

Statistical Review and Evaluation - Atryn

STATISTICAL REVIEW AND EVALUATION

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Product/Application Antithrombin alfa (ATryn)
Sponsor: GTC Biotherapeutics, Inc.
Title of document: Historical Cohort Study to Assess the Incidence of Thromboembolic Events Following Prophylactic Intravenous Administration of Plasma Antithrombin to Hereditary Antithrombin (AT) Deficient Patients Undergoing High-risk Elective Procedures
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Executive Summary:

The treatment of ATryn is proposed as an indication for the prevention of peri-operative and peri-partum thromboembolic events, as well as the treatment of such events, in hereditary antithrombin deficient (HD) patients.

Due to the **rarity of HD** patients in the general population and study, FDA agreed that the prophylactic ATryn treatment could be compared with the historical control of hereditary AT deficiency (HD) patients treated with human plasma-derived AT during high risk situations to establish the therapeutic value of ATryn using a non-inferiority margin of 20%.

The study was to assess the non-inferiority of ATryn compared to plasma-derived AT. The acceptance criterion of non-inferiority was based on the lower 95% confidence bound of the incidence difference (95% LL of Plasma AT-ATryn \geq -0.20). The results of the study have met the stated goal of non-inferiority.

Introduction:

Antithrombin (AT) concentrate is used for the prophylaxis of the occurrence of venous thromboembolisms in hereditary AT deficient patients in high risk situations, e.g. surgery or baby delivery. The target is to restore plasma AT activity levels in order to cover the

period during which chronic anticoagulation often needs to be interrupted and ensure that the current thromboprophylaxis is effective.

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

Due to the **rarity of HD** in the general population, FDA agreed that the prophylactic ATryn treatment could be compared with the historical control of hereditary AT deficiency (HD) patients treated with human plasma-derived AT during high risk situations to establish the therapeutic value of ATryn.

In the submission, the efficacy analysis consists of the patients treated in two separate prospective trials (GTC ATIII01002n and GTC AT HD 012-04), studying the efficacy of ATryn in preventing thromboembolic complication in HD patients during a high risk situation.

OBJECTIVES:

- **Primary Objective :** To estimate the **incidence of thromboembolic events** [acute deep venous thrombosis (DVT) and/or thromboembolic events other than acute DVT] in hereditary **Antithrombin (AT)** deficient (HD) patients who have received prophylactic treatment with plasma-derived AT during elective procedures with a high risk for the occurrence of a thromboembolic event, and **to assess the non-inferiority of ATryn compared to plasma-derived AT** in combination with data from two other ATryn studies for prevention of any thromboembolic event.
- **Secondary Objective :** To estimate the **incidence of acute DVT and the incidence of thromboembolic event other than acute DVT in HD patients** who have received prophylactic treatment with plasma AT during elective procedures having a high risk for the occurrence of a thromboembolic event and, in combination with data from two other studies of ATryn, to assess the non-inferiority of ATryn compared to plasma AT for prevention of acute DVT and thromboembolic events other than acute DVT.

Study Design:

The basic study approach can be summarized as follows:

1. Use of a historical cohort design involving a minimum 35 and maximum of 70 patients at approximately 5 to 15 U.S. and European sites who (1) have HD and a personal history of thromboembolic events, (2) underwent an elective procedure having a high risk for the occurrence of a thromboembolic event, and (3) at the time of the high-risk procedure, were treated prophylactically with plasma AT.
2. Selection of sites will be based on the availability of a listing or automated medical record system that identifies all patients who have HD and/or those patients who received plasma AT since 01 January 1997.
3. Using patient records identify all eligible patients at each study site and obtain informed consent/medical records release and Health Insurance Portability and Accountability Act (HIPAA) authorization (where applicable).
4. Collection of screening information to document whether or not each plasma AT-treated HD patient in the listing or automated medical record system is enrolled in the study and, if not, the reason not enrolled.
5. Abstraction of relevant medical record information onto case record forms (CRFs) by an independently contracted organization.

6. Using the standard statistical methods to estimate the incidence of any thromboembolic event, acute DVT, and thromboembolic events other than acute DVT for patients treated with plasma AT and subsequently.
7. Comparing the incidence of any thromboembolic event, acute DVT, and thromboembolic events other than acute DVT associated with plasma AT administration as estimated in the historical cohort study with the incidence for patients treated with ATryn as determined in protocols GTC AT III 01002 and GTC AT HD 012-04 in order to assess the non-inferiority of ATryn.

Endpoint :

Primary Endpoint :

The primary endpoint is the incidence of **any thromboembolic event** occurring during the treatment with ATryn (or in the 7 days follow-up period after cessation of ATryn) and plasma-derived AT treatment.

Secondary Endpoint : The incidence of confirmed acute of DVT and of confirmed thromboembolic events other than acute DVT, respectively.

Acceptance Criteria :

Non-inferiority of 20% will be demonstrated if the lower 95% confidence bound of the incidence difference (Plasma AT-ATryn) is ≥ -0.20 .

Sample size :

The sample size was computed based on the following assumptions:

1. 80% power,
2. type I error 5%,
3. common incidence of any thromboembolic event in the two groups is 0.1
4. non-inferiority margin 0.2.

Comments:

- Based on the above assumptions, the sample size of 32, was obtained for each group (using ---b(4)--- software); however the final sample sizes in the study were 31 in ATryn group and 35 in Plasma AT group.

Results:

Demography Descriptions :

Table of RACE by TREAT

Freq. (Percent)		Treatment		TOTAL
		PLASMA	ATryn	
RACE	ASIAN	1 (1.52%)	0	1 (1.52%)
	CAUCASIA	34 (51.52%)	29 (43.94%)	63 (95.45%)
	EGYPTION	0	1 (1.52%)	1 (1.52%)
	INDIAN	0	1 (1.52%)	1 (1.52%)
TOTAL		35 (53.03%)	31 (46.97%)	

Table of RACE by SEX

Freq. (Percent)		Treatment		TOTAL
		PLASMA	ATryn	

GENDER	MALE	5 (7.58%)	6 (9.09%)	11 (16.67%)
	FEMAL	30 (45.46%)	25 (37.88%)	55 (83.33%)
TOTAL		35 (53.03%)	31 (46.97%)	

TREAT	N Obs	Var	N	Mean	Std Dev	Minimum	Maximum
Plasma_A	35	AGE	35	44.0000000	14.3383484	24.0000000	78.0000000
		WTKG	34	78.9000000	14.8553021	58.0000000	118.0000000
		HTCM	33	166.7363636	6.4816963	152.0000000	175.0000000
ATryn	31	AGE	31	37.1290323	12.7951604	21.0000000	74.0000000
		WTKG	31	80.2741935	19.0393096	45.0000000	140.0000000
		HTCM	28	167.8071429	8.7938079	145.0000000	180.0000000

T-Tests

Variable	Method	Variances	DF	t Value	Pr > t
AGE	Pooled	Equal	64	2.04	0.0452
AGE	Satterthwaite	Unequal	64	2.06	0.0437
WTKG	Pooled	Equal	63	-0.33	0.7455
WTKG	Satterthwaite	Unequal	56.7	-0.32	0.7484
HTCM	Pooled	Equal	59	-0.55	0.5869
HTCM	Satterthwaite	Unequal	48.9	-0.53	0.5964

Wilcoxon Two-Sample Test (two sided test)

Variable	Normal Approx. (p-value)	T Approx. (p-value)
AGE	0.027	0.0305
WTKG (Weight)	0.718	0.719
HTCM (Height)	0.4506	0.4536

- In this study, 95% of the subjects are Caucasian and 83% are women, however the race and sex are distributed approximate evenly between treatments.

- The mean age in Plasma group (44 yrs) is older than the mean age in ATryn group (37 yrs). The difference shows statistically significant by using either parametric or non-parametric approach.

- The weight and the height between two groups are not significantly different.

Primary objective:

- **95% CI for incidence.**

	ATryn	Plasma
Positive	1	0
Negative	30	35
Total	31	35

	Risk	ASE	(Asymptotic) Confidence	95% Limits	(Exact) Confidence	95% Limits
Plasma	0.0000	0.0000	0.0000	0.0000	0.0000	0.1000
ATryn	0.0323	0.0317	0.0000	0.0945	0.0008	0.1670

- No patient in plasma AT group experienced a confirmed thromboembolic event, either acute DVT or a thromboembolic event other than acute DVT. The 95% confidence interval for the thromboembolic event is (0%, 10%).
- Only 1 patient in the ATryn treatment group experienced a thromboembolic event (Acute DVT) and no patient experience confirmed thromboembolic event other than acute DVT. The 95% confidence interval for the thromboembolic event is (0.08%, 16.7%).

1. **95% CI for the incidence difference between Plasma (control) and ATryn (treatment) groups.**

Binomial Proportions [col1]: piHat_1 (control)	0.03226
Binomial Proportions [col2]: piHat_2 (treatment)	0
Difference of Proportions: piHat_2 - piHat_1	-0.03226
Std. Error: (pooled estimate of stdev of piHat_2-piHat_1)	0.03013
Standardized Difference: (piHat_2-piHat_1)/Stderr	-1.071

Type	P-value		95% confidence interval (P(plasma)-P(ATryn))	
	1-sided	2*1-sided	Lower Limit	Upper Limit

Type	P-value		95% confidence interval (P(plasma)-P(ATryn))	
Asymptotic	0.1422	0.2843	-0.1634	0.06979
Exact	0.2401	0.4801	-0.167	0.07768

- The lower 95% confidence bound of the incidence difference between treatment groups was -0.167 which is greater than the protocol-specified lower confidence bound of -0.2. This demonstrates that ATryn **is non-inferior to** plasma AT in terms of the prevention of thromboembolic events.
- In this study, there is only one event in ATryn treatment, no event in Plasma AT treatment; and this event is Acute DVT; the secondary objective is to estimate the incidence of acute DVT and the incidence of thromboembolic event other than acute DVT in HD patients, thus the results of secondary is the same as primary objective.
Comments to CBER:
- The lower 95% confidence limit for the incidence difference between Plasma AT and ATryn groups was -0.167 (1/31 vs. 0/35 using --b(4)----) which is different from the sponsor's result, -0.1722. The value, -0.1722, is the exact lower 95% confidence limit for the incidence difference between 1/30 and 0/35. Based on these results, the study has achieved the stated goal of non-inferiority.
- However, based on the trial design with historical control and a large non-inferiority margin in the comparison to the incidence rates of thromboembolic events, there are some limitations for the ATryn treatment to be considered as non-inferior to plasma AT treatment.