Safety, pharmacokinetics and pharmacodynamics of PF-05280602 (recombinant FVIIa variant): results from a single ascending dose phase I study in hemophilia A and B subjects

Ralph Gruppo MD,[1] *Daniel Malan MD,*[2] *Judit Kapocsi MD,*[3] *Charles Hay MD,*[4] *Lisa Boggio MD,*[5] *Pratima Chowdary MD,*[6] *Giuseppe Tagariello MD,*[7] *Annette von Drygalski MD,*[8] *Fei Hua PhD,*[9] *Matthew Scaramozza MA,*[9] *Harry Shi MA*[9] *and Steven Arkin MD*[9]

[1]*Cincinnati Children's Hospital Medical Center,* [2]*Phoenix Pharma Pty Ltd,* [3]*Semmelweis University 1st Department of Medicine,* [4]*Manchester Royal Infirmary,* [5]*Rush University Medical Center, HTC,* [6]KD Haemophilia Centre and Thrombosis Unit, Royal Free Hospital London, [7]*Castelfranco Veneto Hospital,* [8]*Univ California San Diego,* [9]*BioTherapeutics Clinical Research, Rare Disease Research Unit, Pfizer Inc, Cambridge, MA, USA (This study was sponsored by Pfizer)*

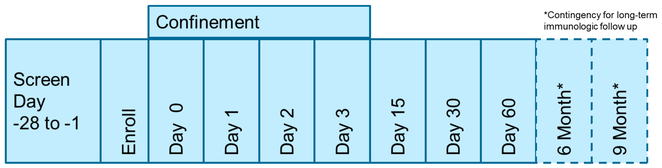
BACKGROUND

- PF-05280602 (also known as CB813d) is a variant of activated recombinant human factor VII (FVIIa) in development for treatment and prophylaxis to prevent bleeding episodes in hemophilia patients with inhibitors to factor VIII or factor IX.
- In hemophilic dogs it is characterized by a relative potency advantage and at equipotent doses, a longer duration of pharmacodynamic effect relative to wild type FVIIa/eptacog alfa (1).
- The purpose of this first in human phase I study was to investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose intravenous bolus of PF-05280602 in non-bleeding hemophilia subjects.

METHODS

- **Study Design**
  - Ascending single dose cohorts (4.5, 9, 18, or 30 µg/kg of PF- 05280602)
  - Open label multicenter study, no placebo
  - Washout of all hemostatic treatments 72-96 hours prior to dosing in the non-bleeding state
  - Enrollment pause after first subject at 4.5 and 9.0 µg/kg and after each of the first three subjects at 18 and 30 µg/kg dose levels
  - Dose escalations based on sponsor and external Data Monitoring Committee (eDMC) review of safety, PK/PD data through post treatment day 15. Abnormal findings meeting protocol-defined quantitative stopping rules required additional clinical assessment. Two or more treatment emergent clinically significant events in a given dose group would trigger a stop in dose escalation.

Figure 1. Study Schedule & Cohort Assignment (protocol amendment 3)



Dosage µg/kg	N
4.5	6
9.0	6
18.0	6
30.0	6

- Key eligibility criteria: severe hemophilia A or B male patients (factor activity level ≤1%), with or without inhibitors, aged 18-65 years
- Surveillance for antibody immune response at baseline and day 15, 30 and 60 post treatment:
  - Assay for anti-drug (anti-PF-05280602) antibody was performed (any positive assay would be further characterized for titer).
  - Assay for inhibitors to PF-05280602
    - ❖ Any specimen positive for inhibitor to PF-05280602 to be tested for inhibitor to NovoSeven®RT and FVII

RESULTS

- 25 subjects received at least 1 dose of PF-05280602. Prior to protocol amendment 3, one subject was treated at the 0.5 µg/kg dose level. Under amendment 3, six subjects each were assigned to the 4.5, 9, 18, and 30 µg/kg groups. All subjects were male. 4/25 subjects had hemophilia B (factor IX activity ≤ 1%).
- 8 subjects had a prior history of inhibitor to either FVIII or FIX replacement therapy (32%)
- 5 subjects (20%) had prior exposure to eptacog alfa (FVIIa)

Table 1: Subject Demography and Hemophilia History

Demography	0.5 µg/kg	4.5 µg/kg	9 µg/kg	18 µg/kg	30 µg/kg
Sex	1 male	6 males	6 males	6 males	6 males
Race	1 white	5 white; 1 black	4 white; 2 other	4 white; 2 black	3 white; 3 black
Age (18-44)	0	5 subjects	4 subjects	5 subjects	4 subjects
Age (45-64)	1	1 subject	2 subjects	1 subject	2 subjects
Mean Weight (range)	72.3 kg	74.7 (62-90) kg	78.2 (66-95) kg	78.9 (60-95) kg	72.7 (62-83) kg
Mean BMI (range)	23.3 kg/m^2	24.6 (18.5-30.2) kg/m^2	25.0 (22.0-29.7) kg/m^2	25.2 (18.9-27.2) kg/m^2	24.4 (19.5-28.7) kg/m^2
Hemophilia History	**0.5 µg/kg**	**4.5 µg/kg**	**9 µg/kg**	**18 µg/kg**	**30 µg/kg**
Number of subjects with inhibitor history	1	0	2	3	2
Number of subjects with prior exposure to FVIIa (NovoSeven)	1	0	2	1	1

Please scan this QR code with your smartphone app to view an electronic version of this poster. If you do not have access to a smartphone, please access this poster via the following link: http://congress-download.pfizer.com/isth2015_isth_benefix_gruppo_r_xxx.html

- Protocol stopping rules for dose escalation were not triggered at any dose level. *Treatment Emergent Adverse Events (TEAEs) (any adverse event occurring after dosing with study drug) are presented as non-hemophilia related TEAEs (Table 2) and hemophilia related TEAEs (Table 3). All TEAEs were mild or moderate in severity. There were no treatment emergent serious adverse events (SAEs). No adverse events lead to study discontinuation. Events deemed related/possibly related to study drug included: 1 mild event of blood creatinine increased and 1 mild event of blood urea increased (both occurred in the same subject), 1 mild event of dizziness, 1 mild event of tinnitus, 1 mild event of dysgeusia. There was no evidence of antibody immune or inhibitor response to treatment with PF-05280602 at Days 15, 30 or 60 of the study.
- ≤1 similar clinically significant laboratory abnormality occurred at any respective dose level. Post treatment lab abnormalities included 1 subject with elevated serum creatinine (reported as an adverse event in Table 2 and listed above), 2 subjects with elevated non-fasting blood glucose (in different dose groups), 1 subject with elevated potassium, 1 subject with elevated fibrinogen, and 1 subject with elevated d-dimer on study day 15 with a normal baseline value.
- ≤1 similar vital sign abnormality occurred at any respective dose level. There were 5 subjects with post-treatment vital sign fluctuations (change from baseline of ≥ 30 mmHg systolic or ≥ 20 mmHg diastolic blood pressure). These values were deemed not clinically significant by the study investigators.

Table 2: Non-hemophilia Related Treatment Emergent Adverse Events

MedDRA Preferred AE Term	PF-05280602 0.5 µg/kg (n=1)	PF-05280602 4.5 µg/kg (n=6)	PF-05280602 9 µg/kg (n=6)	PF-05280602 18 µg/kg (n=6)	PF-05280602 30 µg/kg (n=6)
Diarrhea	1	0	0	0	0
Nasopharyngitis	1	0	0	0	0
Prurigo	1	0	0	0	0
Abdominal pain	0	0	1	0	0
Anxiety	0	1	0	0	0
Arthralgia	0	0	0	1	0
Blood creatinine increased	0	1	0	0	0
Blood glucose increased	0	0	1	0	0
Blood urea increased	0	1	0	0	0
Chills	0	0	0	1	0
Contusion	0	1	0	0	0
Cough	0	0	0	1	0
Dizziness	0	1	1	0	0
Dysgeusia	0	0	1	0	0
Dyspnoea	0	0	0	1	0
Hematoma	0	0	1	0	1
Headache	0	0	1	1	0
Influenza-like illness	0	0	0	0	1
Nausea	0	0	1	0	0
Oropharyngeal pain	0	0	1	1	0
Pain	0	0	0	1	0
Peripheral swelling	0	1	0	0	0
Pyrexia	0	0	0	1	0
Tinnitus	0	0	1	0	0
Upper respiratory tract infection	0	0	0	1	0
Visual impairment	0	1	0	0	0
Vomiting	0	0	1	0	0

Table 3: Hemophilia Related Treatment Emergent Adverse Events

MedDRA Preferred AE Term	PF-05280602 0.5 µg/kg (n=1)	PF-05280602 4.5 µg/kg (n=6)	PF-05280602 9 µg/kg (n=6)	PF-05280602 18 µg/kg (n=6)	PF-05280602 30 µg/kg (n=6)
Arthralgia	1	1	1	0	0
Flank pain	1	0	0	0	0
Joint swelling	0	0	1	0	1
Muscle swelling	0	0	0	0	1

Figure 2: Summary of PK Parameters

Summary of the Pharmacokinetic Parameters of PF-05280602 after Single Dose IV Bolus Administration

Dose (µg/kg)	[a]N,n	T_{max} (hr)	C_{max} (ng/mL)	AUC_{inf} (ng·hr/mL)	$t_{1/2}$ (hr)	CL (mL/hr/kg)	Vss (mL/kg)
4.5	6,6	0.167 (0.0830-0.200)	86.25 (22)	303.3 (14)	3.533 (16)	15.17 (16)	122.1 (31)
9.0	6,6	0.242 (0.117-0.367)	188.7 (26)	650.0 (20)	3.637 (22)	14.48 (21)	82.63 (26)
18.0	6,6	0.142 (0.0830-0.333)	500.5 (14)	1580 (18)	3.303 (19)	11.67 (20)	57.50 (19)
30.0	6,6	0.150 (0.0830-0.333)	833.5 (25)	2905 (34)	3.580 (16)	11.27 (26)	57.15 (31)

Arithmetic mean (%CV) for all the parameters except median (range) for T_{max}
[a]N= total number of subjects in the treatment group, n=Number of subjects contributing to the summary statistics . Vss = volume of distribution at steady state

*Note: Treatment Emergent Adverse Event (TEAE): any adverse event occurring after dosing with study drug

- Both clearance and volume of distribution appear to decrease across the 3 lower doses (4.5 to 18 µg/kg), but then remained similar from 18 to 30 µg/kg dose level. The terminal half-life of PF-05280602 was similar across all dose groups (~3.5 hours).
- Transient and dose-dependent shortening of activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin generation assay (TGA) lag time and dose-dependent increase of TGA peak, TGA ETP, prothrombin fragments 1+2 (PF1+2) and thrombin-antithrombin (TAT) complexes were observed.

Figure 3: Pharmacokinetic Profile of PF-05280602

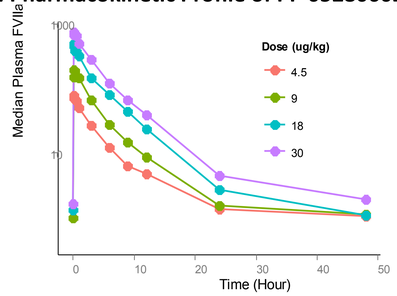
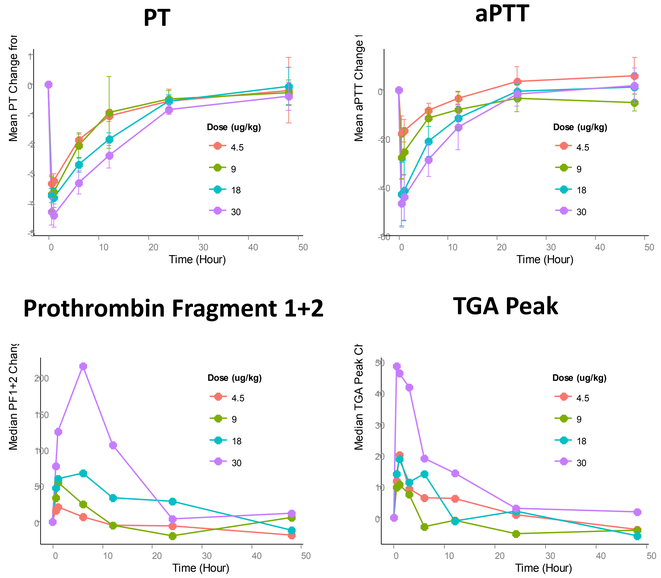


Figure 4: Pharmacodynamic Changes with PF-05280602



PK and PD data are not shown for the 0.5 µg/kg group as only 1 subject was enrolled.

CONCLUSIONS

- Single doses up to 30 µg/kg were well tolerated when administered to hemophilia A and B patients in the non-bleeding state.
- There were no instances of antibody immune response or thrombosis
- The terminal half-life of PF-05280602 was approximately 3.5 hours and was similar across all dose groups.
- Pharmacodynamic effects were observed with dose-dependent changes of PT, aPTT, PF1+2 and TGA
- The results for safety and pharmacologic activity support further clinical development of PF-05280602 for treatment of individuals with hemophilia and inhibitors to FVIII or FIX.

Reference: Pitman et. al. Blood, Nov 2011; 118: 2252 abstract