
SYNOPSIS OF FINAL REPORT

TITLE OF THE STUDY:	CATHFLO® ACTIVASE® (ALTEPLASE) PEDIATRIC STUDY (CAPS)
SPONSOR:	Genentech, Inc.
INDICATION:	Restoring function to dysfunctional central venous access devices (CVADs) in pediatric subjects 2–16 years old and <2 years old
INVESTIGATORS:	Forty-two investigators participated in the study (for a listing of investigators, see Appendix A).
STUDY CENTERS:	The study was conducted at 42 investigational sites (see Appendix A).
PUBLICATIONS:	No publications have resulted from this study.
STUDY DESIGN:	<p>This was a Phase IV, open-label, single-arm, multicenter trial that was to be conducted at ~60 sites in the United States. Approximately 300 pediatric subjects with dysfunctional CVADs (including catheters with valves, multiple lumens, umbilical catheters, and implanted ports) were to be treated with up to two serially instilled doses of Cathflo Activase.</p> <p>Subjects weighing ≥ 30 kg were to receive 2-mL instillations of Cathflo Activase within the catheter lumen, and subjects weighing < 30 kg were to receive instillations of Cathflo Activase equal to 110% of the estimated internal lumen volume of the dysfunctional CVAD (dose rounded to the nearest 0.1 mL, not to have exceeded 2 mL).</p> <p>For subjects weighing ≥ 10 kg, catheter dysfunction was defined as the inability to withdraw 3 mL of blood. For subjects weighing < 10 kg, catheter dysfunction was defined as the inability to withdraw 1 mL of blood.</p> <p>Subjects were treated with up to two serially instilled doses of Cathflo Activase, each with a dwell time of up to 120 minutes. Assessment of CVAD function occurred at 30 minutes after administration of each dose. If function was not restored at 30 minutes, another assessment of function occurred at 120 minutes. CVAD function was assessed by first attempting aspiration of blood and, if successful, attempting infusion of normal saline solution. Subjects exited the treatment algorithm when restoration of CVAD function was established or following assessment of CVAD function after the 120-minute dwell time for the second instillation, whichever occurred first.</p> <p>Assessment of safety had two components. All serious adverse events were to be recorded during the treatment period. Additionally, all serious adverse events were to be elicited from all subjects or subjects' representatives either by telephone or in person at 48 hours following completion of the treatment algorithm. Per the protocol, the posttreatment contact for the assessment of safety events was targeted to occur at 48 hours, but could occur up to 96 hours following completion of the treatment algorithm. Serious adverse events of specific interest included intracranial hemorrhage (ICH), major hemorrhage, thrombosis, embolic events, sepsis, and catheter-related complications. Non-serious adverse events were not to be recorded.</p>

OBJECTIVES:	<p>The primary objective of this study was to evaluate the safety, as measured by the incidence of intracranial hemorrhage (ICH) during the treatment period and within 48 hours following completion of treatment with Cathflo Activase, in restoring function to dysfunctional CVADs in two pediatric populations: subjects 2–16 years of age and subjects < 2 years of age.</p> <p>The secondary objectives of this study were to estimate the rate of restoration of function to dysfunctional CVADs at 30 and 120 minutes following administration of up to two instillations of Cathflo Activase and to determine the rate of the following specific serious adverse events that occurred within 48 hours of treatment: major hemorrhage, thrombosis, embolic events, sepsis, catheter-related complications, or any other serious adverse events.</p>
CLINICAL PHASE:	IV
PERIOD OF STUDY:	Initiation: 22 April 2002 Completion: 28 May 2003
NO. OF SUBJECTS:	The planned enrollment was 300 subjects; 321 subjects were enrolled, of whom 310 received Cathflo Activase.
DEMOGRAPHIC DATA:	The composition of safety-evaluable subjects was 56.1% male and 43.9% female, and the majority of subjects were White (70.3%). The mean age was 7.2 years (range, 0.04–18.3 years). The mean weight of subjects was 30.3 kg (range, 2.2–107.0 kg).
REFERENCE DRUG:	Cathflo Activase (alteplase)
CRITERIA FOR EVALUATION:	As specified in the protocol, safety and efficacy analyses were based on all enrolled subjects who received treatment with Cathflo Activase (safety-evaluable population). Subjects who received at least one complete or partial instillation of Cathflo Activase were considered as treated. Supplemental per-protocol efficacy analyses were also performed based on the subset of enrolled and treated subjects without major protocol deviations (efficacy-evaluable population).
PROCEDURES:	<p>Following the first instillation of Cathflo Activase, CVADs were to remain undisturbed for 30 minutes (\pm 10 minutes), at which time an assessment of function was performed. CVADs in which function was not restored at the 30-minute posttreatment assessment were to remain undisturbed for an additional 90 minutes (for a total posttreatment dwell time of 120 minutes [\pm 10 minutes]), at which time an assessment of function was again performed. Restoration of CVAD function following Cathflo Activase administration was defined as successful withdrawal and infusion function.</p> <p>CVADs remaining dysfunctional after a single administration of Cathflo Activase were to be treated subsequently with a second instillation of Cathflo Activase; the second instillation was to be administered within 10 minutes following the 120-minute assessment for the first instillation. Assessment of CVAD function was repeated after a 30-minute (\pm 10 minutes) dwell time and, possibly, after a 120-minute (\pm 10 minutes) dwell time. Subjects were to exit the treatment algorithm when restoration of CVAD function was established or following assessment of CVAD function after the 120-minute dwell time for the second Cathflo Activase administration, whichever occurred first.</p>

STATISTICAL METHODS:

Safety was assessed by collecting and analyzing specific serious adverse events elicited at the posttreatment assessment contact (see Section 4.5.3), as well as any additional serious adverse events spontaneously reported during the treatment and follow-up periods. Non-serious adverse events were not to be recorded for this study.

For the primary efficacy endpoint (cumulative restoration rate of CVAD function following up to two instillations of Cathflo Activase, each with up to a 120-minute dwell time) and for each of the secondary and other efficacy endpoints (restoration rate at 30 minutes following the first instillation, cumulative and incremental restoration rates at 120 minutes following the first instillation, cumulative and incremental restoration rates at 30 minutes following the second instillation, and incremental restoration rate at 120 minutes following the second instillation), the restoration rate was calculated and a 95% confidence interval (CI) is provided for the safety-evaluable population. The 95% CI for restoration rate was calculated using exact methods. The event rates and corresponding exact 95% CIs were also calculated for the two subgroups: subjects < 2 years old and subjects ≥ 2 years old.

PATIENT POPULATION: Pediatric subjects with dysfunctional CVADs

SAFETY RESULTS:

No subjects died during the treatment or follow-up study periods (95% CI: 0.0%, 1.2%). One subject who experienced two serious adverse events, both assessed by the investigator as related to the underlying disease and concurrent medication rather than study drug, is known to have died 15 days following treatment with Cathflo Activase and 13 days following completion of the study.

A total of 8 subjects (2.6%) experienced at least one serious adverse event during the study: 1 subject in the <2 year age stratum (1.8%) and 7 subjects in the ≥2 year age stratum (2.7%). Of the 8 subjects, 1 subject experienced two serious adverse events and the remaining 7 subjects experienced one serious adverse event each.

Overall, sepsis was the most frequent serious adverse event, with three cases reported (1.0%). Of the three sepsis cases, one case was suspected by the investigator to be caused by the study drug.

Of the nine total serious adverse events reported, only two events were suspected by the investigators to be caused by study drug; one case of sepsis mentioned above and one case of a burst catheter lumen with infusion of the Cathflo Activase dose. One subject (0.3%) was discontinued from the treatment algorithm because of a serious adverse event (burst catheter lumen).

EFFICACY RESULTS:

The primary efficacy outcome measure was the overall (cumulative) rate of restoration of CVAD function following serial administration of up to two instillations of Cathflo Activase, each followed by up to a 120-minute dwell time. Overall, the proportion of subjects with restored CVAD function was 82.9% (257 of 310 subjects) (see table). Restored CVAD function was achieved in 80.0% of the subjects (44 of 55) aged < 2 years and in 83.5% of the subjects (213 of 255) aged ≥ 2 years.

EFFICACY RESULTS (cont'd):

Cumulative Restoration Rates of CVAD Function
at the End of Treatment : Safety-Evaluable Subjects

	Age < 2 Yr (n=55)	Age ≥ 2 Yr (n=255)	Total (n=310)
Restored function ^a	44 (80.0%)	213 (83.5%)	257 (82.9%)
95% CI	(67.0%, 89.6%)	(78.4%, 87.9%)	(78.2%, 86.9%)

Source: Appendix C, Table 21.

Note: Following administration of up to two instillations of Cathflo Activase, each with a dwell time of up to 120 minutes.

^a Presented as number (percentage) of subjects.

Overall, restoration of CVAD function was achieved for 53.5% of subjects after the first instillation of Cathflo Activase with a 30-minute dwell time, increasing to 75.2% of subjects with a 120-minute dwell time. Following up to a second dose of Cathflo Activase, restoration of CVAD function was achieved for 80.3% of subjects after a 30-minute dwell time and 82.9% of subjects after up to a 120-minute dwell time.

Exploratory analyses examining the incremental and cumulative rates of restored CVAD function for each assessment timepoint by subgroup are presented in Section 5.4.3. In addition, supplemental efficacy analyses examining the rate of restored CVAD function for each assessment timepoint are presented for the efficacy-evaluable subjects in Section 5.4.3.

CONCLUSIONS:

This study demonstrates that serial administration of up to two instillations of Cathflo Activase, each followed by up to a 120-minute dwell time, is safe and effective for restoration of catheter function in pediatric subjects with occluded central venous access devices.

Date of Report:

2 March 2004
