

Final Review Memo:

To: STN 125284/0

SPONSOR: GTC Biopharmaceuticals

PRODUCT: Antithrombin III (Human), ATryn™

FROM: Nisha Jain, M.D., Clinical Review Branch, HFM-392

SUBJECT: Final review of the B LA (STN 125284/0)

TO: Pratibha Rana Regulatory Project Manager, HFM-380

THROUGH: Basil Golding, M.D.

CHAIRPERSON: Roman Drews, M.D.,

RECOMMENDATION:

ATryn at the recommended dose is effective in reducing prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients. The safety profile is acceptable. The immunogenicity on repeat exposure will be evaluated in a postmarketing study.

EXECUTIVE SUMMARY:

Efficacy was evaluated in studies GTC AT III 01002 and GTC AT HD 012-04 for prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients. The data from the two studies demonstrate similar efficacy in preventing peri-operative and peri-partum thromboembolic events in congenital deficient patients when compared to historical data for patients treated with plasma derived ATIII. The studies conducted support the dosing recommendations for surgical and pregnant patients.

Immunogenicity

Immunogenicity to ATryn™ was assessed by measuring serum antibodies against ATIII, plasma derived ATIII, goat ATIII and goat milk proteins at baseline and at various times after dosing up to 90 days. Development of antibodies was not reported in any patient in the two studies listed above and the other supportive studies. However, data on repeat exposure with the product is very limited. Only one patient with hereditary ATIII deficiency received the product a second time. That patient did not develop any antibodies. The immunogenicity of the product on repeat exposure will be further evaluated in a post- marketing study.

Safety

The safety profile of ATryn™ when used for prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients at the recommended dose schedule is acceptable. Adverse events that were noted were likely due to the surgical interventions and peri-partum related rather than due to ATryn. There were no deaths and no adverse events that led to study discontinuation. Safety with repeat exposure will be evaluated in a post marketing study.

REVIEW RESPONSIBILITIES:

Chair and CMC: Roman Drews

Medical: Nisha Jain, M.D.

Statistician: Paul Hseish

RPM: Pratibha Rana

BIMO: Joseph Manik

CVM: Larissa Rodenko and Jeff Jones

APLB: Mary Ann Gallagher

OCBQ: Syin Chang

Pharmacovigilance: Faith Barash

TRADE NAME:

The sponsor has proposed ATryn® as the trade name. APLB's review finds this trade name acceptable.

ORPHAN DRUG STATUS:

Orphan drug designation granted in November 2007.

FINANCIAL DISCLOSURE:

Financial disclosure statements have been submitted in the application.

INDICATION SOUGHT:

ATryn is indicated for the prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients.

REGULATORY HISTORY:

There is currently one plasma derived Antithrombin III product licensed in the US:

Thrombate III ® manufactured by Talecris Biotherapeutics.

The following summarizes the regulatory chronology of this B LA:

March 2001

Pre-IND Meeting with sponsor to discuss clinical development of the product for prevention of thrombosis in hereditary AT deficient patients

December 2002

Second pre-IND meeting for the above indication

March 2003

IND received by OTRR, CBER

August 2003

IND transferred to OBRR, CBER

August 2003

IND placed on Clinical Hold because of deficiency in the clinical protocol and safety concerns

November 2003

Clinical Hold removed

April 2004

GTC requests a pre-B LA meeting. CBER advises that a second study will be needed to support licensure. CBER also advises GTC to develop a sensitive assay for evaluation of immunogenicity.

July 2004

Phase 3 protocol submitted.

November 2005

Phase 3 study initiated

October 2007

Pre-B LA meeting

November 2007

Orphan drug designation

December 2007

Fast track designation granted.

January 2008

Rolling B LA submitted

August 2008

Clinical module of the B LA submitted and PDUFA timeline initiated

August 2008

Priority review granted

February 2009

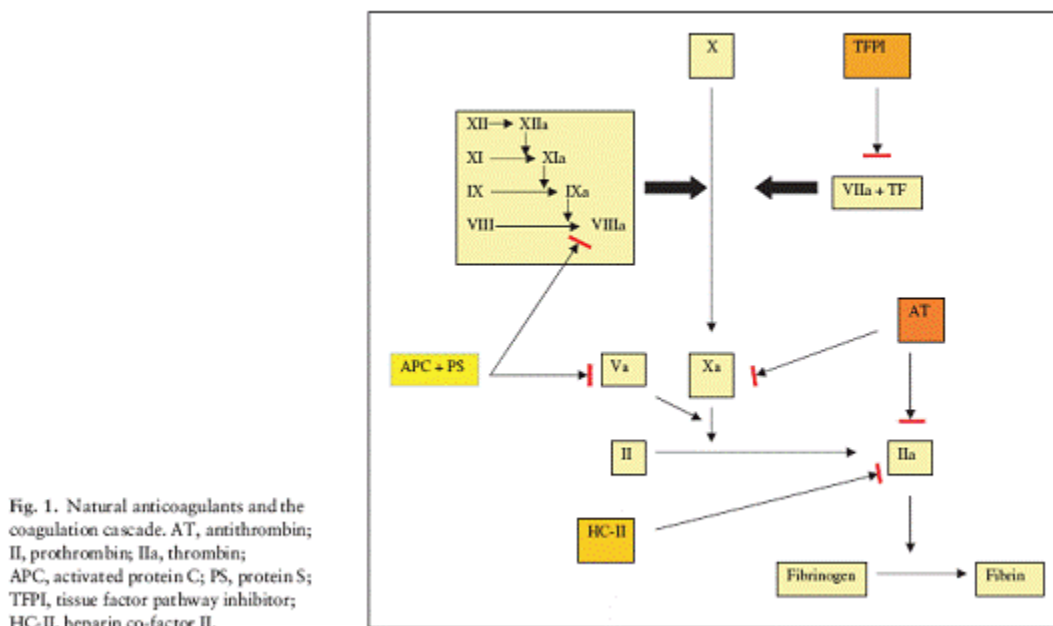
Regulatory action due date

INTRODUCTION:

Antithrombin (ATIII) is a 58 kDa single chain glycoprotein that contains 423 amino acids and has a carbohydrate content of about 15%. The protein has 3 disulfide bridges and 4 N-linked glycosylation sites (Asn 96, 135, 155, and 192).

ATIII is a serine protease inhibitor that is the principal inhibitor of the blood coagulation serine proteases thrombin (Factor IIa) and Factor Xa, and to a lesser extent, Factors IXa, XIa, XIIa, trypsin, plasmin, and kallikrein. ATIII neutralizes the activity of thrombin and other serine proteases by forming an irreversible 1:1 stoichiometric complex between enzyme and inhibitor. In the presence of heparin, the normally slow formation of complex becomes dramatically accelerated. The ability of ATIII to inhibit thrombin can be enhanced by more than 1000 fold when ATIII is bound to heparin. The thrombin-antithrombin complex (TAT) is rapidly removed by binding to a receptor in the liver. The half-life of TAT complex is less than 5 minutes in humans. ATIII is also referred to as heparin cofactor. Localization of a fraction of the ATIII on the endothelial surface, where enzymes of intrinsic coagulation cascade are commonly generated, enables ATIII to rapidly neutralize these activated clotting factors and protect natural surfaces against thrombus formation.

The mean concentration of ATIII in human plasma is about 0.1 g/L. The biological activity of 1mL of pooled human plasma in a thrombin or FXa inhibition assay is defined as 1 IU/mL. Normal ranges for the assay are between 80% and 120%.



Hemophilia (2008)14, 1229-1239

Congenital ATIII deficiency (Hemophilia 2008, 14, 1229-1239: Patnaik and Moll)

Antithrombin (AT) deficiency was first described in 1965 by Olav Egeberg in a family in which several family members had venous thromboembolism (VTE). Egeberg also established the deficiency to be an autosomal dominant disorder. Most cases are heterozygous. Homozygosity for AT deficiency is always fatal in utero. Inherited AT deficiency is uncommon with prevalence rates for AT deficiency of 1 in 2000- 5000 in the overall population. The types of AT deficiency are shown in the table below:

Table 1. Types of antithrombin (AT) deficiency.

Type of defect		Defect where?	Results of laboratory assays			Prevalence in general population	Prevalence in patients with thrombosis	Prevalence of VTE in persons with this subtype of deficiency (%)
			AT activity		AT antigen			
			Heparin co-factor assay*	Progressive AT assay†				
Type I	Quantitative		Low	Low	Low	12% of all ATD	60% of all ATD	53
Type II	Qualitative					88% of all ATD	40% of all ATD	6–66
	Ila	Thrombin-binding domain	Low	Low	Often normal			58
	IIb	Heparin-binding domain	Low	Normal	Often normal			6
	IIc	Pleiotropic	Low	Varied	Low			66

*Inactivation of thrombin or factor Xa in the presence of heparin.

†In the absence of heparin or with low concentration of heparin.

Patients with congenital deficiency present with thromboembolic events (TE). TE in hereditary AT deficient patients are uncommon prior to puberty but increase thereafter, particularly during periods of high risk, such as pregnancy, surgery, or bed rest. Hereditary AT deficiency causes a life-long increased risk of venous thromboembolism and up to 70% of cases do develop a venous thromboembolic event (VTE) during their lives. Often VTEs are recurrent and may be life-threatening. The risk of development of VTEs as compared to the normal population in these situations is increased by a factor of 10 to 50. Failure to properly treat hereditary AT deficient patients, especially during high risk situations such as surgery or trauma or for pregnant women, during the peripartum period, may result in VTE. Asymptomatic hereditary AT deficient patients generally do not require anticoagulant prophylaxis, except in settings of increased risk. Hereditary AT deficient individuals with a history of one thrombosis are treated with chronic oral anticoagulant prophylaxis.

CLINICAL OVERVIEW

Synopsis of the study protocols:

PHARMACOKINETIC STUDIES:

AT III-009-00: Randomized Pharmacokinetics of AT III in Patients with hereditary AT III deficiency receiving two doses 50 and 100 IU/kg:

This was an open-label, single dose pharmacokinetic study in male and female patients (≥ 18 years of age) with hereditary AT III deficiency. The patients received either 50 (n = 9 all females) or 100 (n = 6, 2 males and 4 females) IU/kg ATryn intravenously. Blood samples were collected before the administration of the drug and at 5, 10, 15, 30, 45, and 60 minutes and at 2, 4, 6, 8, 24, 48, and 72 hours. The clearance and half-life of ATryn were 9.6 and 7.2 mL/hr/kg and 11.6 and 17.7 hours following 50 and 100 IU/kg dose, respectively. The incremental recovery was 2.07 ± 1.54 %/IU/kg.

AT III-009-00: Population pharmacokinetic analysis of recombinant human antithrombin and comparison to human plasma-derived antithrombin:

The objective of this investigation was to compare the pharmacokinetics of ATryn and plasma-derived antithrombin (pdAT) using population-pharmacokinetic approach.

The pharmacokinetics of ATryn were evaluated in 15 patients with congenital antithrombin deficiency following a short intravenous infusion of 50 or 100 IU/kg. The pharmacokinetics of pdAT were evaluated from a study performed in 1984 in the USA in 8 patients with congenital AT deficiency, following intravenous infusion of administration of 25 to 225 IU/kg pdAT. The following Table summarizes the PK parameters of the two products.

A PK comparison between ATryn and plasma derived AT

Parameters	rhAT	pdAT
CL (mL/hr/kg)	9.5	1.3
Half-life (hrs)	10.2	91.2
Vss (liters)	7.7	9.8

Conclusions: Plasma-derived AT has almost a 9-fold longer half-life and 7-fold slower clearance than ATryn.

EFFICACY AND SAFETY STUDIES

Study Objectives and Endpoints

The objective of the two studies was to assess the incidence of thromboembolic events following prophylactic IV administration of ATryn in situations associated with a high risk for thromboembolic events and to evaluate the safety of ATryn in patients with hereditary AT deficiency.

The primary endpoint of the two studies (combined) was non-inferiority of incidence of TE during and within seven days of treatment with ATryn compared with a historical cohort control of comparable patients treated with plasma derived ATIII.

GTC AT III 01002: “Phase 2 study to assess the incidence of thromboembolic events following prophylactic intravenous (iv) administration of antithrombin (rhAT) to hereditary antithrombin (AT) deficient patients in high-risk situations.”

This was a single arm, multicenter, multinational, open-label study with blinded evaluation of the ultrasonographic images. 15 hereditary AT deficient patients (documented AT activity \leq 60% of normal and with previous history of thromboembolism) scheduled for surgery, Caesarean section, or vaginal delivery qualified for the study were treated prophylactically with ATryn. Dosing with ATryn was individualized to increase and maintain target AT activity levels between 80% and 120% of normal. Functional AT activity levels were used to monitor and adjust dosing.

ATryn administration to patients scheduled for surgery and patients scheduled for Caesarean section or delivery was initiated approximately 24 hours before the planned procedure and continued for a minimum of 3 days. ATryn therapy was continued, until effective chronic anticoagulation therapy was established and the patient was mobilized and ready for hospital discharge (See APPENDIX 1).

In pregnant patients not scheduled for Caesarean section or induction of delivery, treatment was initiated only when the patient was hospitalized and in active labor.

Treatment of these patients was also continued for a minimum of 3 days and continued until effective chronic anticoagulation therapy was established and the patient was mobilized and ready for hospital discharge.

A blinded, independent determination of the incidence of acute DVT based on duplex ultrasound examination was the primary measurement of the outcome of treatment with ATryn. Standardized duplex ultrasound examination of the lower extremities was used to establish the presence or absence of acute DVT. Duplex ultrasound studies were performed and interpreted by qualified specialists within the same hospital/institution on a real time basis for the timely and appropriate clinical care of the patient. Venography could be used, when clinically indicated, if the study investigator felt that duplex ultrasound results were inconclusive. For other TE relevant diagnostic modalities were used.

GTC AT HD 012-04: “Phase 3 study multicenter, multinational study to assess the safety and efficacy of antithrombin III in hereditary antithrombin (AT) deficient patients in high-risk situations for thromboembolic events”

The trial design for this study was similar to the phase 2 study. This was a single arm, open-label multi-center, multinational study in 18 patients. Congenital AT deficient patients scheduled for surgical procedures (with personal histories of TE and documented AT levels less than 60%) and pregnant patients were enrolled in the study. Dosing with ATryn was to be individualized to increase and maintain target AT activity levels between 80% and 120% of normal. Functional AT activity levels were used to monitor and adjust dosing. For elective procedures (i.e. non-pregnant surgery patients and pregnant patients scheduled for Caesarean section or delivery induction), treatment with ATryn was initiated up to 24 hours prior to the scheduled procedure. For pregnant patients not scheduled for Caesarean section or delivery induction, treatment with ATryn was started as soon as they were admitted to the hospital and active labor had begun. The dosing algorithm was revised for pregnant patients based on phase 2 results.

Administration of ATryn was continued for a minimum of 3 days for all study patients and continued until effective chronic anticoagulation therapy was established and the patient was mobilized and ready for hospital discharge. The protocol-specified maximum duration of treatment was limited to 14 days.

The incidence of thromboembolic events was assessed clinically in all patients who were treated with ATryn. Signs and symptoms indicative of the occurrence of a thromboembolic event were monitored during treatment with ATryn and up to and including 7 days after cessation of ATryn treatment. If signs and symptoms indicated the occurrence of a thromboembolic event appropriate diagnostic tests were performed to confirm or exclude the presence of the event.

GTC AT HD-R 013-04: Historical cohort study to assess the incidence of thromboembolic events following prophylactic intravenous administration of plasma-derived antithrombin to hereditary antithrombin (AT) deficient patients in high-risk situations. Both studies (GTC ATIII 01002 and GTC ATHD 012-04) were compared to the historical control.

This was an international, multi-center, prospectively designed retrospective cohort study of hereditary AT deficient patients who had a history of thromboembolic events, an elective procedure performed since 1 January 1997 that placed them at high risk for

the occurrence of a thromboembolic event, and at that time, were treated prophylactically with intravenous administration of plasma-derived AT for a minimum of 2 days.

Approximately 5 to 15 sites were planned for participation in the study. All eligible study sites had a listing or automated medical record system that identified patients who had hereditary AT deficiency and /or those patients who had received plasma AT during high-risk elective procedures since 1 January 1997.

All the patients identified were selected. A minimum of 35 up to a maximum of 70 patients identified from the listing or automated medical record system of all patients eligible patients at the sites were included in the study. The eligibility criteria were the same as for the study conducted with ATryn. Clinical outcomes in terms of TE were noted in the case report form.

Statistical Methods for Determining the Efficacy End-Point

The statistical approach used was to establish non-inferiority by comparing the incidence of any TE event with plasma-derived ATII vs. ATryn (results were combined from Phase 2 and 3 studies). The non inferiority margin was set at 20%. Use of a one-sided lower confidence bound, instead of a confidence interval, consistent with use of a one-sided test for a non-inferiority study was adopted (see table below). The 95% confidence interval based on the exact (Clopper-Pearson) method for the proportion of patients with presence of DVT for both groups was presented.

CASE	TREAT: X1/N1	CONTROL X2/N2	95% EXACT CI
1	0/31	0/35	-0.0921*
2	1/31	0/35	-0.1441*
3	2/31	0/35	-0.1895*
4	2/31	1/35	--0.1561*
5	3/31	1/35	0.1987*
6	3/31	2/35	0.1725*

*Non-inferiority of 20% is acceptable.

X1 and X2 number of TEs

N1 patients in the ATryn arm

N2 patients in the control group

Safety Monitoring

In both studies the patients were evaluated for laboratory parameters of coagulation (INR, aPTT, and anti-Xa activity) and immunogenicity (up to 90 days after treatment). Active assessment of any bleeding complications was performed and included a brief physical examination, hemoglobin and hematocrit measurements, and urinalysis every day during ATryn administration through the last day treatment. In addition, blood serum samples were collected to allow for retrospective infectious or immunological evaluations in the future, if indicated.

RESULTS OF PHASE 2 AND PHASE 3 EFFICACY AND SAFETY STUDIES

Results of the Phase 2 AT III 01002 study:

FDA analysis consists of intent to treat population defined by all patients who received at least one dose of ATryn. Of the 14 patients enrolled one patient had baseline DVT

and hence was not included in the efficacy evaluation. Of the 13 patients 5 were treated peri-operatively and 8 were treated during the peri-partum period. All 13 patients had a prior history of TE. Patients' ages ranged from 21 to 74 years with a mean of 36.7 years. The mean baseline AT activity levels for surgical patients were 50% and the median was 53% and for pregnant patients the mean AT levels were 46% and the median was 45%.

All 13 patients were observed for clinical signs and symptoms of thromboembolic events. One patient had lower leg edema and venous distension for several days during Atryn treatment and another patient had venous distention before, during and following the dosing period. Both the patients were negative for acute DVT by ultrasound examination.

All patients were evaluated for acute DVT by duplex ultrasonography examinations, which were interpreted both locally as well as under blinded conditions centrally by an independent imaging laboratory. Acute DVT was identified for one surgery patient during treatment, i.e. a treatment failure. This patient received Atryn for a total of nineteen days and was diagnosed with DVT of left popliteal vein and superficial femoral vein on the thirteenth day of Atryn treatment based on an unscheduled Doppler ultrasound done when the patient presented with signs and symptoms. The treatment with Atryn maintained the targeted AT activity level between 80% to 120% of normal at all times, except immediately following surgery when AT activity was measured at 69%. It is possible that the clot formation had initiated during the time when AT activity levels were 69% of normal and propagated despite bringing the AT activity levels to 80% to 120% of normal by bolus administrations (8 boluses). It appears that Atryn may be not effective in clot resolution at the recommended target levels.

Diagnostic imaging was performed in three patients to exclude the presence of suspected thromboembolic events [to rule out pulmonary embolism (PE) and cranial thrombosis]. All testing for these patients was negative for the presence of any thromboembolic event.

Administration of Atryn according to the protocol-defined dosing and monitoring scheme resulted in adequate control of AT activity levels within the desired 80 to 120% range in four of the five surgical patients. Four of the 5 surgery patients received an average of 2.5 (range 1-8) bolus Atryn administrations during the course of their treatment period (see table below).

AT activity levels dropped below the lower limit of normal for all 5 surgery patients when rhAT administration was discontinued. Central laboratory AT activity levels at 30, 60, and 90 days following discontinuation of rhAT treatment were above or near baseline AT activity levels documented just prior to initiation of rhAT treatment. In all patients anti-coagulation was established by heparin prior to cessation of Atryn therapy.

For the 8 delivery patients, administration of Atryn according to the protocol defined dosing and monitoring scheme resulted in adequate control of AT activity levels within the desired 80 to 120% range. Bolus dosing increased AT activity levels to within or above the normal range with the exception of 3 of the 8 delivery patients who required between 12-15 dose adjustments to keep the levels between 80-120% as specified in the dosing regimen schedule. Because of the numerous dose adjustments needed in one third of the pregnant patients, FDA advised the sponsor to revise the dosing algorithm for these patients.

ATryn treatment duration, rhAT dose administration and dose adjustments

Group/Patient Number	Treatment Duration (days)	Total loading doses (IU/kg)	Dose per day (IU/kg/day)	Dose adjustments
Surgery group	12	50.0	166.0	3
-b(6)-	8	47.1	157.1	4
-b(6)-	13	38.2	79.5	4
-b(6)-	19	35.1	179.9	8
-b(6)-	10	21.0	113.7	1
Pregnant Group	10	48.6	293.0	12
-b(6)-	3	21.0	222.0	2
-b(6)-	3	26.9	331.6	4
-b(6)-	3	27.2	207.0	14
-b(6)-	4	19.7	249.5	2
-b(6)-	4	23.7	286.5	2
-b(6)-	5	81.4	451.7	6
-b(6)-	3	25.3	167.0	1
-b(6)-	3	20.3	277.4	15
-b(6)-				

IU= international units

Safety:

In this study no deaths and immunogenicity were reported.

Overall safety results:

Type of procedure/ No of patients	Surgery N=5	Pregnancy N=9	Overall N=14
Any AEs	4 (80%)	6 (66.7%)	10 (71.4%)
SAEs	3 (60%)	1(11.1%)	4 (28.6%)

List of SAEs

Patient #	Type	FDA assessment of causal relationship
-b(6)-	Fever	unlikely
-b(6)-	Hypotension	Hypotension was due to hemorrhage, instead of 5,000 U of heparin,
	Wound hemorrhage patient received 25,000 U	

-b(6)-	Fracture due to trauma Gr and Mal seizures	unlikely unlikely
-b(6)-	DVT	Treatment failure

Results of the Phase 3 GTC AT HD 012-04 study:

A total of 23 patients were enrolled in the study with 18 (78.3%) of the 23 patients receiving treatment with ATryn. All 18 (100.0%) ITT population patients completed the study. The reasons for five of the enrolled patients who were not included as ITT population of the study were: (i) ineligible due to DVT at baseline, (ii) went into spontaneous labor, (iii) spontaneous amniorrhexis, (iv) fetal Doppler results were pathological hence withdrew consent and (v) signed an informed consent form and had some study procedures performed and then withdrew consent.

In the safety and the ITT population, six of the ATryn-treated patients were non-pregnant surgery patients and 12 were pregnant patients. The Per Protocol population was comprised of 6 non-pregnant surgery patients and 11 pregnant patients. One patient was not included in the Per Protocol population because the patient's treatment started after delivery, instead of before delivery as specified in the protocol.

The mean patient age was 37.2 years (21-62 years). The mean screening AT activity level was 50.9% and ranged from 29.0% to 65.7% with Although some screening AT activity levels were above 60%, patients met all the inclusion criteria, and had historical levels confirming hereditary AT deficiency.

Concomitant medications for all patients included the heparin group of anticoagulants. For the primary efficacy endpoint, the Intent-to-Treat Population (ITT) was defined as those patients who received ATryn and had at least one follow-up assessment after initiation of treatment with ATryn. The ITT population included 6 non-pregnant surgery patients and 12 pregnant patients.

The Per Protocol Population included those patients who received ATryn and met inclusion criteria of a personal history of venous thromboembolic events and a history of congenital deficiency that included 2 or more plasma AT activity values $\leq 60\%$ of normal, and received at least 3 (calendar) days of treatment with ATryn with at least one follow-up.

The Per Protocol population included 6 non-pregnant surgery patients and 11 pregnant patients.

Safety Population: This population included all patients who received at least 1 dose of ATryn. The Safety population included 6 non-pregnant surgery patients and 12 pregnant patients.

The efficacy of ATryn for the prophylaxis of thromboembolic events in surgical and pregnant patients with congenital deficiency undergoing medical high risk procedures was evaluated by assessment for clinical signs and symptoms of any thromboembolic events. This was followed by the appropriate diagnostic testing. The occurrence of a thromboembolic event was confirmed if symptoms occurred and diagnostic testing was positive.

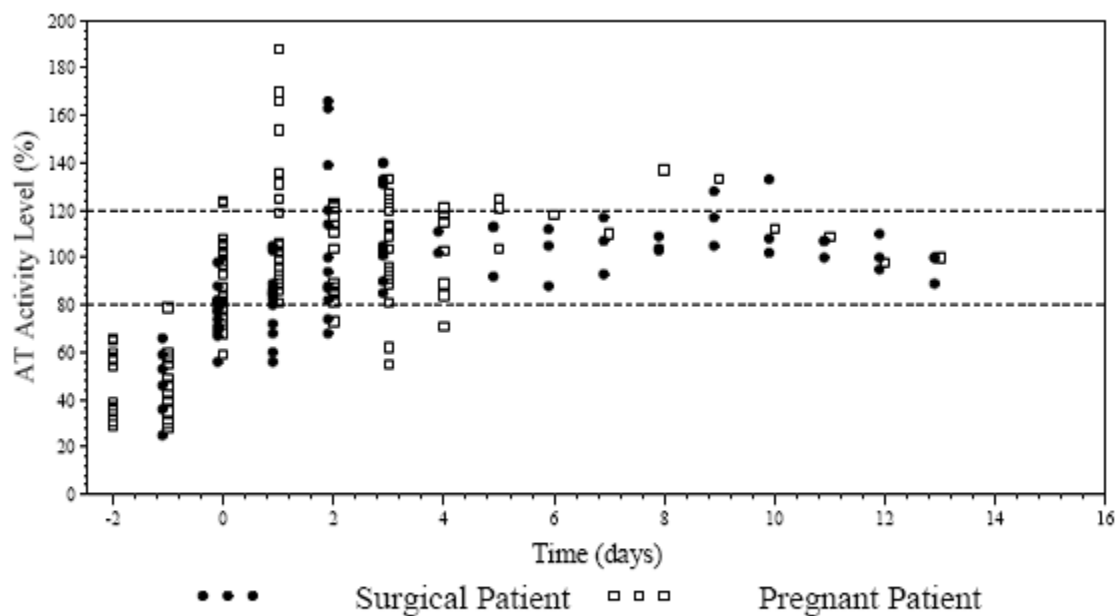
During treatment and during the follow-up period of 7 days after cessation of treatment with ATryn, no thromboembolic events occurred in the intent to treat population (n = 18). The patients included in this study all had significant prior personal histories of venous

thromboembolic events which elevated the risk for recurrence of such events in this study.

On the basis of the efficacy results, it is concluded that ATryn is effective in preventing potentially life-threatening thromboembolic events in patients with congenital deficiency during the peri-operative or peri-partum period.

There were 2 venous thromboembolisms reported in the study after the 7-day post-treatment follow-up period. A DVT was reported 11 days after discontinuation of treatment with ATryn and a PE occurred 14 days after stop of ATryn treatment. Given the short half-life of ATryn (approximately 10 hours), it is not expected that ATryn will have a beneficial effect that long after stopping treatment. It can, therefore, be concluded that these events were not due to a lack of efficacy of ATryn, but due to the potential lack of efficacy of the anticoagulant medication being administered at the time of each event.

In conclusion, the data from the current study demonstrates the efficacy of ATryn for the prevention of thromboembolic events in congenital deficient patients in high risk situations and the effectiveness of the dosing formula for both surgical patients and pregnant women (shown in graph and table below)



Only includes AT activity data from baseline up to the end of treatment.

Day -2 is the screening visit.

Day -1 represents baseline.

Treatment duration and dose administration and dose adjustments

Group	Treatment Duration (days)	Total loading doses (IU/kg)	Dose per day (IU/kg/day)	Dose adjustments
Surgery group	7	21.6	37.8	2.5
N=6	3	19.2	21.2	2.0
Mean	3-14	13.5-34.4	15-78.5	1-6.0
Median				

Group	Treatment Duration (days)	Total loading doses (IU/kg)	Dose per day (IU/kg/day)	Dose adjustments
Range				
Pregnant Group				
N=12	4.4	36.3	38.9	1.5
Mean	3.6	35.5	30.2	1.0
Median	1-14.0	13.0-57.6	7.2-139.9	0.0-6.0
Range				

Please note with the revised dosing algorithm for pregnant patients, the number of dose adjustments needed was significantly reduced compared to the Phase 2 Study.

Conclusion of overall Efficacy:

Patients for the control group (pdATIII) were matched, as far as possible, for demographics, medical/surgical history, history of prior TEs, surgical procedure, baseline AT activity levels and concomitant medication with the Atryn group. The two studies conducted with Atryn, when pooled together, show that Atryn is as effective as plasma derived ATIII in preventing peri-operative and peri-partum thromboembolism in congenital ATIII deficient patients when analyzed by prespecified statistical parameters and methods (see table below)

	Test (31)	Control (35)
TE Outcome		
Positive	1	0
Negative	30	35

Binomial Proportions [col1]: piHat_1 0.03226

Binomial Proportions [col2]: piHat_2 0

Difference of Proportions: piHat_2 - piHat_1 -0.03226

Std. Error: (pooled estimate of std dev of piHat_2-piHat_1) 0.03013

Standardized Difference: (piHat_2-piHat_1)/Stderr -1.071

	P-value		95% Confidence Interval (P 2-P 1)	
Type	1-sided	2*1-sided	Lower Limit	Upper limit
Asymptotic	0.1422	0.2843	-0.1634	0.0698

Exact	0.2401	0.4802	-0.167	0.0778
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The primary efficacy endpoint is the incidence of any thromboembolic event after the start of treatment (plasma AT or rhAT) and within 7 days following discontinuation of treatment. Clopper Pearson exact 95% confidence interval for the proportion of patients with a thromboembolic event is presented for each treatment group, as well as the exact 95% lower confidence bound for the difference between treatments. Non-inferiority is demonstrated as the lower 95% confidence bound of the difference (plasma-rhAT) is ≥ -0.20 .

The overall efficacy of ATryn is presented in the table below by comparing incidence of thromboembolic events before, during and after treatment.

No Patients	Patient Identification	Prior Personal History of VTEs	During Treatment	VTE Events	
				Within 7 days After DC of ATryn	> 7 days After DC of ATryn (Day)
1	-b(6)-	DVT & PE			
2	-b(6)-	DVT			
3	-b(6)-	DVT x 6 & PE			
4	-b(6)-	DVT			
5	-b(6)-	DVT & PE			
6	-b(6)-	DVT x 3 & PE			
7	-b(6)-	DVT, SVT & PE	DVT* (Day 13 of Rx)		
8	-b(6)-	DVT x 3			
9	-b(6)-	MVT			
10	-b(6)-				
11	-b(6)-	DVT & PE			
12	-b(6)-				
13	-b(6)-	DVT x 2 & PE			
14	-b(6)-	DVT & PE			
15	-b(6)-	PE			DVT (11 Days after DC of ATryn)
16	-b(6)-	PE			PE (14 days after DC of ATryn)
17	-b(6)-	DVT			
18	-b(6)-	DVT & PE x 2			
19	-b(6)-	DVT x 3, PE & TE of VG			
20	-b(6)-	DVT			
21	-b(6)-	DVT			
22	-b(6)-	DVT x 2 & PE			
23	-b(6)-	DVT x 2 & PE			
24	-b(6)-	DVT x 3 & PE			
25	-b(6)-	DVT x 6			
26	-b(6)-	PE			
27	-b(6)-	DVT x 3			
28	-b(6)-	DVT x 4, PE &			

No	Patient	Prior Personal	VTE Events
		Cerebral TP	
29	-b(6)-	DVT x 3, PE x 3 & SVT	
30	-b(6)-	DVT x 2 & PE	
31	-b(6)-	DVT x 4	

* Asymptomatic DVT diagnosed by protocol mandated ultrasound.

DC = Discontinuation DVT = Deep Vein Thrombosis SVT= Sinus Vein Thrombosis

MVT= Mesenterial Vein Thrombosis PE=Pulmonary Embolism TP = Thrombophlebitis

TE of VG = Thromboembolism of Vein Graft

Safety:

There were two patients who did not experience any treatment emergent adverse events (TEAEs) during their participation in the study. During dosing, all patients experienced one or more TEAE. The majority of TEAEs reported during dosing with ATryn were of mild or moderate severity. Four (22.2%) of the 18 study patients experiencing a TEAE were rated severe (shown below). The AE rated as severe included one surgery patient and three pregnant patients:

	Surgery (N=6 patients)	Pregnant (N=12 patients)
AEs	6 (100%)	10 (83.3%)
SAE	2(33%)	3 (25%)

Table showing AEs that were severe in intensity

Patient	Type of AE	Relationship to ATryn
Surgery	Severe headache	Not related
Pregnant	Dilutional anemia with no evidence of bleeding.	Not related
	Muscle spasm	Not related
Pregnant	Enterobacter sepsis	Not related
Pregnant	Vaginal tear	Not related

TEAE occurring in two or more patients treated with ATryn due to all causes are presented below:

Body System/ preferred term	TEAE incidence (N=18)	Number of events
Total number of patients	16 (88.9)	63
Anemia	3 (16.7)	3 (4.8)
Vaginal laceration	3 (16.7)	3 (4.8)
Non cardiac chest pain	2 (11.1)	2 (3.2)
Edema peripheral	2 (11.1)	2 (3.2)
Urinary tract infection	2 (11.1)	2 (3.2)
Post procedural hemorrhage	2 (11.1)	2 (3.2)
Headache	2 (11.1)	5 (7.9)
Syncope	2 (11.1)	2 (3.2)
Hematoma	2 (11.1)	2 (3.2)

7 SAEs occurred in 5 patients. 5 events were considered not related [septicemia, epistaxis, PE, DVT and chest pain (time-frame within which the events occurred) and 2 events were considered probably related.

Details of SAEs in two subjects considered to be possibly related to ATryn
Patient -b(6)- underwent a right knee total replacement. After 24 hours of surgery the knee was reported to be swollen and the investigator used the term hemarthrosis to report this event. This patient received ATryn for three days and needed one dose adjustment. The AT activity levels on three days were 104, 88, 96%. He received concurrently heparin group of anticoagulation. The event completely resolved within 7 days with no adjustments in anti-coagulation or any other intervention. Because of its

close relationship with administration of ATryn, this event is considered to be probably related to the product.

Patient -b(6)- underwent cesarean section after difficult labor and failed induction. The patient experienced intra-abdominal hemorrhage from the hysterotomy wound after two days of completion of dosing with ATryn. This patient received subcutaneous Enoxaparin 250mg concurrently with ATryn. This patient had baseline decreased hemoglobin and elevated PTT. The baseline AT levels 40% and then 104 % on two days of dosing, dropped to 60% day after dosing. Because of the temporal relationship between the use of the ATryn and event, it was considered probably related

System Organ Class Protocol/ Patient Number	Preferred Term	Reported Term	Severity	Relation	Outcome
<i>Gastrointestinal Disorders</i>	Intra-abdominal Hemorrhage	Intra-abdominal Bleeding	Severe	Definite/ Probable	Recovered
<i>General Disorders and Administration site</i>	Pyrexia	Fever Unknown Origin	Moderate	Not Related	Recovered
<i>Injury, Poisoning and Procedural Complications</i>	Femur Fracture	Traumatic Fracture of Left Femur	Severe	Remote/ Unlikely	Recovered
<i>Infections and Infestations</i>	Enterobacter Sepsis	Septicemia Enterobacter Cloacae	Severe	Not Related	Recovered
<i>Investigations</i>	Hemoglobin Decreased	Low Hemoglobin Level	Moderate	Possible	Recovered
<i>Musculoskeletal and Connective Tissue disorders</i>	Hemarthrosis	Clinical Hemarthrosis R Knee	Moderate	Not Related	Recovered
<i>Nervous System Disorders</i>	Grand Mal Convulsions	Grand Mal Seizures	Severe	Remote/ Unlikely	Recovered
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	Pulmonary Embolism	Bilateral Pulmonary Embolism	Severe	Not Related	Recovered with Sequelae
<i>Vascular Disorders</i>	Hypotension	Hypotension	Moderate	Remote/ Unlikely	Recovered
	Wound Hemorrhage	Wound Hemorrhage Muscular Vein	Moderate	Remote/ Unlikely	Recovered
	Deep Vein Thrombosis	Thrombosis Left Upper Leg Popliteal Non-occlusive Thrombus in RLE	Mild	Remote/ Unlikely	Recovered
	Deep Vein Thrombosis		Moderate	Not Related Remote/ Unlikely	Recovered
	Hematoma	Hematoma	Moderate		Recovered

Immunogenicity:

No patients developed anti ATIII antibodies. Data on repeat exposure to the product is very limited and is being evaluated in post marketing studies.

PHARMACOVIGILANCE PLAN:

Please see OBE's review for details on pharmacovigilance plan.

POSTMARKETING STUDY:

Because of the infrequency with which patients may require treatment with ATryn on more than one occasion additional clinical data assessing the immunogenic potential of ATryn, especially in those patients requiring re-exposure to ATryn, will be evaluated in a post-marketing immunosurveillance program. The sponsor has proposed to implement a patient registry in which physicians will collect serum samples from patients treated

with ATryn and have the samples analyzed for the development of IgE, IgM and/or IgG antibodies to recombinant antithrombin. Testing of the serum samples for antibodies to recombinant antithrombin will be offered as a free service to physicians and patients. In this postmarketing immunosurveillance study a total of 50 patients or over a period of five years, whichever occurs first will be evaluated.

The details of the information captured in the registry are outlined below:

Physicians Information

- Name, title, affiliation, phone/fax numbers and addresses (mail and e-mail)
- Reason for request (i.e., because of an adverse event or for routine immunosurveillance)
- Date sample(s) submitted

Patient Information

- Patient identifier (initials only)
- Demographics (date of birth, sex, ethnic origin, known thrombophilic disorders, etc)
- Indication for treatment and type of medical procedure (surgical or obstetric)
- Date of treatment (start and stop)
- Dates and time of serum sample collections
- Dosing information (loading dose, continuous infusion, etc.)
- Number of prior treatments with ATryn or human plasma-derived antithrombin, if any, and dates of such treatments
- Use of concomitant anti-coagulants
- Date(s) and time of adverse drug reactions, if any, including lack of efficacy

Forms will be provided to the physician to capture the detailed baseline information. The baseline information form will be completed by the treating physician and forwarded to the sponsor via telefax. The sponsor will check it for completeness.

A unique patient ID number will be assigned by the Applicant for future reference and communicated to the treating physician. The unique patient ID number will be used to avoid potential complications in the database in the event that a patient has the same initials, is of the same sex and has the same date of birth. Data about the physician and the patient will be entered into a database for storage and subsequent generation of tables and reports.

Collection of Serum Samples

The sponsor will provide detailed instructions about the collection, processing, labeling and storage conditions of all serum samples. In addition, the sponsor will provide the collection and storage tubes, as well as labels to be affixed to tubes, and detailed shipping instructions. Upon receipt, the sponsor will acknowledge receipt of the samples.

Analysis of Samples

Serum samples will be collected from each patient prior to treatment and then on days 1, 7 and 28 after initiation of treatment with ATryn. The samples will be tested for IgE, IgM and IgG antibodies to recombinant human antithrombin as described below.

Serum samples will be batched for periodic analysis. In the event of an adverse reaction that is suspected of being an IgE mediated event then the samples will be processed on an expedited manner.

Analysis for IgE Antibodies

Samples collected at Day 1 following initiation of treatment will only be tested for IgE antibodies if an adverse reaction is reported that is believed to be IgE mediated. If needed, both pre-treatment and Day 1 serum samples will be screened for IgE antibodies using an -b(4)- test method. If the post-treatment sample is reactive, then a confirmatory inhibition of binding assay will be performed to determine the specificity of the reactivity observed in the screening -b(4)-.

Analysis for IgM Antibodies

Pre-treatment and Day 7 samples will be tested for IgM antibodies first using an -b(4)-- screening test method. If the Day 7 sample is deemed reactive by -b(4)-, then samples will be tested using a confirmatory binding of inhibition assay.

Analysis for IgG Antibodies

Pre-treatment and Day 28 samples will be tested for IgG antibodies first using an -b(4)- screening test method. If the Day 28 sample is deemed reactive by -b(4)-, then the samples will be tested using a confirmatory binding of inhibition assay.

Reporting of Results

The results of all tests performed on each patient's serum samples will be reported back to the physician who submitted the samples. The results will be conveyed to the physician by written letter.

Summary Results

Periodic updates on the status of the immunosurveillance program will be submitted to CBER.

APPENDIX 1

DOSE ADMINISTRATION AND DOSE MONITORING FOR PHASE 2 STUDY GTC AT III 01002

For a patient with a pretreatment baseline AT activity of X%, the dose required to increase and maintain the AT activity level at 100% will be as follows:

Loading Dose (IU) = ((100 – X)/2.28) x Patient Weight

(Loading dose in international units equals 100 minus 'X' divided by 2.28, then multiplied by patient weight (in kg), where 'X' is the patient's pre-dose AT activity level.) The loading dose should be given as a 15 minutes infusion immediately followed by the maintenance dosing. For easier programming of the infusion pump, the calculated bolus dose can be multiplied by 4 (four) to obtain the IU/h to be given for a period of 15 minutes.

Maintenance Dose (IU/day) = ((100 – X)/0.426) x Patient Weight

(Maintenance dose in international units per day equals 100 minus 'X' divided by 0.426, then multiplied by patient weight (in kg), where 'X' is the patient's pre-dose AT activity level.)

Therapeutic monitoring and Dose Adjustment:

After the **start of the maintenance dose infusion**, blood for AT activity levels should be drawn at 0.5 hour (i.e. this is 45 minutes after the start of the loading dose infusion). Based on the result of this AT activity level, the infusion rate (and consequently the dose) should be adjusted using the following guideline:

1. If the AT activity level is between 80% and 120%, no dose adjustment is needed. Take an AT activity level 4 hours calculated from the time of the previous AT activity blood draw.

2. If the AT activity level is less than 80%, increase the maintenance infusion rate by 50% and take a blood AT activity level 0.5 hour after the infusion rate adjustment.
3. If the AT activity level is greater than 120%, decrease the infusion rate by 30% and take a blood AT activity level 0.5 hour after the infusion rate adjustment.

When the next AT activity level is available, based on these results the dose will be adjusted again using the following guideline:

1. If the AT activity level is between 80% and 120%, no dose adjustment is needed. In case this is the second consecutive AT activity level that is within the target range, next blood sample should be taken at least every 24 hours afterwards (calculated from the start of treatment) for the duration of treatment with rh AT. In case this is the first AT activity level that is within the target range, take an AT activity level 4 hours calculated from the time of the previous AT activity blood draw.
2. If the AT activity level is less than 80%, increase the maintenance infusion rate by 50% and take a blood AT activity level 0.5 hour after the infusion rate adjustment.
3. If the AT activity level is greater than 120%, decrease the infusion rate by 30% and take a blood AT activity level 0.5 hour after the infusion rate adjustment.

This cycle of AT activity checking will be repeated until there are two consecutive samples that show an activity in the target range of >80% and <120%, and at least every 24 hours afterwards (calculated from the start of treatment) for the duration of treatment with rh AT.

It is possible that the procedure or delivery will influence AT activity levels. Therefore, an additional check of the AT activity level should be done approximately one hour after the surgery or delivery. In case the activity level is below 80% a 15 minutes bolus infusion of AT can be given to quickly restore the AT activity level. The dose can be calculated with the formula:

$$\text{Bolus Dose (IU)} = ((100 - Y)/2.28) \times \text{Patient Weight}$$

(Bolus dose in international units equals 100 minus 'Y' divided by 2.28, then multiplied by patient weight (in kg), where 'Y' is the patient's post-surgery or delivery AT activity level.)

For easier programming of the infusion pump, the calculated bolus dose can be multiplied by 4 (four) to obtain the IU/h to be given for a period of 15 minutes. In order to check the effect of this, an AT activity level blood sample is recommended 0.5 hour after the bolus dose administration was stopped.

All administrations of rh AT will be carefully documented in the patient's CRF.

APPENDIX 2

DOSE ADMINISTRATION AND DOSE MONITORING FOR PHASE 3 STUDY GTC AT HD 012-04

Dosing for Non-pregnant Surgical Patients

For non-pregnant surgical patients the required loading dose is determined using the following formula:

$$\text{Loading Dose (IU)} = [(100 - \text{patient's pre-treatment antithrombin activity in \%}) \text{ divided by } 2.28] \times \text{Patient Weight in kg}$$

For example, a loading dose in a non-pregnant surgical patient with a baseline AT activity of 50% would be approximately 22 IU/kg bodyweight. The loading dose should be given as a 15 minute infusion immediately followed by initiation of the maintenance infusion.

For easier programming of the infusion pump, the calculated loading dose can be multiplied by 4 to obtain the IU/hour to be given over a period of 15 minutes.

The required maintenance dose for non-pregnant surgical patients is given as a continuous infusion and is determined using the following formula:

Maintenance Dose (IU/hour) = [(100 – patient’s pre-treatment antithrombin activity in %) divided by 10.22] x Patient Weight in kg

For example, a maintenance dose in a non-pregnant surgical patient with a baseline AT activity of 50% is approximately 5 IU/kg/h. See the AT activity monitoring and dose adjustment recommendations

Dosing for Pregnant Patients

For pregnant patients the required loading dose is determined using the following formula:

Loading Dose (IU) = [(100 – patient’s pre-treatment antithrombin activity in %) divided by 1.25] x Patient Weight in kg

For example, a loading dose in a pregnant patient with a baseline AT activity of 50% is approximately 41.5 IU/kg bodyweight. The loading dose should be given as a 15 minute infusion immediately followed by initiation of the maintenance infusion. For easier programming of the infusion pump, the calculated bolus dose can be multiplied by 4 to obtain the IU/hour to be given over a period of 15 minutes.

The required maintenance dose for pregnant patients is given as a continuous infusion and is determined using the following formula:

Maintenance Dose (IU/hour) = [(100 – patient’s pre-treatment antithrombin activity in %) divided by 5.43] x Patient Weight in kg

For example, a maintenance dose in a pregnant patient with a baseline AT activity of 50% is approximately 9 IU/kg/h. The patient weight used for both the loading and maintenance dose is the actual weight of the pregnant patient just before initiation of treatment.

Therapeutic AT activity Monitoring and Dose Adjustment Guidelines (Non-pregnant surgical and pregnant patients)

The maintenance dose should be adjusted on the basis of laboratory measurements of antithrombin activity. Response to rhAT may vary in individual patients, achieving different levels of in vivo recovery and different half-lives. Frequent antithrombin activity assessments and dosing adjustments may be necessary when starting treatment and just after surgery or delivery.

Antithrombin activity should be checked 2 hours after initiation of the loading dose. In case the antithrombin activity is below 80% or above 120%, the maintenance infusion rate should be increased or decreased by 30%, respectively.

Two hours after a dose adjustment or if no adjustment was made, approximately 6 hours after the start of infusion, another antithrombin activity sample should be taken. Again, in case the antithrombin activity is below 80% or above 120%, the maintenance infusion rate should be increased or decreased by 30%, respectively.

Subsequently, antithrombin activity should be checked 1-2 times a day and dose adjustments made accordingly. The antithrombin activity should be maintained above 80% for the duration of the treatment.

All administrations of rhAT and any dose adjustments should be carefully documented in the patient’s CRF .

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