is a human, plasma-derived (pd) factor VIII (FVIII) concentrate accomplishing the highest standards of haemophilia therapy. All coagulation FVIII present in octanate® is bound to its natural stabilizer, von Willebrand factor (VWF), in a VWF:RCo/FVIII:C ratio of approximately 0.4. The manufacturing process comprises two virus inactivation steps, namely solvent / detergent treatment and terminal dry-heat treatment. octanate® is supplied as lyophilized powder in vials of 250, 500 and 1000 IU to be reconstituted with 5 ml (250 IU) or 10 ml (500 and 1000 IU) of Water for Injection. octanate® with 50% volume-reduced formulation (500 and 1000 IU in 5 ml) is already available on the German market and will soon be available on other markets. Since 1998, more than 6.5 billion IUs of octanate® have been safely infused worldwide. octanate® has now been approved in 83 countries and is extensively studied in Good Clinical Practice (GCP) clinical trials. Five prospective GCP studies with octanate® were conducted in 77 previously treated patients (PTPs) with severe haemophilia A. None of these 77 PTPs treated exclusively with octanate® developed an inhibitor. To assess the immunogenicity of octanate® in previously untreated patients (PUPs), an ongoing prospective clinical trial has been initiated in 2000. To date we can report on an excellent safety profile of octanate® with emphasis on inhibitor development in PUPs.

Materials and Methods

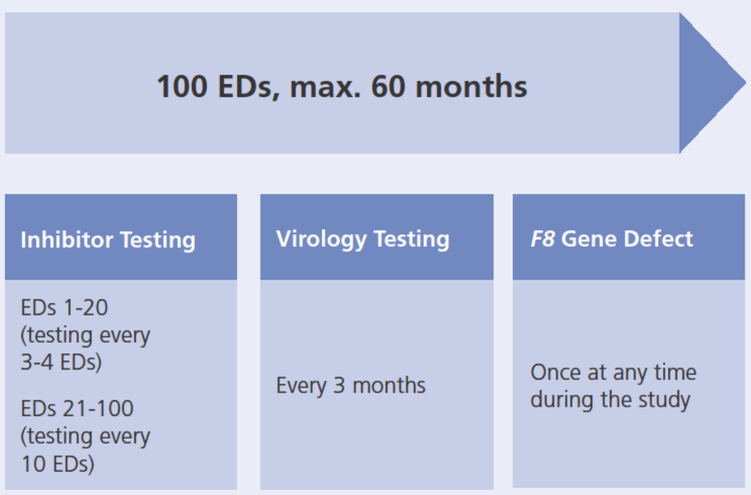
Study design (Figure 1)

- Open, prospective multi-centre, multi-national GCP trial performed at European Haemophilia Centres.
- Main inclusion criteria: Severe haemophilia A and no previous exposure to any FVIII containing product.
- Immunogenicity is assessed by the Bethesda assay according to Nijmegen modification (laboratory of Prof. Budde in Hamburg, Germany; cut-off 0.6 BU) at pre-treatment, every 3 – 4 exposure days (EDs) up to ED 20 and every 10th ED between EDs 21 – 100. Patients are followed until ED 100 or for a maximum period of 60 months. Patients who develop inhibitors may be followed for a longer period of time.

Patient population (Table 1)

- To date, a total of 51 patients meeting the inclusion criteria have been enrolled in the study and have received at least one dose of octanate®.
- The majority of patients were initially treated on-demand; a number of them were switched to prophylactic treatment during the course of the study:
  - 14 of 51 subjects (27%) were treated exclusively on-demand for ≥ 50 EDs
  - 15 of 51 patients (29%) had on-demand treatment for ≥ 20 EDs prior to being switched to prophylactic administration
  - 20 of 51 subjects (39%) were treated exclusively prophylactically for ≥ 50 EDs

Figure 1. Flowchart of the study



Results

In total there were >7'000 EDs with octanate®, with a mean of 139 EDs per patient. Patients were followed for a mean of 2.8 years (1'024 days or 34 months). A summary is presented in Table 1.

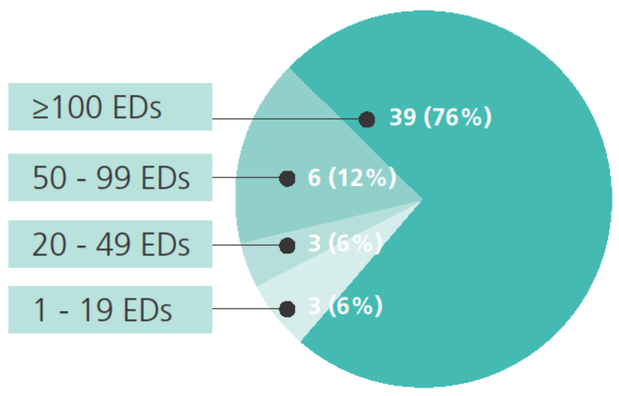
Table 1. Demographics, observation period, exposure days, and mutation analysis

Patients (n)	51
Population	
Caucasians	51
FVIII:C < 1 % (n)	48
FVIII:C 1 – 2 % (n)	3
Median age at first substitution (years)	0.99, range: 0.01 - 5.61
Family history of inhibitors to FVIII	3
Exposure	
Observation period, mean / patient (days)	1'024, range: 136 - 2'387
Exposure days (total)	>7'000
Exposure days (mean / patient)	139, range: 1 - 117 excluding ITI
Mutation analysis*	
Intron 22 inversion (n)	27
Large deletion (n)	5
Other mutation (n)	18

* n = 50

- Out of 51 patients, 48 had 20 or more EDs and 45 had 50 or more EDs to octanate® as illustrated in Figure 2.

Figure 2. Overview of the number of patients and their exposure days to octanate®



- Five out of 51 patients (9.8%) developed inhibitors. Three patients (6%) developed a clinically relevant inhibitor (defined during analyses as persistent over time without spontaneous resolution) over the course of the study. Another two subjects (4%) displayed inhibitors that disappeared spontaneously with continued on-demand therapy with octanate® (without dose change).
- The overall inhibitor incidence in 45 patients with at least 50 EDs, is 11% (5/45). Additional details on the inhibitor patients are shown in Tables 2 and 3. One transient inhibitor gradually disappeared over the course of 3 years of on-demand treatment, and the other over the course of 2 months (Table 3). All inhibitors developed before ED 50 after on-demand treatment. All inhibitor subjects were found to have large *F8* gene defects, either intron 22 inversions or large deletions.

Table 2. Characteristics of subjects who developed a clinically relevant FVIII inhibitor (n=3)

Subject	1	2	3*
Type of inhibitor	High responding	High responding	High responding
EDs prior to detection	6	3	
Treatment regimen	On-demand	On-demand	Prophylactic
Genetic analysis	Large deletion of exons 7 - 12	Intron 22 inversion	Intron 22 inversion
Family history of inhibitors	No	Yes	No
Inhibitor development	High responder (> 5 BU)	High responder (> 5 BU)	High responder (> 5 BU)
Max. inhibitor titre (BU)	328.0	445.0	

* No more information available for the new inhibitor patient, yet.

Table 3. Characteristics of subjects who developed a transient FVIII inhibitor (n=2)

Subject	1	2
Type of inhibitor	Transient	Transient
EDs prior to detection	19	48
Treatment regimen	On-demand	On-demand
Genetic analysis	Intron 22 inversion	Intron 22 inversion
Family history of inhibitors	No	Yes
Inhibitor development	High responder (> 5 BU)	Low responder (< 5 BU)
Max. inhibitor titre (BU)	7.0	2.1

Conclusions

- Appearance of inhibitors in severe haemophilia A is the most serious complication. Inhibitors occur mainly within the first 50 EDs.[1] The effect of product type on inhibitor development is the subject of heated debates.[2-7]
- The study with octanate® is a prospective Good Clinical Practice (GCP) trial in PUPs suffering from severe hemophilia A, unselected with regard to characteristics associated with inhibitors.
- 5 out of 51 patients (9.8%) developed inhibitors. Three patients (6%) developed clinically relevant (symptomatic) inhibitors. Another two cases (4%) were transient inhibitors that resolved without any change in the octanate® administration regimen.
- The current overall inhibitor rate in patients with ≥ 50 EDs, including the two transient inhibitors, is 11% (5/45).
- All inhibitors developed within the first 50 EDs after on-demand treatment. No inhibitors were reported in patients undergoing prophylaxis.
- The incidence of inhibitors in our interim analysis is low compared with the literature, which reports incidences as high as 37%.[7]

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