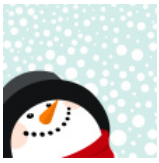
THAOS

Winter 2009



News Update

Issue 3

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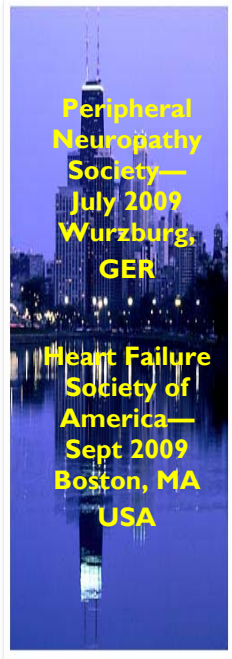
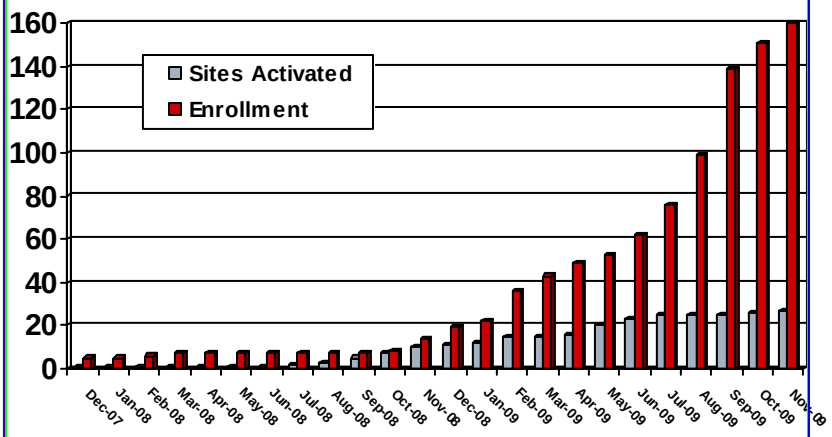
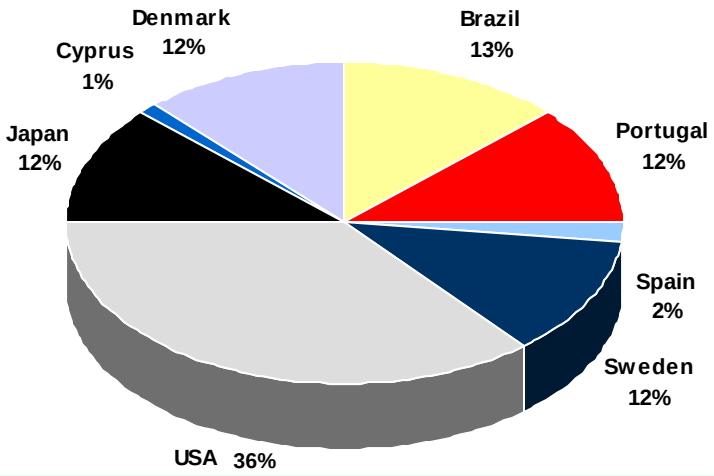
2009/2010 THAOS Posters



Over this past year, THAOS has expanded to include 28 sites in 11 countries. Enrollment has been steady, averaging 7 subjects per month. A surge in enrollment occurred in September when 40 subjects were enrolled in anticipation of the second data extraction and analysis. We anticipate recruitment to climb when 6 additional countries are initiated in the coming months. We want to thank all our centers for such a phenomenal effort in identifying and enrolling subjects. In particular, we wish to congratulate Márcia Waddington-Cruz of the Hospital Universitario Clementino Fraga Filho, in Brazil, and Mat Maurer, Columbia University Medical Center, USA, as our highest enrolling sites each with 21 subjects enrolled. We would also like to acknowledge Shû-ichi Ikeda, Shinshû University Hospital, Japan, with 20 subjects; and Ole Suhr, Umeå University Hospital, Sweden, and Henning Mølgaard, Åarhus University Hospital, Denmark each with 19 subjects enrolled. We thank all of you for your efforts and look forward to a spectacular 2010!

Congratulations THAOS Team!!!
160 Subjects Enrolled in 8 Countries





Clinical Trial Subjects to Enter THAOS

An amendment to the THAOS protocol will be sent to participating sites in early January 2010. The purpose of the amendment is to allow subjects participating in clinical trials to enroll in THAOS. The amendment removes the exclusion criteria prohibiting clinical trial subjects from participating in THAOS and clarifies data entry for open-label and double-blind investigational clinical trials. If a patient elects to participate in a double-blind investigational clinical trial, collection of THAOS data will be temporarily suspended during the period that the patient is taking study drug (or device), as it is not known whether the patient is receiving active drug or placebo. Data collected prior to a patient receiving treatment in a double-blind investigational trial (e.g., baseline, pre-treatment assessments, or any historical data), as well as data collected after the patient's completion or withdrawal from a double-blind investigational trial, can be entered into the THAOS database. Subjects participating in an open-label trial are receiving active drug; therefore, all data collected during the open-label trial can be entered into THAOS. As the goal of the Survey is to document the course (or natural history) of TTR amyloidosis, the use of known interventions, including investigational agents or devices, will be permitted.

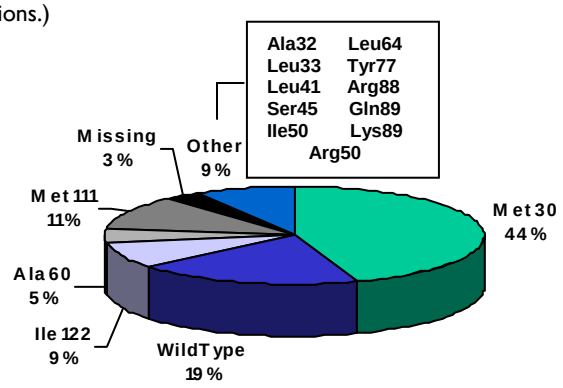
BASELINE AND ENROLLMENT ANALYSIS: THAOS Progress

Baseline Characteristics

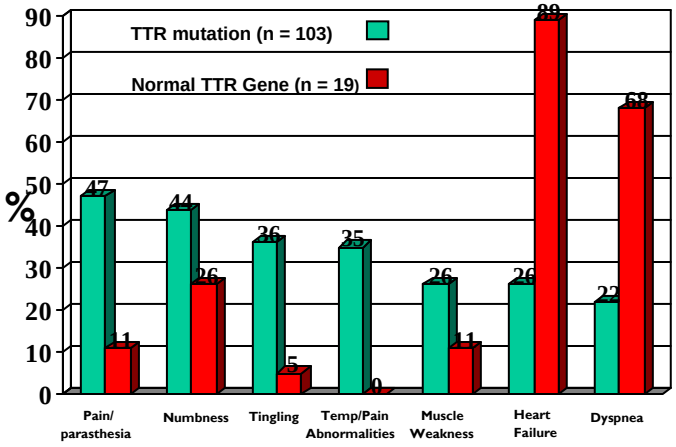
126 Patients enrolled in 7 Countries

	Gender		TTR Genotype		All Subjects
	Male N=80	Female N=46	Normal TTR N=19	TTR Mutation N=103	126
Age (mean yrs)	60.4	50.1	77.7	52.6	56.7
Race/Ethnicity n (%)					
Caucasian	55 (68.8%)	37 (48.4%)	17 (89.5%)	73 (70.9%)	92 (73%)
African/ Descent	13 (16.3%)	2 (4.3%)	1 (5.3%)	12 (11.7%)	15 (11.9%)
Asian	7 (8/8%)	4 (8.7%)	0 (0.0%)	11 (10.7%)	11 (8.7%)
Other	4 (5.0%)	3 (6.6%)	0 (0.0%)	7 (6.8%)	7 (5.6%)
Missing	1 (1.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (0.8%)

Trigger for our second data extraction and analysis was the enrollment of 100 subjects, and the goal was set for October 2, 2010. The THAOS Team easily surpassed this number and enrolled 140 subjects. Of these, 126 subjects had signed data that were available for analysis. Males outnumbered females by 2 to 1; the average age for all subjects was 56.7 years, and 73% were Caucasian. There were 122 subjects with recorded TTR Genotype: 19 Normal TTR (18 males) and 103 subjects with mutations (a total of 15 different mutations.)



Most Commonly Reported TTR-Related Symptoms



Pain/parasthesia topped the list of TTR-related neurologic symptoms with 58% of subjects reporting this as the most common symptom. Heart failure was the most common cardiovascular symptom. Although data are based on a small number of subjects, please note that all genotypes report both neurologic and cardiovascular symptoms.

Demographics of Top 2 Genotypes

	Male n = 80	Female n = 46	All Subjects n = 126
Val30Met	**n = 31**	**n = 28**	**n = 59**
Age (mean yrs)	51.0	48.1	49.6
Race n (%)			
Caucasian	21 (67.7%)	22 (78.6%)	43 (72.9%)
African-descent	1 (3.2%)	0 (0.0%)	1 (1.1%)
Latino-American	2 (6.5%)	1 (3.6%)	3 (5.1%)
Asian	5 (16.2%)	3 (10.7%)	8 (13.6%)
Other	2 (6.5%)	2 (7.1%)	4 (6.8%)
Normal TTR Gene	**n = 18**	**n = 1**	**n = 19**
Age (mean yrs)	78.1	71.0	77.7
Race n (%)			
Caucasian	16 (89.9%)	1 (100%)	17 (89.5%)
African-descent	1 (5.6%)	0 (0.0%)	1 (5.3%)
Missing	1 (5.6%)	0 (0.0%)	1 (5.3%)

Biopsies = 90 Subjects with a total of 117 Biopsies

	Male n = 80	Female n = 46	Normal TTR n = 19	TTR Mutation n = 103	All Subjects n = 126
No Subjects with Biopsy	66/80	24/46	19/19	70/103	90/126
Total No of Biopsies Done	89	28	23	93	117
Cardiac	37/89	5/28	19/23	22/93	42/117
Abdom/Fat Pad	19/89	9/28	2/23	26/93	28/117
Nerve	9/89	3/28	0	12/93	12/117
GI	9/89	0	0	9/93	9/117
Rectal	4/89	1/28	1/23	4/93	5/117
Other	9/89	8/28	1/23	16/93	17/117

Organ Transplants = 31 patients received a total of 36 transplants

No Subjects with Transplants	23	8	1	29	31

24 subjects with Liver transplants
3 subjects with Heart
3 subjects with Liver and Heart
1 subject with Liver, Heart, Kidney

Other Data Reported

	Normal TTR Gene n = 19	TTR Mutation n = 103	All Subjects n = 126
Electrocardiogram n(%)	14 (73.7%)	37 (35.9%)	53 (42.1%)
Abnormal	14/14 (100%)	22/37 (59.5%)	38/53 (71.7%)
Echocardiogram n(%)	9 (47.4%)	28 (27.2%)	39 (31%)
Nerve Conduction Study n(%)	0 (0.0%)	29 (28.2%)	30 (23.8%)

THAOS is growing and already providing much-needed information. The Scientific Board reviewed the data and was comfortable with the baseline demographics and description of the subjects from a medical history perspective, but expressed concern that not enough objective data were being recorded at baseline. This will limit the analysis of change over time. The Board recommended that there should be a minimum evaluation for all TTR subjects regardless of mutation. On the following page, the minimal dataset for each patient enrolled in THAOS, regardless of genotype or phenotype, including asymptomatic carriers will be discussed.

THAOS Scientific Board to Expand

The Scientific Board (the "Board") is a group of scientific and clinical experts in the field of amyloid disease who provide scientific oversight, analysis, and interpretation of the data originating from THAOS and all THAOS sub-studies. The current Board includes Teresa Coelho, Chairperson; Violaine Planté - Bordeneuve, Ole B. Suhr, Shû-ichi Ikeda, Mathew Maurer, Rodney Falk, Pedro Trigo, Bö -Goran Ericzon (representing FAPWTR), and Donna Grogan (FoldRx). The Board is intended to include experts in the field and at the same time have geographical representation. The Board will now be transformed into a larger body with more site and country representatives. Any site enrolling at least 20 subjects (with the minimal dataset for evaluation-defined in the Appendix and discussed below) can request representation to the Board. In addition, any country enrolling at least 20 subjects (with the minimal dataset) across two or more sites can request a representative to the Board. The 'country' representative will be selected by national collaborative groups, where such groups exist. The Board will appoint a national representative when a national collaborative group does not exist. Due to the heterogeneity of patients affected by TTR amyloidosis and the complexity of studying its natural history and associated outcomes, it is desirable that multiple disciplines and areas of expertise be represented. The Scientific Board Charter has been amended and will be forwarded shortly to all participating THAOS sites.

Minimal Dataset for Evaluation

(*continued from previous page and above.*)

THAOS, a natural history database, is following subjects over a ten-year period. Although the protocol does not require any specific tests or procedures to be performed, the value of the database lies in the completeness and careful recording of all data obtained from the clinic visit. The following is the recommended minimal dataset for each patient enrolled in THAOS, regardless of genotype or phenotype, including asymptomatic carriers:

- Registration
- TTR data
- Family History
- Medical History (general assessment on follow-up)
- Physical Examination
- Serum albumin levels
- Electrocardiogram
- Serum NT-ProBNP or BNP levels (if abnormal, then echocardiogram would be recommended)
- Pinprick, touch and vibration of great toe (both sides); ankle and patellar reflexes; muscle strength of toes and ankles (if abnormal, then either perform full neurologic examination or refer to neurology for evaluation).

Yearly follow-up is recommended, with re-evaluation of the minimal assessments at the least. It is requested that complete clinic visit evaluation data along with Quality of Life are entered into THAOS

THAOS Reminders

Patient Follow-up—Remember to enter follow-up data for your patients each year. The database is being revised to send an email to each site when a patient is nearing their one-year anniversary date.

Continuing Review—If your site requires EC/IRB approval yearly for THAOS/ Substudy, please send a copy of the Continuing Review Approval and updated ICF for record keeping.

Database—'Medical History' records symptom history and is to be completed during the baseline visit. 'General Assessment' records symptom follow-up and is to be completed during all follow-up visits. Please do not complete the 'general assessment' at the baseline visit.

For Payment—a 'Patient Visit' is defined as completing and signing the following sections: Baseline visit— *Registration, TTR data, Family History, Medical History; Visit Data (General Exam, Concom Meds (if any), Labs, Transplant History (if any); Assessments (Neurologic and other Assessments if appropriate.)* Follow-up visit—*Visit Data and Assessments*

Our next **Goal**

200 subjects

First THAOS publication - baseline and enrollment data for the first 200 enrolled subjects.