CLINICAL PHARMACOLOGY BLA REVIEW

Division of Clinical Evaluation and Pharmacology/Toxicology Branch
Office of Tissues & Advance Therapies (OTAT)

STN 125612
Sponsor: Octapharma
Product: Human Fibrinogen (Fibryna)
Indication: For the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients
Submission Date: June 9, 2016
Reviewer: Iftekhar Mahmood, Ph. D.
RPM: Thomas Maruna
Through: Lei Xu, M. D.

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INTRODUCTION

FIBRYNA is a human plasma-derived, sterile, purified, virus inactivated and nanofiltered (20 nm) fibrinogen concentrate. FIBRYNA is supplied as a lyophilized powder for reconstitution for intravenous injection. FIBRYNA contains no preservative. The diluent for reconstitution of the lyophilized powder is water for injection. Each bottle contains 20 mg/mL fibrinogen. (b) (4) of FIBRYNA is (b) (4) of total protein.

All units of human plasma used in the manufacture of FIBRYNA are provided by FDA-approved blood establishments, and are tested by FDA-licensed serological tests for HBsAg, antibodies to HCV and HIV and Nucleic Acid Test (NAT) for HCV and HIV-1 and found to be non-reactive (negative).

The FIBRYNA manufacturing process has the capability to inactivate/remove viruses by a solvent/detergent (S/D) virus inactivation step and a virus removal nanofiltration step. These steps have been validated independently in a series of *in vitro* experiments for their capacity to inactivate and/or remove both enveloped and non-enveloped viruses.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12.1 Mechanism of Action

Fibrinogen (factor I) is a soluble plasma protein that, during the coagulation process, is converted to fibrin, one of the key components of the blood clot. Fibrinogen is a heterohexamer with a molecular weight of 340 kDa and composed of ~~two sets of~~ *alpha*, *beta*, and *gamma* polypeptide chains.

Following coagulation activation and thrombin generation, fibrinogen is cleaved by thrombin at specific sites on the *alpha* and *beta* chains to remove fibrinopeptide A (FPA) and fibrinopeptide B (FPB). The removal of FPA and FPB exposes binding sites on the fibrinogen molecule and leads to the formation of fibrin monomers that subsequently undergo polymerization. The resulting fibrin is stabilized by activated factor XIII. Factor XIIIa acts on fibrin to form cross links between fibrin polymers and renders the fibrin clot more resistant to fibrinolysis. The end product of the coagulation cascade is cross-linked fibrin which stabilizes the primary platelet plug and achieves secondary hemostasis.

12.2 Pharmacodynamics

Administration of FIBRYNA to patients with congenital fibrinogen deficiency replaces the missing, or low coagulation factor. Normal plasma level is in the range of 2 - 4.5 g/L.

1.3 Pharmacokinetics

An open label, prospective, randomized, controlled, two-arm cross-over study was conducted in 22 patients with congenital fibrinogen deficiency (afibrinogenemia), ranging in age from 12 to 53 years (6 adolescents, 16 adults). ~~In this cross-over study, these results were compared to the same parameters of another fibrinogen concentrate available on the US market in the same subjects.~~ Each subject received a single intravenous 70 mg/kg dose of FIBRYNA. ~~and the comparator product.~~ Blood samples were drawn from the patients to determine the fibrinogen activity at baseline and up to 14 days after the infusion. The pharmacokinetic parameters of FIBRYNA are summarized in Table 2.

~~No statistically relevant difference was observed between males and females for fibrinogen activity. In the per protocol analysis , subjects less than 18 years of age (n=5) had small differences including a shorter half-life than in adults. The number of subjects less than 18 years of age in this study limits statistical interpretations.~~

The incremental *in vivo* recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was 1.8 mg/dL (range 1.08 – 2.62 mg/dL) increase per mg/kg. The median *in vivo* recovery indicates that a dose of 70 mg/kg will increase patients' fibrinogen plasma concentration by approximately 125 mg/dL.

Table 2: Pharmacokinetic Parameters (n=21) for Fibrinogen Activity

Parameters	**Mean ± SD (range)**
Half-life [hr]	75.9± 23.8 (40.0-157.0)
Cmax [mg/dL]	139.0 ± 36.9 (83.0-216.0)
AUC_{norm} for dose of 70 mg/kg [mg*hr/mL]	113.7± 31.5 (59.7-175.5)
Clearance [mL/hr/kg]	0.67 ± 0.2 (0.4-1.2)
Mean residence time [hr]	106.3 ± 30.9 (58.7-205.5)
Volume of distribution at steady state [mL/kg]	70.2 ± 29.9 (36.9-149.1)

C_{max} = maximum plasma concentration; AUC_{norm} = area under the curve normalized to the dose administered; SD = standard deviation

RECOMMENDATION

The pharmacokinetic study design and results are acceptable. The applicant should modify the clinical pharmacology labeling as suggested by the FDA.

Study #1

Title of Study: A prospective, controlled, randomized, crossover study investigating the pharmacokinetic properties, surrogate efficacy and safety of Octafibrin compared to Haemocomplettan P/RiaSTAPTM in patients with congenital fibrinogen deficiency (FORMA-01).

The objectives of the study were as follows:

- To determine the single-dose pharmacokinetic (PK) profile of Octafibrin and Haemocomplettan® P/RiaSTAPTM in patients with congenital fibrinogen deficiency.
- To determine maximum clot firmness (MCF) as a surrogate marker for haemostatic efficacy before and after administration of Octafibrin and Haemocomplettan® P/RiaSTAPTM in patients with congenital fibrinogen deficiency.
- To assess the safety of Octafibrin in patients with congenital fibrinogen deficiency.

This was a multinational, multicenter, prospective, randomized, controlled, crossover phase II PK study in 22 patients with congenital fibrinogen deficiency. PK of Octafibrin and Haemocomplettan® P/RiaSTAPTM was determined in a crossover design. MCF was assessed as a surrogate marker of efficacy. Safety was monitored throughout the study. In total 27 patients were screened and 22 patients were treated in the study. All 22 treated patients completed the study. The eligible patients were ≥12 years of age and had documented congenital fibrinogen deficiency (afibrinogenaemia) (plasma fibrinogen activity and antigen at screening below detection limit (<20 mg/dL)). There were 6 subjects between 12 and 18 years of age and 16 subjects >18 years of age (18-53 years). There were 7 males and 15 females in the study. There were 14 Caucasians and 8 Asian in the study.

This study consisted of two periods. Each study period lasted 45 days. Patients were randomized to receive a single infusion of either Octafibrin or Haemocomplettan® P/RiaSTAPTM in the two study periods. The reference therapy in this study was Haemocomplettan® P/RiaSTAPTM, which is a marketed fibrinogen concentrate. Octafibrin was administered at a dose of 70 mg/kg body weight (based on the labeled potency) as an intravenous bolus injection at a maximum rate of 5 mL/min.

Blood samples for PK analyses were taken at the following time points: at baseline, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 312 hours post infusion. A washout period of at least 14 days was required prior to the administration of Octafibrin or Haemocomplettan® P/RiaSTAPTM. Fibrinogen activity for PK analysis was measured by validated (b) (4) assay (fibrinogen activity) and fibrinogen (b) (4) . The (b) (4) assay used in this study was modified and validated in the central laboratory to be able to achieve a limit of quantification (LOQ) of (b) (4)).

For the comparison of PK parameters of Octafibrin and Haemocomplettan®P/RiaSTAPTM, the 90% confidence intervals (CIs) for the ratio of Octafibrin over Haemocomplettan® P/RiaSTAPTM were calculated. In addition, a statistical crossover analysis of variance (ANOVA) was performed to test whether the 90% CI for the ratio of mean AUC was within 80% to 125% bioequivalence range.

The PK parameters of Octafibrin and Haemocomplettan are summarized in Table 1. The concentration-time profile of Octafibrin or Haemocomplettan are shown in Figure 1.

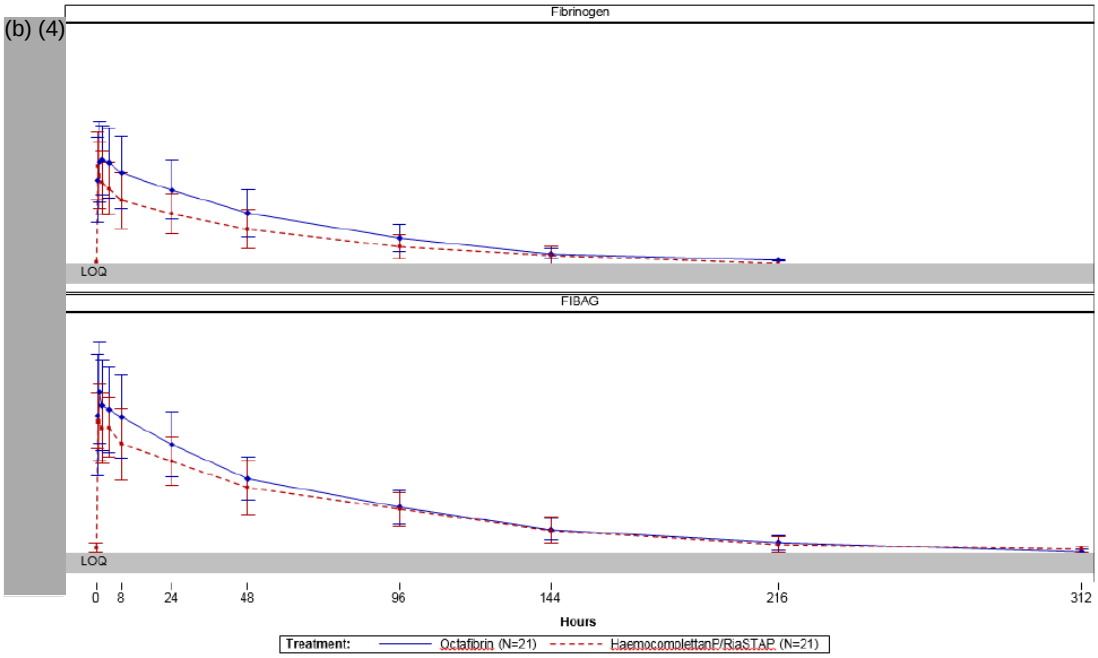
Table 1: PK Parameters for Octafibrin or Haemocomplettan® P/RiaSTAPTM (Fibrinogen Activity)

Parameter Treatment	Mean	SD	Median	Range
C_{max}, g/L				
Octafibrin	1.390	0.369	1.360	0.83–2.16
Haemocomplettan® P/RiaSTAP™	1.265	0.309	1.200	0.85–1.99
$C_{maxnorm}$, kg·g/L/mg				
Octafibrin	0.018	0.005	0.018	0.01–0.03
Haemocomplettan® P/RiaSTAP™	0.018	0.005	0.017	0.01–0.03
C_{max}, standardised to 70 mg/kg (g·h/L)				
Octafibrin	1.266	0.338	1.236	0.75–1.96
Haemocomplettan® P/RiaSTAP™	1.271	0.312	1.217	0.85–1.99
Incremental IVR, mg/dL/(mg/kg)				
Octafibrin	1.787	0.458	1.766	1.08–2.62
Haemocomplettan® P/RiaSTAP™	1.770	0.442	1.700	1.21–2.84
Classical IVR, %				
Octafibrin	64.397	11.519	64.830	40.89–88.13
Haemocomplettan® P/RiaSTAP™	66.046	11.635	66.756	50.17–92.46
T_{max}, h				
Octafibrin	2.148	1.475	2.000	0.50–4.08
Haemocomplettan® P/RiaSTAP™	1.417	2.054	0.500	0.45–8.00
$T_{1/2}$, h				
Octafibrin	75.940	23.831	72.854	40.03–156.96
Haemocomplettan® P/RiaSTAP™	69.378	16.006	64.644	48.60–101.94
MRT, h				
Octafibrin	106.272	30.927	98.975	58.72–205.47
Haemocomplettan® P/RiaSTAP™	98.977	20.812	93.462	72.38–141.21
CL, mL/h/kg				
Octafibrin	0.665	0.197	0.630	0.40–1.17
Haemocomplettan® P/RiaSTAP™	0.804	0.255	0.804	0.41–1.31
V_{ss}, mL/kg				
Octafibrin	70.158	29.860	61.037	36.89–149.11
Haemocomplettan® P/RiaSTAP™	76.631	19.579	77.701	47.89–113.68

C_{max} = maximum plasma concentration; $C_{maxnorm}$ = maximum plasma concentration normalised to the dose administered; CL = clearance; IVR = in vivo recovery; MRT = mean residence time; PK = pharmacokinetics; PP = per-protocol; SD = standard deviation; $T_{1/2}$ = half-life; T_{max} = time to reach maximum plasma concentration; V_{ss} = volume of distribution at steady state.

The half-life of octafibrin was about 7 hours longer and clearance was 17% slower than haemocomplettan.

Figure 1: Mean (+/-SD) fibrinogen concentration for Octafibrin and Haemocomplettan®P/RiaSTAP.



Upper panel: fibrinogen activity according to the (b) (4) method. Lower panel: (b) (4)

In Tables 2 and 3, confidence interval (CI) on AUC values is shown. The CI values on both AUCs indicate that octafibrin and haemocomplettan are not bioequivalent (CIs are the outside the acceptable range of 80 to 125%). However, in order to proceed with the development of octafibrin, it is not necessary that these two products be equivalent.

Table 2: AUC and AUCnorm (Fibrinogen Activity) for octafibrin and haemocomplettan

Parameter	Concentrate	Mean	SD	Median	Range
$AUC_{0\text{-inf}}$, g·h/L					
	Octafibrin	124.84	34.58	119.40	65.74–193.32
	Haemocomplettan® P/RiaSTAP™	95.97	32.72	87.03	53.42–171.84
AUC_{norm}, h·kg·g/L/mg					
	Octafibrin	1.62	0.45	1.59	0.85–2.51
	Haemocomplettan® P/RiaSTAP™	1.38	0.47	1.24	0.76–2.46

AUC = area under the curve; AUC_{norm} = area under the curve normalised to the dose administered

Table 3: Ratios of octafibrin Relative to haemocomplettan for AUC and AUCnorm Based on Fibrinogen Activity

Parameter Ratio	Mean*	90% CI of Mean* Ratio	p-value†
AUC	1.319	1.232, 1.413	<0.0001
AUC_{norm}	1.196	1.117, 1.281	0.0002

* Geometric mean derived from the ANOVA model on log transformed values.
† p-values for treatment effect from the ANOVA type 3 tests of fixed effects.
ANOVA = analysis of variance; AUC = area under the curve; AUC_{norm} = area under the curve normalised to the dose administered; CI = confidence interval; PK = pharmacokinetic; PP = per-protocol.

The PK of octafibrin was not different between adults and adolescents. The half-life of octafibrin in adolescents was 72.8 ± 16.5 hr as compared to 76.9 ± 26.1 hr for the adults. The clearance was similar in both age groups, 0.68 ± 0.18 and 0.66 ± 0.21 mL/hr per kg respectively.

Pharmacodynamics

Maximum Clot Firmness (MCF):

Thromboelastography (TEG) using rotational thromboelastometry (ROTEM®) was used to measure MCF (surrogate marker of efficacy) at baseline and 1 hour after administration of octafibrin or haemocomplettan. Both treatments resulted in significant increases from baseline in MCF. The mean increase in 1-hour MCF after octafibrin administration from baseline (all with MCF of 0) was 9.7 mm and the mean increase after haemocomplettan administration was 10.00 mm. (Table 4).

Table 4: MCF at Baseline and 1 Hour after Infusion by Treatment Group

	MCF at Baseline (mm)	MCF at 1 hour (mm)	Change in MCF from Baseline to 1 hour (mm)	
Concentrate	Mean ± SD Median (range)	Mean ± SD Median (range)	95% CI	p-value*
Octafibrin	0 ± 0 0 (0–0)	9.68 ± 2.950 10.00 (4.0–16.0)	8.37, 10.99	<0.0001
Haemocomplettan® P/ RiaSTAP™	0 ± 0 0 (0–0)	10.00 ± 4.353 10.50 (0.0–17.0)	8.07, 11.93	<0.0001

* Two-sided p-value was calculated at 5% level of significance by using paired t-test for comparison.
CI = confidence interval; FAS = full analysis set; MCF = maximum clot firmness; SD = standard deviation.

The design of pharmacodynamic study is such that it is not possible to relate hemostatic efficacy (one of the goals of the sponsor) with MCF in patients with congenital fibrinogen deficiency. An increase of approximately 10 mm at one hour post-dosing of octafibrin was noted as compared with baseline MCF. However, the clinical efficacy related to a single point increase in MCF value over baseline is not known and is difficult to evaluate due to the paucity of data.

Pharmacodynamic modeling:

The Agency asked the applicant to explore pharmacodynamic models to relate octafibrin concentration with their efficacy marker MCF. The Agency suggested several pharmacodynamic models such as liner, log-liner model, E_{max} and sigmoidal E_{max} models. The results of the pharmacodynamic modeling exercise can be found in Appendix ((Agency's evaluation).

The sample size for the pharmacodynamic analysis was small (n = 22). The predictive performance of several pharmacodynamics models developed from the MCF data obtained from study FORMA 01 was tested (for validation) on the MCF data from study FORMA 02 (Agency's evaluation). After evaluating several pharmacodynamic models, it was noted that the predictive performance of a simple linear model is as good as other robust pharmacodynamic models. The paucity of data (only one concentration at one hour) did not allow an appropriate pharmacodynamic evaluation of octafibrin.

Study #2

Title of Study: Prospective, open-label, uncontrolled, Phase III study to assess the efficacy and safety of Octafibrin for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in subjects with congenital fibrinogen deficiency (FORMA -02).

The objectives of this study were as follows:

- To demonstrate the efficacy of Octafibrin for on-demand treatment of acute bleeding episodes (BEs) (spontaneous or after trauma).
- To show an association between the overall clinical assessment of hemostatic efficacy and the surrogate endpoint 'clot strength' or 'clot firmness' (referred to as 'maximum clot firmness' (MCF) in the protocol) that was used as a surrogate endpoint for hemostatic efficacy and determined via thromboelastography (TEG) in the pivotal pharmacokinetic (PK) study FORMA-01. Therefore, MCF as surrogate efficacy parameter was determined before first infusion and 1-hour after end of first and last infusion.
- To achieve a peak target plasma fibrinogen level of 100 mg/dL in minor bleeds and 150 mg/dL for major bleeds 1-hour post-infusion.
- To determine the response to Octafibrin based on incremental in vivo recovery (IVR).
- To demonstrate the efficacy of Octafibrin in preventing bleeding during and after surgery.
- To assess the safety of Octafibrin in subjects with congenital fibrinogen deficiency, including immunogenicity, thromboembolic complications, and early signs of allergic or hypersensitivity reactions.

This was a multinational, multi-center, prospective, open-label, uncontrolled, Phase III study in patients with congenital fibrinogen deficiency. The hemostatic efficacy of Octafibrin in acute bleeding and surgical prophylaxis was assessed. Of the 13 patients with congenital fibrinogen deficiency included in this interim analysis, 6 were female and 7 were male. Median age was 30 years. Two patients were between 12 and 18 years. Nine patients were Caucasians, 3 were Asians and 1 was from the Middle East. All patients had afibrinogenaemia, as diagnosed by the undetectable fibrinogen levels at baseline. The target fibrinogen plasma levels were defined as follows:

• Minor bleeding/minor surgery: 100 mg/dL and an accepted lower limit of 80 mg/dL.
• Major bleeding/major surgery: 150 mg/dL and an accepted lower limit of 130 mg/dL.

Clot strength (MCF):

Rotational thromboelastometry (ROTEM®) was used to measure MCF (surrogate marker of efficacy) before the first infusion and 1 hour after the end of the first and last infusion as well as

changes of MCF from pre-infusion. MCF was 0.0 mm at all baseline measurements. Change in MCF from baseline to one hour after octafibrn administration is shown in Table 1.

Table 1: Change in MCF from baseline (or before the last infusion) to 1 hour after first Octafibrin infusion for all bleeding episodes

		Change in MCF from Baseline to 1 hour (mm)		
Population	**n**	**Mean ± SD Median (range)**	**95% CI**	**p-value***
FAS-Bleeding	23	6.5 ± 2.0 7.0 (0–10)	5.65, 7.40	<0.0001
PP-Bleeding	21	6.9 ± 1.5 7.0 (4-10)	6.25, 7.56	<0.0001

* Two-sided p-value was calculated at 5% level of significance by using paired t-test for comparison.
CI = confidence interval; FAS = full analysis set; MCF = maximum clot firmness; n = number of infusions; SD = standard deviation.

Recovery:

IVRs were calculated as the maximum increase in plasma fibrinogen activity between pre-infusion and 1 and 3 hours post-infusion for the first and last infusion for each bleeding episode (BE) and pre-infusion and 1-hour post-infusion for all other BEs.

IVR was analyzed for the first infusion of the treatment of the first BE and all BEs. The mean (±SD) IVR value for first BE was 1.87±0.53 mg/dL/mg/kg. The range was (1.27-3.20 mg/dL/mg/kg). The mean (±SD) IVR value for all BEs was 1.84±0.41mg/dL/mg/kg. The range for all BEs was (1.27-3.20 mg/dL/mg/kg).

Comment: No extensive PK study was conducted in this study. Overall, this study from PK perspective does not provide any additional information about PK which was obtained from the previous study FORMA-01. Similarly clot strength (MCF) study does not yield any new information which was obtained from study FORMA-01.

APPENDIX

FORMA-01

The clinical pharmacology reviewer asked the sponsor to explore pharmacodynamic models to relate octafibrin concentration with their efficacy marker maximum clot firmness (MCF). The reviewer suggested several pharmacodynamics (PD) models such as liner, log-liner model, and E_{max} models. However, the sponsor did not accurately evaluate these models and the clinical pharmacology reviewer analyzed the data. Following are the results of the pharmacodynamic modeling exercise conducted at the FDA.

Three PD models (liner, log-liner model, and E_{max}) were evaluated as shown in Figures 1-3. The models (octafibrin concentrations at 1 hour vs MCF measured at 1 hour) were developed from FORMA 01 study (n =23). The model was validated on data obtained from FORMA 02 study (n = 21). Root mean square error (RMSE) as the percent of mean values was used for accuracy comparison among the models. The results of the study are shown in Table 1.

Parameters	Observed	Linear	Log-linear	E_{max}
Mean± SD	9.8 ± 3.0	8.3 ± 2.8	7.8 ± 1.9	7.6 ±1.6
% error (mean)	NA	15	21	23
%RMSE	NA	23	28	30

After evaluating several pharmacodynamic models, it was noted that the predictive performance of a simple linear model is as good as other robust pharmacodynamic models. Table 1 indicates that the prediction error (observed vs predicted) of the mean MCF value was only 15% for the linear model, much lower than the other two models. Similarly, precision wise the lowest RMSE was obtained by the linear model. The prediction error in MCF in an individual subject remained <50% for all three models. There were 18, 17, and 15 subjects (out of 21) for which prediction error was ≤30% by liner, log-liner model, and E_{max}, respectively. Overall, the predictive power of all three models was similar (linear model being slightly better than other models). However, the clinical efficacy related to a single point increase in MCF value over baseline is not known and is difficult to evaluate due to the paucity of data.

The sample size for the pharmacodynamic analysis was small (n = 22). The paucity of data (only one concentration at one hour) did not allow an appropriate pharmacodynamic evaluation of octafibrin. The fact that all three models yielded similar results indicates that more refined/robust model cannot be used due to lack of appropriate data. An E_{max} model without baseline appeared to be like a linear model and an E_{max} model with baseline produced a baseline value of -9.97 which is implausible (at concentration 0).

In short, the data are not rich enough for an appropriate pharmacodynamic modeling and the MCF values generated by the sponsor do not accurately relate hemostatic efficacy with MCF in patients with congenital fibrinogen deficiency.

Figure 1: Linear Model

Intercept = -1.29
Slope = 7.47
R^2 = 0.457

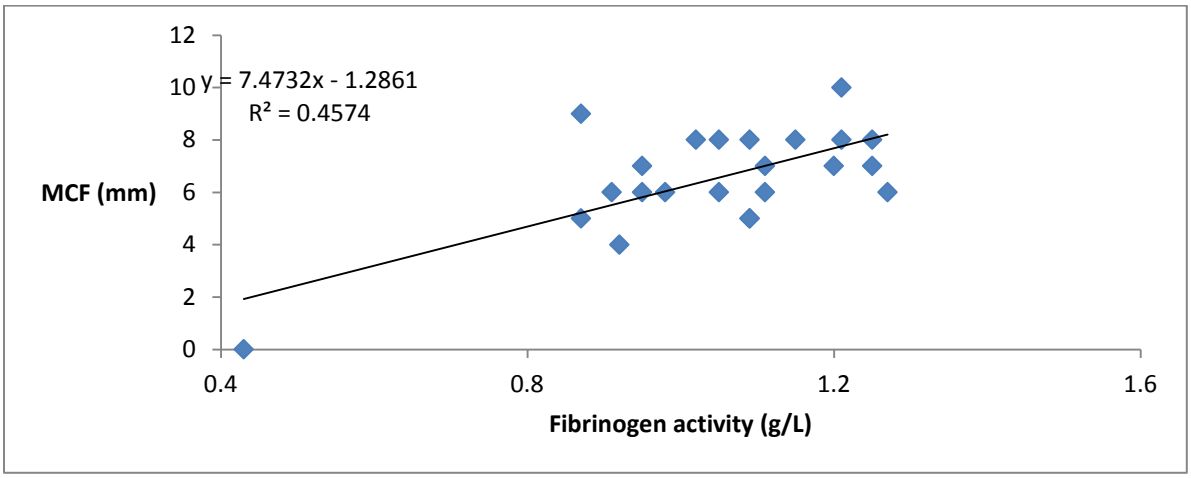


Figure 2: Log-Linear Model

Intercept = 6.37
Slope = 15.05
R^2 = 0.519

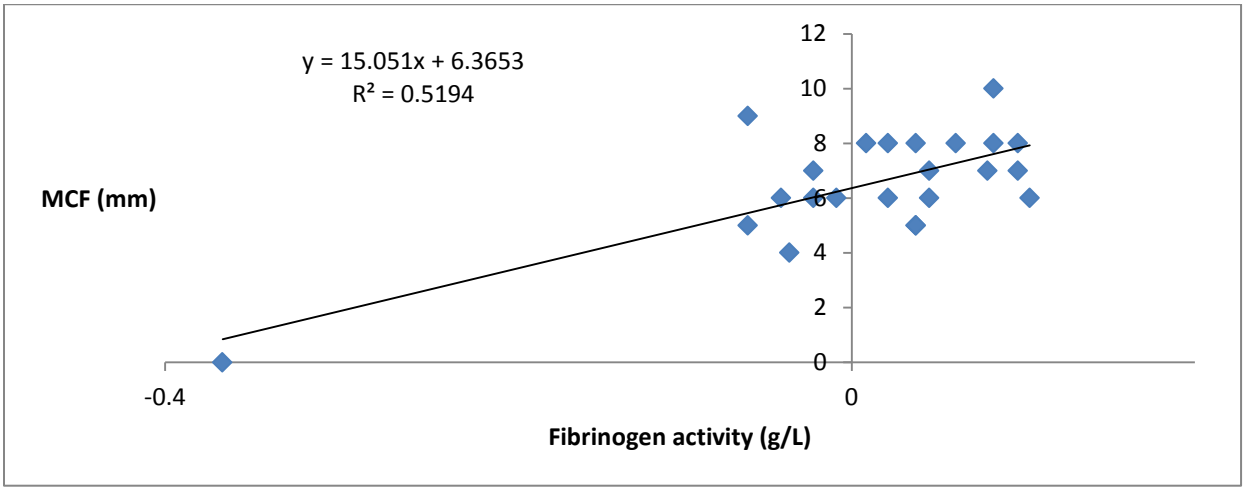


Figure 3: E_{max} Model with Baseline

E_0 = -9.97; EC_{50} = 0.6; E_{max} = 26.2