NEW CORRESP ORIGINAL

genzyme

GENZYME CORPORATION
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January 9, 1998

4/8/98 Data /S/

/S/ 1/13/98

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
General Correspondence

CENTER FOR DRUG EVALUATION AND RESEARCH RECD JAN 12 1998 HFD-510

Noted /S/ Information requested by Dr. Ju for audit 4/13/98

H.W. Ju, M.D.
Division of Scientific Investigation
Food and Drug Administration
HFD-344, Room 125
7520 Standish Place
Rockville, MD 20855

RE: Thyrogen® NDA: Clinical Audits

Dear Dr. Ju:

Further to your request during our conversation December 16 and your conversation with Loan Tran December 31, I have enclosed information to assist your efforts to audit several investigational sites as a part of the Thyrogen® NDA (20-898) review process.

This submission consists of four volumes. The first volume is for your reference and contains this letter, the tables of contents for each of the four volumes, and some additional information for your reference relevant to the consistency of data acquisition across the 14 investigational sites of the second Phase III multi-national trial, TSH95-0101. Volumes 2-4 contain the information you requested for the investigational sites of Dr. Bruce Weintraub (NIH), Dr. David Cooper (Baltimore), and Dr. E. Chester Ridgway (Denver).

In addition please make note of the following issues:

- Dr. Weintraub has left NIH since the TSH92-0601 study was completed. He remains the responsible investigator for the study but at the site Dr. Monica Skarulis will also be available to assist. Dr. Skarulis was the principal investigator at NIH in the most recent Thyrogen study, TSH95-0101.

- A randomization schedule for Dr. Weintraub's site does not exist. Patients were not randomized for TSH92-0601 because the study consisted of a single arm with one dosing regimen.

- Enclosed with the CRFs for patient 801 from Dr. Cooper's site is a Medwatch form documenting a Serious Adverse Event which was determined to be unrelated to the use of Thyrogen. This form is a part of Genzyme's in-house file for this patient but this specific form may or may not be located at the site.

- One of the patients for whom you requested CRFs, patient 805 from Dr. Cooper's site, withdrew from the study after randomization and before any study procedures were conducted.

• Enclosed with the CRFs for a few patients are "Notes to File" which are specifically related to patient data. Copies of these records are at the site but may or may not be located in each patient file. However, the data was verified by site personnel as indicated by the appropriate signature on each note.

I will also send a copy of this submission to the attention of Steve McCort in the Division of Metabolism and Endocrine Drug Products for his information and for the IND file.

Thank you and if you have any questions please do not hesitate to call me at (617) 252-7676.

Sincerely,

Matthew R. Patterson
Senior Regulatory Affairs Associate

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

genzyme

GENZYME CORPORATION
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December 12, 1997

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products
HFD-510
Document Room, 14-B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Thyrogen® (thyrotropin alfa)
New Drug Application #20-898

Dear Dr. Sobel:

In accordance with the Federal Food, Drug, and Cosmetic Act and the regulations contained in Section 314.50 of Title 21 of the Code of Federal Regulations, Genzyme hereby submits a New Drug Application for Thyrogen® (thyrotropin alfa). This product has been studied under IND [redacted]

Thyrogen® is proposed for use as an adjunct to radioiodine imaging and/or serum thyroglobulin testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients [redacted] For this use, Thyrogen has been granted orphan drug status under Orphan Drug Designation [redacted] approved February 14, 1992.

Genzyme hereby requests consideration for accelerated review of this New Drug Application, as provided for in Title 21CFR 314, subpart H. In clinical trials, Thyrogen has been shown to be safe and effective for the diagnosis of thyroid cancer, a serious life-threatening condition; and results indicate that the use of Thyrogen confers meaningful benefit over current procedure which causes debilitating hypothyroid signs and symptoms.

Reference is made to the pre-NDA meeting between Genzyme and the Division of Metabolic and Endocrine Drug Products on June 16, 1997. During the meeting, the format for this NDA was discussed and agreed upon. This included the modified application format and the electronic submission of the SAS data sets, case report forms (CRFs) and patient data listings (in place of CRF tabulations). Additionally, Genzyme agreed to provide an independent expert opinion on the risks and benefits of Thyrogen®, especially as it relates to the possible risk of missing cancer patients. This report is provided with the company's integrated summary of benefits/risks.

Please contact me directly at 617-761-8924 or Matthew R. Patterson, Senior Regulatory Affairs Associate at 617-252-7676 with any questions regarding this submission.

We look forward to your review and comments on this New Drug Application.

Sincerely,

Loan T. Tran, Pharm.D.
Director, Regulatory Affairs

Enclosure: Thyrogen NDA, Volumes 1-68

APPEARS THIS WAY
ON ORIGINAL

genzyme

GENZYME CORPORATION
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December 2, 1997

Ref: IND#

IND Serial No. 135

Dr. Solomon Sobel
Director
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Parklawn Bldg., HFD-510, Rm. 14-B-30
5600 Fishers Lane
Rockville, MD 20857

RE: Thyrogen® NDA (Pre-assigned #20-898)
User Fee Waiver

Dear Dr. Sobel:

Reference is made to the above cited Investigational New Drug Application submitted on July 10, 1991.

The purpose of this submission is to notify FDA that Genzyme does not plan to include a User Fee with the upcoming submission of the Thyrogen® NDA, planned for December 12, 1997. This omission is justified because Thyrogen® is designated as an Orphan Drug Product (Orphan Drug Designation and according to recent legislation passed by the U.S. Congress, User Fees are waived for Orphan Drug Products. The "Food and Drug Administration Modernization Act of 1997" was signed into law by the President on November 21, 1997.

The relevant reference of the Act is Title 1-Improving Regulation of Drugs: Subtitle A-Fees Relating to Drugs: Section 103 (a)(2)(C). This information can be found on page S.830-5 of the Act.

Thank you and please do not hesitate to call me with any questions at (617) 252-7676.

Sincerely,

Matthew Patterson
Senior Regulatory Affairs Associate

NDA 20-898
Thyrogen (thyrotropin alfa)
Genzyme Corporation
Date of submission: December 12, 1997
Date of review: April 20, 1998

Medical Team Leader's comments on NDA

Background and overview of NDA

Thyrogen proposed use

Thyrogen (thyrotropin alfa, recombinant human TSH, rTSH) has been developed for use as an alternative to thyroid hormone withdrawal (WD) in follow up testing to assess progression of thyroid cancer in patients status post surgical and/or radioactive iodine (RAI) ablation of normal and cancerous tissue. In effect, it is intended to replace what might well be called "the endogenous TSH stimulation test" that is performed by withdrawal of exogenous suppressive doses of thyroid hormone.

Target population

According to the sponsor's summary, 28,000 new cases of thyroid cancer are diagnosed in the U.S. each year, of which 80-90% are well-differentiated tumors variably TSH responsive, iodine concentrating, and thyroglobulin (Tg) producing. The prevalence of thyroid cancer is approximately 188,000 in the U.S., and 2,300 deaths in the U.S. annually are attributed to the disease. Local recurrences in the thyroid bed and cervical area occur in 5 to 15% of thyroid cancer patients, and distant metastases occur in 10-15% of patients.

As discussed further below, virtually all patients with well-differentiated thyroid cancer will undergo Tg testing and RAI scanning after withdrawal of thyroid hormone at least once in follow up after initial surgery with or without post-operative RAI ablation. Many patients, depending on risk category and course of disease will be withdrawn for Tg measurement and scanning multiple times through the courses of their cancers. Thus, as a substitute for withdrawal, the use of Thyrogen is potentially quite extensive, both in terms of patient numbers and overall courses of treatment.

Thyroid cancer treatment and follow up

The first step in the treatment of newly diagnosed thyroid cancer is total thyroidectomy. After recovery from the surgery, thyroid hormone replacement therapy is withdrawn and patients undergo whole body scanning (WBS) with radioactive iodine (131-I) to reveal the presence of residual normal tissue, local residual tumor, and/or metastatic disease. Most patients will then receive an ablative dose of radioiodine as therapy for residual cancer and/or to obliterate any residual normal tissue in order that future follow up testing will not be confounded by the presence of the latter. Patients are then maintained on doses of thyroid hormone sufficient to suppress TSH to below the limits of detection while not inducing clinical hyperthyroidism. This, then, is standard chronic "treatment" of

differentiated thyroid cancer, obviously necessary for survival in thyroidectomized individuals, but also assumed to suppress the growth of tumor.

Physiology in follow up testing

Follow up thereafter involves periodic monitoring for recurrence or progression of disease. Several principles are active here. First, the presence of detectable Tg in the serum and/or foci of RAI uptake indicate functional follicular cell derived tissue (FCDT). Second, well-differentiated thyroid cancers are TSH-sensitive, and can be stimulated to function (produce Tg, take up RAI) in the setting of elevated TSH.

Clinical follow up

Tg on THST

Because frequent withdrawal is impractical, many, if not most, clinicians follow low-risk patients with periodic measurements of Tg on thyroid hormone suppressive therapy (THST). Presumably because of the extreme-TSH-dependent nature of certain thyroid cancers and, of course, dependent upon the amount of FCDT present, there may significant numbers of false negative Tg measurements on THST.

Withdrawal testing

As a rule, most clinicians render definitive clinical decisions based on the results of both scanning and Tg testing after WD of thyroid hormone. It is on the basis of these complementary tests of the presence of functional FCDT, performed essentially simultaneously, that the decisions about further follow up and about whether or not to treat with radioactive iodine are made.

Assumptions in testing after withdrawal

Two assumptions underlie the reliance on the data from these tests. First, prolonged TSH elevation accompanying withdrawal of thyroid suppressive therapy is a potent and consistent (reproducible within a given patient) stimulator of FCDT. Second, in individual patients, as a function of tumor differentiation, the Tg level after WD is a direct correlate of the burden of FCDT. Thus, even if absolute response to withdrawal differs from patient to patient, the consistency of the "endogenous TSH stimulation test" permits comparison of serial test results within a given patient as a measure of disease stability, progression, or regression. Finally, it has long been known that stimulation by TSH of previously suppressed FCDT is a function of both TSH level and duration of elevation. Thus, withdrawal of thyroid hormone for a time sufficient to permit endogenous TSH to rise to at least 25 mU/L has been shown to lead to optimal Tg elevation and RAI uptake in patients with well-differentiated thyroid cancer.

The complexity of clinical decision-making in thyroid cancer follow up

Thyroid cancer is a disease that is highly variable in its course. This appears related to degree of differentiation of the tumor (thus its rate of growth, tendency to metastasize, ability to concentrate iodine and thus susceptibility to ablation with RAI), individual host factors as age, and stage of disease at diagnosis and initial treatment. Because of this variability and despite the use in follow up of disease status that can be made of the

thyrotrophic hypothalamic-pituitary axis described above, clinical decision-making is based on more than just an objective "scoring" of the scan and Tg data. Physicians practicing in this area consider this information as well as information pertaining to the individual's risk of having residual or recurrent disease in light of their own experience (thus their personal approaches to the disease) and often in the context of institutional guidelines or consensus. In short, for many patients, especially those at low risk and/or with apparent small burden of disease, clinical decisions regarding further investigation of, for example, a low but detectable Tg on THST, or regarding administration of a therapeutic dose of radioiodine, are "judgment calls." There are few fixed, universal rules guiding management in this disease, though guidelines abound.

What is required of Thyrogen as a substitute for withdrawal?

In light of this, what are the critical characteristics necessary in a testing method using exogenously administered TSH in order that it can replace thyroid hormone withdrawal? As a first approach, the obvious ideal would be an administration protocol that would be bioequivalent to the endogenous test. That is, the concentration-time curve for Thyrogen would mimic that achieved on WD. Short of that, an administration procedure accomplishing pharmacodynamic equivalence could be established empirically. The goal in these two instances then, would be similar (and consistent within a given patient) degrees of Tg elevation and RAI uptake as seen on WD. With regard to scanning, adjustment of RAI dose for the increased renal iodine clearance in the euthyroid state is assumed. Short of absolute equivalence, at the very least, the relationship between endogenously stimulated and Thyrogen-stimulated Tg secretion and RAI uptake should be constant.

The experience with Thyrogen in clinical trials

The results of the Phase III studies of Thyrogen demonstrated none of the above. Thyrogen, as administered in the studies and as is recommended in proposed labeling, was generally less potent and clearly inconsistent as a stimulator of FCDT as measured by scan and Tg. Among discordant scan pairs, Thyrogen tended to underdiagnose disease relative to WD and there were significant numbers of false negative scans on Thyrogen (Thyrogen scan Class 0, WD or post-therapy scan Class$\geq$1) in both Phase III studies. Finally, there was no fixed mathematical relationship between Tg on Thyrogen and after WD. Generally, Thyrogen Tg's tended to be lower, but there was no constant whereby one value could be converted to the other. It is this evidence of the inconsistent effect of Thyrogen, in particular, that supports the conclusion that Tg on Thyrogen is not a reliable indicator of burden of disease. To the extent that Tg levels after WD are followed with precisely this assumption in mind, that they provide to the experienced physician information of both a qualitative and quantitative nature, and are critical in clinical decision making, Thyrogen Tg levels are at best limited in their diagnostic utility.

Comments on NDA

Thyrogen pivotal clinical trials

Design flaws and limitations

With regard to the design and conduct of the Phase III trials, several points bear mention. First, neither study was designed to test the overall utility of Thyrogen as compared to WD as a diagnostic modality in follow up of patients with thyroid cancer. Though many outcome variables were prospectively defined, both studies were effectively limited by their designs to permitting a comparison of the quality of the RAI scans derived by the two methods and of the Tg levels obtained after the alternative methods of FCDT stimulation.

Related to this is a second problem: that the scan readers were not appropriately blinded in either study. The readers always knew that they were reading scans in pairs, whether doing so sequentially or side-by-side. That they did not know which was Thyrogen and which was WD is immaterial. This lack of complete blinding defines the absence of an independent evaluation of the Thyrogen scans. Furthermore, as the readers knew the nature of the study in which they were involved, this would be expected to bias them, potentially towards erring on the side of judging concordance over discordance.

Scan results

Notwithstanding the potential for bias in interpretation, the scan data are still troubling. In the first pivotal study (TSH92-0601), the concordance rate cited by the sponsor is 83%. This is misleading because approximately half the WD scans were class 0. With the knowledge in retrospect that Thyrogen is a less "potent" stimulator of follicular tissue than WD, as would be expected, the concordance rate among these patients was 65/66 (99%). By contrast, there were 61 patients with WD scans of Class $\geq$1, and among these patients only 41 of the Thyrogen scans were concordant (67%). Indeed, among the 17 scan pairs (out of the 20 discordant pairs) in which the WD scan showed more disease that the Thyrogen scan, 12 were false negative Thyrogen scans. These were made up of 9 false negatives among the 46 Class 1 patients for a rate of 20%, 2 false negatives among 9 class 2 patients (22%), and one false negative among 4 Class 3 patients (25%). While these are likely inaccurate point estimates of the true false negative rates for Thyrogen scanning, one can only conclude that expected rates would be substantial and therefore clinically significant.

In the second pivotal study, TSH95-0101, the determination of concordance was based on cross-scan identity with regard to location and extent of disease, and did not require that the number of lesions counted be identical. In this study, scans were evaluated side-by-side. Tg was measured in a central lab using an assay with a limit of sensitivity of 0.5 ng/ml. All samples were measured in a single run, thus interassay variation is not an issue in the interpretation of these data.

The scan concordance rate given for TSH95-0101 was 89% in Arm I and 88% in Arm II. Again, the overall concordance rate is weighted by a high percentage of patients with negative WD scans. What is relevant to actual use is the Thyrogen false negative rate among the patients with positive WD scans. It is no surprise that Thyrogen can be used to accurately confirm a negative WD scan. Any benefit of Thyrogen is in its capacity to obviate the need for WD. In its simplest form, this would require that a negative

Thyrogen scan be, reliably, a true negative. In TSH95-0101, there were 7 false negative Thyrogen scans among 48 class ≥1 patients in Arm I (15%) and 7 false negatives Thyrogen scans among 60 class ≥1 patients in Arm II (12%). Most were among patients with WD class 1 scans, as these were the majority of the patients studied. Again, this is a clinically significant false negative scan rate.

Thyroglobulin data

In TSH92-0601, Tg levels were not measured in a central lab. One expects, however, that Tg pairs were assayed together. Despite this, there is still no correlation between Tg after Thyrogen and after WD.

In TSH 95-0101, as in the first study, there was no correlation between Tg after Thyrogen and after WD.

With clinical decisions always tempered by assessment of the pre-test likelihood of persistent or recurrent disease, the use of Tg is of particular importance in patients with negative scans. All else being equal, in such patients, an undetectable Tg provides assurance of the absence of significant FCDT. Current recommendations are that levels up to 10 ng/ml alert the clinician to increase his vigilance for recurrence (i.e., with more frequent repeat Tg testing and RAI scanning), and levels >10 ng/ml constitute an indication for an ablative dose of RAI. Here, it is important to emphasize that in individual patients, Tg is evaluated as a continuous variable (taking into account the interassay variation in Tg quantitation). Thus, even for levels below 10 ng/ml, a rising trend is clinically distinct from a falling or stable level over time.

These guidelines for monitoring and treatment suggest clearly that the utility of Thyrogen Tg can only be established if levels correlate closely with those on WD. The linear regression analysis performed by the statistical reviewer of this NDA of the Tg levels on Thyrogen versus WD in the subgroup of patients with Thyrogen Tg <10 ng/ml and with WD scan class 0-1 clearly shows no correlation. As discussed above, clinical decisions regarding this group are made on the basis of Tg levels and thus consistent, reliable TSH stimulated secretion is essential to appropriate management.

The sponsor's diagnostic utility analysis

First and foremost, this retrospective assessment of diagnostic utility is a flawed and invalid analytic approach. In effect, it asks the question, knowing the diagnosis, whether one could have arrived there using the Thyrogen data. This was a retrospective manipulation of the data seeking a "best fit" of the Thyrogen combined data with the combined WD data examining different Tg cutoffs as diagnostic of residual or recurrent cancer. The Phase III studies were designed to assess whether RAI scanning after WD and Thyrogen were comparable. A study assessing the diagnostic utility of Thyrogen should prospectively investigate the comparability to WD in guiding intervention in patients who are evaluated blindly by a group of experienced clinicians.

Notwithstanding the basic criticism above, the sponsor has relied on the diagnostic utility analyses to suggest that Thyrogen is of comparable utility to WD in diagnosing recurrent or metastatic cancer when Scan and Tg data are combined. These analyses assume and at the same time purport to demonstrate that Tg levels on Thyrogen are directly related to those on WD. This is simply not the case. Based on the clinical trial data, Thyrogen Tg levels may be similar to, greater than, or less than WD Tg levels. Importantly, no correlation exists between the two.

Finally, the idea of cutoffs for Tg employed in the diagnostic utility analyses ignores the fundamental fact that Tg is and is used clinically as a continuous variable, not a binary one. The utility of Thyrogen Tg under the current approaches to this disease requires that it correlate directly with WD Tg and thus with burden of disease in a given patient.

Additional points

Proposed labeling clearly recommends Thyrogen as a substitute for WD, gives no guidelines for interpretation of results (e.g. relative to the "historical" standard of WD), and thus implies that clinicians should base decisions on the Thyrogen data as though they were data on WD. That is, a one-to-one correlation is implied. As stated and shown above, this is clearly not supported by the clinical trial data. In addition, no discussion of the inconsistent nature of the Thyrogen stimulation relative to WD is included.

The sponsor's submission of March 16, 1998, "Assessment of the clinical utility of Thyrogen for thyroid cancer management" reviews current approaches to the follow up of thyroid cancer patients using WD scanning and Tg testing. It includes revised algorithms integrating Thyrogen scanning and Tg testing as part of the primary treatment phase of thyroid cancer, in the follow up management of thyroid cancer, and finally in follow up in patients where only a Tg on THST is performed. In all its proposed uses, the problem of the high false negative scan rate coupled with the "non-quantitative" nature of the Tg stimulation sorely limit its usefulness. As stated above, the benefit of Thyrogen is as a withdrawal-sparing diagnostic modality. This requires that negative or low level scans and Tg levels accurately reflect absence or low level of disease. This is not the case. The ability to detect extensive disease is important, but does not spare withdrawal. Finally, the use of Thyrogen Tg testing as an alternative to Tg on THST was raised by the sponsor here and elsewhere in the NDA. Despite the apparent logic of this approach, the diagnostic utility was not studied in the Thyrogen clinical trials. Whether Thyrogen Tg testing would have benefit that outweighs risk (inconvenience, adverse reactions, cost) in patients followed by Tg on THST on the basis of their assessed low risk for recurrence remains to be demonstrated.

A final point bears mention. It is significant that Thyrogen 0.9mg q24h X 2 cannot be proposed as an alternative to WD for the purposes of RAI ablative therapy. The pharmacodynamic requirements for exogenously administered TSH with regard to stimulation of FCDT should, in principle and in practice, be the same for diagnostic Tg

and scanning as for therapeutic RAI uptake. Always assuming adjustment of RAI dose based on increased GFR in the euthyroid versus hypothyroid state, the obvious lack of utility of Thyrogen for the stimulation of therapeutic RAI uptake is a relevant negative point with regard to its utility for diagnostic purposes.

Conclusions

In sum, the high false negative rate with Thyrogen scanning in patients with positive WD scans, the observed tendency for underdiagnosis by Thyrogen scan coupled with the absence of any consistent correlation between Thyrogen Tg levels and those on WD make Thyrogen unacceptable as an alternative to WD.

Future studies should be directed at determining an administration protocol (dose and schedule) for Thyrogen that renders a stimulation of FCDT comparable to that after WD. Furthermore, studies to assess the diagnostic utility of scanning and Tg after Thyrogen administration should involve blinded (independent) assessment of scans, blinded synthesis of clinical and test data, and blinded clinical decision making. A similar process involving the WD data should be conducted, and only when both independent judgments are rendered should the results be compared to each other and to a "gold standard." As an aside, WD data and the decisions based on them would still be expected to guide actual follow up and therapy of study patients.

Recommendation:

Not approvable.

APPEARS THIS WAY
ON ORIGINAL

David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

/S/
4-20-98

Recommendation code: NA
cc:
NDA 20-898 Arch
HFD-510
HFD-510 Sobel/Temeck/McCort

APPEARS THIS WAY
ON ORIGINAL

NDA: 20,898
Drug: Thyrogen
Sponsor: Genzyme
Date: 6/11/98

Subject: Request to Audit Serum Thyroglobulin (Tg) Assay Done in Dr. Carole Spencer's Laboratory for Protocol TSH95-0101:

Dr. M. Fossler, Biopharmaceutics Reviewer, has informed me that an audit of the TSH assays at Dr. Spencer's laboratory by Dr. Martin Yau, DSI, revealed significant problems, including, in some cases, failure to follow SOPs (Standard Operating Procedures). There were quality control values that did not meet the laboratory's standards, but were, nevertheless, passed. The bottom line is that the validity of the TSH values reported are called into question. Given that the central Tg assay for study TSH95-0101, was also done at Dr. Spencer's lab, and the accuracy of the Tg assay is critical to the proper labeling of Thyrogen, it is essential that FDA be assured of the reliability and accuracy of the Tg data. It is therefore requested, that the biopharmaceutics arm of DSI also inspect the Tg assay performed at Dr. Spencer's laboratory for study TSH95-0101. This laboratory used a sensitive Tg radioimmunoassay with a lower limit of detection of 0.5 ng/ml and ran all the samples in a single run to control for interasssay variability. Among the issues that should be addressed are: Has the assay been validated? Were SOPs followed and were QC values sufficient?

/S/
Jean Temeck, M.D.

/S/
6-11-98

cc. NDA 20.898
HFD-510: Dr. Sobel/Dr. Orloff/Dr. Ahn/Dr. Fossler/Mr. McCort
HFD-510 Division file

/S/
6-11-98